Effective Health Care Program

Future Research Needs Paper
Number 14

Future Research Needs for Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), or Direct Renin Inhibitors (DRIs) for Treating Hypertension

Agency for Healthcare Research and Quality
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Future Research Needs for Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), or Direct Renin Inhibitors (DRIs) for Treating Hypertension

Identification of Future Research Needs From Comparative Effectiveness Review No. 34

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This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2008-10066-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

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

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that are needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Executive Summary

Background

Almost 75 million American adults have hypertension. Advances in antihypertensive therapy have dramatically reduced cardiovascular, cerebrovascular, and renal events.[1-3] Among the effective pharmacotherapies are inhibitors of the renin-angiotensin-aldosterone system (RAS). In 2007, the Agency for Healthcare Research and Quality (AHRQ) sponsored a comparative effectiveness review (CER) of the two most common renin system inhibitors, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), to answer the following three Key Questions for adults with essential hypertension: do ACEIs and ARBs differ in their (1) blood pressure control, cardiovascular events, quality of life, and other outcomes; (2) safety, tolerability, persistence with therapy, or treatment adherence; and (3) effects within important subgroups of patients?[4,5] This 2007 CER was updated in 2011 to incorporate the significant additional direct comparison research published in the interval and to include direct renin inhibitors (DRIs), which are the newest class of RAS inhibitors.[6,7]

The results of the updated CER included 97 studies (36 new since 2007) directly comparing ACEIs versus ARBs and 3 studies directly comparing DRIs to ACEIs or ARBs. The strength of evidence remained high for equivalence between ACEIs and ARBs for blood pressure lowering, and for superiority of ARBs over ACEIs for short-term adverse events (primarily cough). The new evidence did not strengthen the conclusions regarding long-term cardiovascular outcomes, quality of life, progression of renal disease, medication adherence or persistence, rates of angioedema, or differences in key patient subgroups; the strength of evidence for these outcomes remained low to moderate (Table A). Evidence on the comparative effectiveness of DRIs versus either ACEIs or ARBs was limited to 3 studies with 2,049 patients and did not allow definitive conclusions on any of the included outcomes. Few studies involved a representative patient sample treated in a typical clinical setting over a long duration; treatment protocols had marked heterogeneity; and significant amounts of data about important outcomes and patient subgroups were missing.

Given the clinical and economic importance of these medications, the ongoing investment in research, and the remaining areas of uncertainty, we sought to create a prioritized research agenda representing the interests of diverse stakeholders in order to address the remaining areas of uncertainty.

Analytic Framework

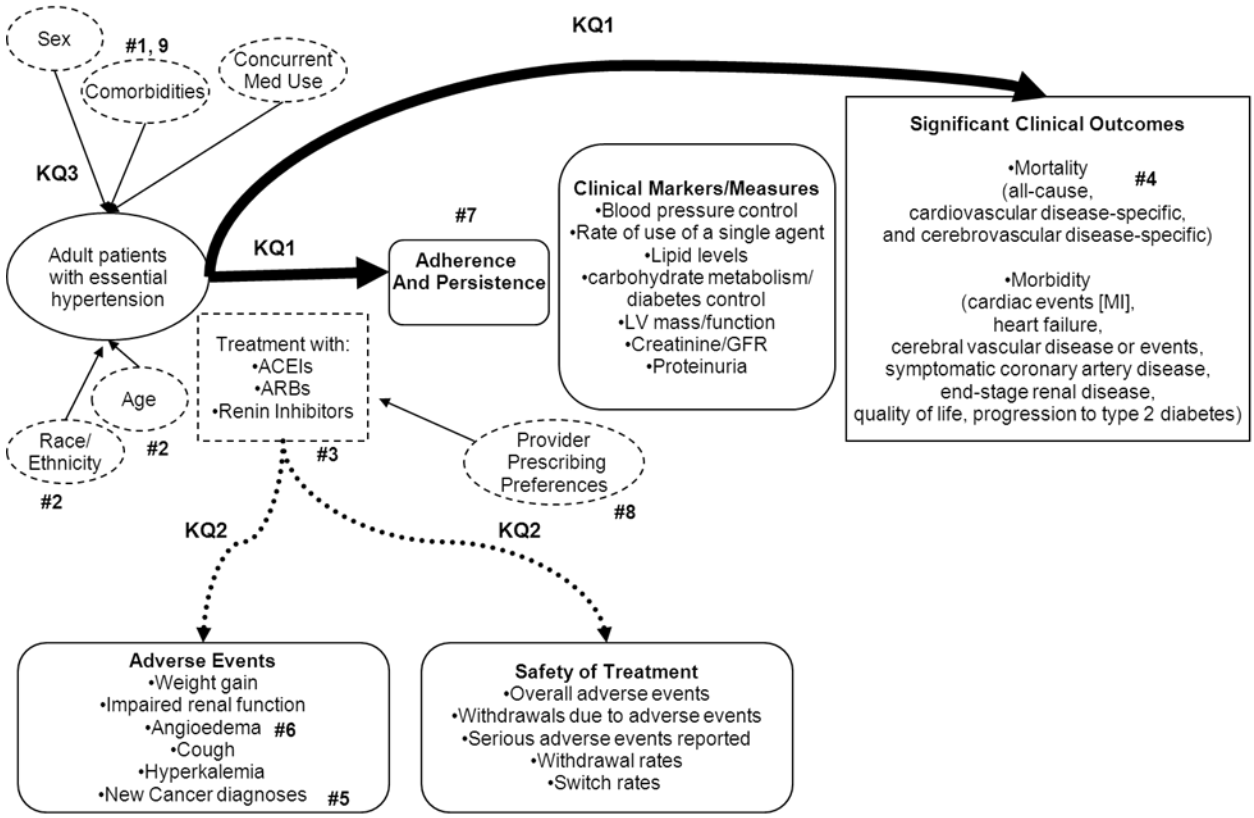
We organized the research areas into an analytic framework depicted in Figure A. The Key Questions are organized within the context of the population, interventions, comparators of interest, and outcomes (PICO) in Table A and displayed accordingly in the analytic framework.

Table A. Initial list of evidence gaps

PICO Element	Evidence Gaps
Population	1. What are the comparative safety and effectiveness of treatment in subgroups of special importance, such as individuals with essential hypertension and at least one of the following: ischemic heart disease, diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia? 2. What are the comparative safety and effectiveness in specific subgroups such as the elderly and ethnic and racial minorities?
Interventions and comparators	3. Are there differential effects of specific ACEIs, ARBs, or DRIs that are not shared by other agents within their respective medication class?
Outcomes	4. What is the comparative effectiveness of these medications on cardiovascular and cerebrovascular events measured over several years? 5. What is the comparative effectiveness of these medications on cancer-related outcomes, which are infrequently reported in the existing literature? 6. What are the incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or DRIs?
Implementation gaps	7. Are there important differences in medication adherence and persistence with drug therapy across the different classes of drug? 8. What are the provider patterns of prescribing these medications, and what interventions are used to support evidence-based decisionmaking about prescribing?
Methods for evidence synthesis	9. What are the best methods for synthesis of data across clinical conditions (e.g. congestive heart failure, ischemic heart disease, and chronic kidney disease) to better understand the comparative effectiveness of ACEIs, ARBs, and DRIs?

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); DRI(s) = direct renin inhibitor(s); PICO = population, interventions, comparators, and outcomes.

Figure A. Analytic framework



Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; GFR = glomerular filtration rate; KQ = Key Question; LV = left ventricular; MI = myocardial infarction.

Methods

Our approach to identifying evidence gaps, prioritizing future research, and developing recommendations for stakeholders is outlined in the following steps:

1. Develop an analytic framework from the original CER in order to understand the clinical and policy context of the review and its initial list of future research needs.
2. Create an initial list of evidence gaps organized according to the PICO (population, interventions, comparators, and outcomes) framework.[8]
3. Form a stakeholder workgroup representing appropriate professional societies, policymakers, and patient perspectives.
4. Expand the list of evidence gaps based on stakeholder input.
5. Perform an updated review of published literature since the last CER (search last updated in December 2010) and a horizon scan for recently published and ongoing studies that may address the evidence gaps, but which are not included in the current CER.
6. Solicit stakeholder prioritization of the identified research gaps based on updated literature review.
7. Determine the most appropriate study designs for the highest priority research areas.[9]

Stakeholders were selected to include researchers involved in some of the primary randomized controlled trials (RCTs) included in the CER, other clinical experts and researchers in the content area, representatives from Federal and nongovernmental funding agencies,

representatives from relevant professional societies, health care policymakers, and representatives from related consumer and patient advocacy groups.

We used the research priorities identified in the CER and also examined a complementary list of priorities taken from a related AHRQ-sponsored project, Future Research Needs for Angiotensin Converting Enzyme (ACE) Inhibitors or Angiotensin II Receptor Blockers (ARBs) added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease.[10] Based on input from the stakeholder workgroup during the first call, we ultimately expanded the list of research priorities from a list of 9 to a total of 25.

We performed three database searches to identify ongoing and recently published studies relevant to the identified evidence gaps. These included a search of ClinicalTrials.gov, an update of the MEDLINE® search used in the original CER, and a search of PubMed® for relevant systematic reviews that may address the evidence gaps considered out of scope in the original review. Based on these searches, a document was created listing all included articles and clinical trials that might pertain to the 25 listed evidence gaps.

The stakeholders were provided with the AHRQ Effective Health Care Program Selection Criteria and instructed to use these criteria as the basis for their decisions regarding research prioritization. The stakeholders performed an online ranking of the identified research priorities (including the additional priorities identified by the stakeholder team). This ranking utilized a forced-ranking prioritization method, whereby participants were given 9 votes to allocate to any of the 25 research priorities, with a maximum of 3 votes per item.

For the top tier future research needs, we considered potential study designs and their advantages and disadvantages.[9] While these proposed methods to address each area are not intended to be restrictive of potential study designs, we comment on each design's potential benefits or limitations for answering these questions.

Results

Based on the 2011 hypertension CER[6], the related ACEI/ARB prioritization project in ischemic heart disease, and our discussion with stakeholders, we identified the 25 potential research areas.[10] The stakeholder voting identified seven highest priority areas of future research, and these results were consistent over two separate prioritization exercises. The research priorities are shown in Table B.

Table B. Final ranking of future research needs for ACEIs, ARBs, and DRIs in hypertension

Question	Score
Top Tier	
Studies of cardiovascular and cerebrovascular events compared across the three medication classes, thereby requiring evaluation of outcomes over several years.	11
Impact of comorbidities (such as ischemic heart disease, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization, single- vs. multi-vessel coronary artery disease) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension.	10
Impact of demographic differences (such as age, race, sex) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension.	8
Practical clinical trials or other or other external validity–oriented studies that compare these medications in practice settings that better represent real-world practice.	8
The impact of ACEI/ARB/DRI on incidence of new cardiovascular or metabolic diagnoses (such as diabetes, atrial fibrillation, CHF with or without preserved LV function).	5

Table B. Final ranking of future research needs for ACEIs, ARBs, and DRIs in hypertension (continued)

Question	Score
The impact of ACEI/ARB/DRI on patient health status including quality of life and functional capacity.	5
Relative medication adherence and persistence with drug therapy across the different classes of drugs.	5
Middle Tier	
*The benefit of ACEI/ARB/DRI relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms. **	*4*
The impact of ACEI/ARB/DRI on utilization and cost of therapy.	*4*
Impact of health risk behaviors such as diet, exercise, smoking, alcohol intake on ACEI/ARB/DRI effectiveness or harms .	3
The impact of ACEI/ARB/DRI on progression of renal insufficiency or development of dialysis dependence.	3
Impact of changing trends in outcome event rates over time on the comparative effectiveness of ACEI, ARBs, and DRIs.	*3*
Better understanding of provider patterns of prescribing these medications, and of interventions used to support evidence-based decisionmaking about prescribing.	*3*
Impact of class effect (impact of differences between specific agents within each class) of ACEI/ARB/DRI on their effectiveness or harms.	2
The impact of ACEI/ARB/DRI on development of non-angioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia).	2
Lower Tier	
Impact of concurrent medications (such as antiplatelet agents, lipid-lowering medications, diuretics, other antihypertensives) on ACEI/ARB/DRI effectiveness or harms.	*1*
Methods for synthesis of data across clinical conditions (e.g., CHF, ischemic heart disease, and chronic kidney disease) to better understand the comparative effectiveness of ACEI, ARBs, and DRIs.	*1*
Methods for individual patient data meta-analysis, to better examine subgroups in the absence of other confounders.	*1*
Impact of the dose response (impact of medication dose or dosing interval) of ACEI/ARB/DRI on their effectiveness or harms.	0
Impact of genetic differences (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB/DRI effectiveness or harms..	0
The impact of ACEI, ARB, or DRI monotherapy compared to ACEI, ARB, and/or DRI combination therapy in hypertension.	*0*
The impact of ACEI/ARB/DRI alone compared to ACEI/ARB/DRI combined with aldosterone receptor antagonists.	*0*
The impact of ACEI/ARB/DRI alone compared to ACEI/ARB/DRI in combination with a diuretic.	*0*
Evaluation of cancer-related outcomes, which are infrequently reported in the existing literature.	*0*
Evaluation of the incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or DRIs.	0

*Out-of-scope research topics are highlighted in italics.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; DRI(s) = direct renin inhibitor(s); LV = left ventricular

Discussion

The recommendations for future research prioritization of ACEIs, ARBs, and DRIs in this report represents the perspectives of a broad range of stakeholders, including general physicians,

physician specialists, researchers, policymakers, and patients. The top tier of seven research priorities remained stable between our first and second prioritization exercise. These areas represent three primary foci: (1) heterogeneity in treatment response (i.e., impact of comorbidities and demographic differences); (2) long-term clinical outcomes (i.e., cardiovascular and cerebrovascular events, incident diabetes or cardiovascular diagnoses, quality of life); and (3) implementation and generalizability (i.e., practical research designs and medication adherence/persistence).

The stakeholder group included several topics that were out of the scope of the original review. The expansion of topics promotes consideration of new areas of research that have not been adequately explored. Nevertheless, the original CER did not comment on the state of current research in these out-of-scope areas, and they should only be promoted with the caveat that the existing literature may already adequately address these areas. Among our highest rated research priorities, there were no topics clearly out of the scope of the original review, but formal means of guiding the prioritization of topics both in and out of scope would be helpful for future projects.

Conclusions

A workgroup of 10 stakeholders identified the following seven research areas as the highest priority for future research for the comparative effectiveness of ACEIs, ARBs, or DRIs in patients with hypertension.

1. What is the comparative effectiveness of these medications on cardiovascular and cerebrovascular events measured over several years?
    a. Recommended study design: if able to combine with chronic conditions other than hypertension, then a systematic review with broader inclusion criteria could provide additional information not included in the CER, which was restricted to patients with hypertension. If not, then large long-term clinical trial or observational study would be preferable.
2. What is the impact of comorbidities (such as ischemic heart disease, CHF, diabetes, peripheral arterial disease, or chronic kidney disease) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension?
    a. Recommended study design: if patient-level data are available from relevant trials, then a patient-level meta-analysis may be the most efficient approach.
3. What is the impact of demographic differences (such as age, race, or sex) on the effectiveness or harms of ACEI/ARB/DRIs in patients with hypertension?
    a. Recommended study design: if patient-level data are available from relevant trials, then a patient-level meta-analysis is most appropriate.
4. Do the results differ in practical clinical trials or other external validity-oriented studies that compare these medications in practice settings that better represent real-world practice?
    a. Recommended study designs: either a large clinical trial with broader inclusion criteria to maximize generalizability, or an observational study of patients in typical community practice.
5. What is the impact of ACEI/ARB/DRIs on incidence of new cardiovascular or metabolic diagnoses such as diabetes, atrial fibrillation, or CHF with or without preserved LV function?

   a. Recommended study design: if patients can be combined across clinical conditions (i.e., not exclusively hypertension), then a systematic review of existing studies is most appropriate.
6. What is the impact of ACEI/ARB/DRIs on patient health status, including quality of life and functional capacity?
   a. Recommended study design: randomized controlled trials (RCTs) with the inclusion of validated quality of life measures as an outcome.
7. Are there important differences in medication adherence and persistence with drug therapy across the different classes of drug?
   a. Recommended study design: new observational studies with a focus on the longitudinal measurement of adherence and persistence

Glossary

ACEI	angiotensin-converting enzyme inhibitor
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
CER	comparative effectiveness review
DRI	direct renin inhibitors
EPC	Evidence-based Practice Center
PICO	population, interventions, comparators, and outcomes
RAS	renin-angiotensin system
RCT	randomized controlled trial

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Background

Hypertension is the most common reason older adults visit the doctor and advances in antihypertensive therapy have dramatically reduced the associated cardiovascular, cerebrovascular, and renal events.[1-3] Inhibitors of the renin-angiotensin system (RAS) are the most frequently used medications for blood pressure control and are highly efficacious for reducing hypertension-related outcomes. In 2007, a comparative effectiveness review (CER) sponsored by the Agency for Healthcare Research and Quality (AHRQ) evaluated the long-term benefits and harms of the two most common classes of RAS inhibitors for treating essential hypertension in adults: angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers/antagonists (ARBs).[4,5] This 2007 CER was updated in 2011 to incorporate the significant additional direct comparison research published in the interval, and to include the direct renin inhibitors (DRIs), which are the newest class of RAS inhibitors.[6,7] The 2011 CER addressed the three following Key Questions:

Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and DRIs differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and DRIs differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?

Key Question 3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—for whom ACEIs, ARBs, or DRIs are more effective, are associated with fewer adverse events, or are better tolerated?

The results of the CER included 97 studies (36 new since 2007) directly comparing ACEIs versus ARBs and 3 studies directly comparing DRIs to ACEIs or ARBs. The strength of evidence remained high for equivalence between ACEIs and ARBs for blood pressure lowering, and for superiority of ARBs over ACEIs for short-term adverse events (primarily cough). The new evidence did not strengthen the conclusions regarding long-term cardiovascular outcomes, quality of life, progression of renal disease, medication adherence or persistence, rates of angioedema, or differences in key patient subgroups; the strength of evidence for these outcomes remained low to moderate (Table 1). Evidence on the comparative effectiveness of DRIs versus either ACEIs or ARBs was limited to 3 studies with 2,049 patients and did not allow definitive conclusions on any of the included outcomes. Few studies involved a representative patient sample treated in a typical clinical setting over a long duration; treatment protocols had marked heterogeneity; and significant amounts of data about important outcomes and patient subgroups were missing.

Table 1. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and DRIs in patients with essential hypertension

Key Question	Strength of Evidence, Updated Report	Conclusions
1. Key Question 1. For adult patients with essential hypertension, how do ACE inhibitors, ARBs, and direct renin inhibitors differ in the following health outcomes:	High (ACE inhibitor vs. ARB);	ACE inhibitors and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 77 studies (70 RCTs, 5 nonrandomized controlled clinical trials, 1 retrospective cohort study, and 1 case-control study) in which 26,170 patients receiving an ACE inhibitor or an ARB were followed for periods from 12 weeks to 5 years (median 24 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.
a. Blood pressure control?	Low (DRI vs. ACE inhibitor or ARB)	Evidence concerning the effect of DRIs on blood pressure is very limited and currently based on only three studies. These studies found the DRI to have a greater reduction in blood pressure compared to the ACE inhibitor ramipril (two studies) and no significant difference compared to the ARB losartan (one study).
b. Mortality and major cardiovascular events?	Low (ACE inhibitor vs. ARB);	Due to low numbers of deaths or major cardiovascular events reported, it was difficult to discern any differential effect of ACE inhibitors versus ARBs versus DRIs with any certainty for these critical outcomes. In 21 studies that reported mortality, MI, or clinical stroke as outcomes among 38,589 subjects, there were 38 deaths and 13 strokes reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.
	Insufficient (DRI vs. ACE inhibitor or ARB)	Only 3 of these 21 studies (including 1 death) evaluated DRIs versus ACE inhibitors or ARBs, and therefore the evidence to discern any differential effects between these drug classes on mortality and major cardiovascular events was insufficient.
c. Quality of life?	Low (ACE inhibitor vs. ARB);	No differences were found between ACE inhibitors and ARBs in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data.
	Insufficient (DRI vs. ACE inhibitor or ARB)	No study evaluated the comparative effectiveness of DRIs for quality-of-life outcomes.
d. Rate of use of a single antihypertensive medication?	High (ACE inhibitor vs. ARB);	There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive for ARBs compared to ACE inhibitors. The trend toward less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACE inhibitor-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching.
	Insufficient (DRI vs. ACE inhibitor or ARB)	There were no relevant studies evaluating DRIs.

Table 1. Summary of Evidence on Comparative Long-Term Benefits and Harms of ACEIs, ARBs, and DRIs in patients with essential hypertension (continued)

Key Question	Strength of Evidence, Updated Report	Conclusions
e. Risk factor reduction and other intermediate outcomes?	Moderate (lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease) (ACE inhibitor vs. ARB);	There were no consistent differential effects of ACE inhibitors, ARBs, on several potentially important clinical outcomes, including lipid levels and markers of carbohydrate metabolism/diabetes control. There appears to be a small difference in change in renal function between ACE inhibitors and ARBs (favoring ACE inhibitors), but this difference is both small and most likely not clinically meaningful or significant. Relatively few studies assessed these outcomes over the long term.
	Insufficient (DRI vs. ACE inhibitor or ARB)	There were no studies that evaluated these outcomes in DRIs.
	Low (progression to type 2 diabetes and LV mass / function: (ACE inhibitor vs. ARB); Insufficient (DRI vs. ACE inhibitor or ARB)	There was no evidence for an impact of ACE inhibitors, ARBs, or DRIs on glucose or A1c, and no included studies evaluated rates of progression to type 2 diabetes mellitus. Although we included 13 studies of LV mass/function, these were dominated by poor-quality studies with small sample sizes, and only one study included evaluation of a DRI.

Table 1. Summary of Evidence on Comparative Long-Term Benefits and Harms of ACEIs, ARBs, and DRIs in patients with essential hypertension (continued)

Key Question	Strength of Evidence, Updated Report	Conclusions
2. Key Question 2. For adult patients with essential hypertension, how do ACE inhibitors, ARBs, and DRIs differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?	Cough: High (ACE inhibitor vs. ARB); Insufficient (DRI vs. ACE inhibitor or ARB)	ACE inhibitors have been consistently shown to be associated with higher risk of cough than ARBs (odds ratio 4.74; 95% CI 3.56 to 6.31). For RCTs, this translates to a difference in rates of cough of 7.8%; however, for cohort studies with lower rates of cough, this translates to a difference of 1.2%. There were only two studies comparing DRIs to ACE inhibitors and these gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933).
	Withdrawals due to adverse events: High (ACE inhibitor vs. ARB); Low (DRI vs. ACE inhibitor or ARB)	The withdrawal rate for ACE inhibitors was found to have an estimated odds ratio of 1.77 (95% CI 1.42 to 2.21) compared with ARBs. For RCTs, this translated to an absolute difference in withdrawals of 2.3% (3.1% versus 5.4%). The DRI trials did not find a statistically significant difference (odds ratio 0.886; 95% CI 0.458 to 1.714) when compared with the withdrawal rate associated with ACE inhibitors. There was no evidence of differences across treatments in rates of other commonly reported specific adverse events.
	Angioedema: Low (ACE inhibitor vs. ARB); Insufficient (DRI vs. ACE inhibitor or ARB)	Although several studies collected data on angioedema, the event rates were very low or zero for all studies; this limited our ability to accurately characterize the frequency of angioedema. In the four studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACE inhibitor (five patients from three studies) or a DRI (one patient in one study).
	Persistence with drug therapy/ treatment adherence: Moderate (ACE inhibitor vs. ARB); Insufficient (DRI vs. ACE inhibitor or ARB)	ACE inhibitors and ARBs have similar rates of treatment adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACE inhibitors; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. The three included studies evaluating DRIs did not find evidence of differences in treatment adherence compared with ACE inhibitors or ARBs. Persistence was not evaluated in any of the studies including DRIs.

Table 1. Summary of Evidence on Comparative Long-Term Benefits and Harms of ACEIs, ARBs, and DRIs in patients with essential hypertension (continued)

Key Question	Strength of Evidence, Updated Report	Conclusions
3. Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—a for whom ACE inhibitors, ARBs, or DRIs are more effective, are associated with fewer adverse events, or are better tolerated?	Insufficient (ACE inhibitor vs. ARB; DRI vs. ACE inhibitor or ARB)	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACE inhibitors, ARBs, and DRIs for any particular patient subgroup.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CI = confidence interval; DRI(s) = direct renin inhibitor(s); GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; OR = odds ratio; RCTs = randomized controlled trials

The 2011 updated report demonstrated that direct comparisons of ACEIs and ARBs continued to be an active area of investigation, with 59 percent more direct comparison studies in the 3 years following the publication of the original report. Nevertheless, data from these new studies have not significantly changed the conclusions, nor have they changed the strength of evidence from the original report, which suggests that this additional research was not efficiently directed at important areas of remaining uncertainty. The lack of clinically useful new information, in spite of many more new publications, is likely explained by several factors. The primary outcomes of many of the new studies were biochemical, and the clinical information abstracted from their reports was sparse. The importance of directly comparing these medications' effects on clinical outcomes is particularly important considering the mixed results of other placebo-controlled and direct comparison studies of ACE inhibitors and ARBs for these outcomes.[8] The incentives for comparative effectiveness research investment differ between public funders and private, for-profit corporations. Therefore, the highest value research may not be the most likely to be funded.

AHRQ supports our Evidence-based Practice Center (EPC) to work with various stakeholders to identify and prioritize the future research that is most needed by decisionmakers. Given the clinical and economic importance of ACEI, ARB, and DRI medications, the ongoing investment in their research, and the remaining areas of uncertainty, we sought to create a prioritized research agenda that would represent the interests of diverse stakeholders and allow the remaining areas of uncertainty to be addressed. This report is a summary of that process and our findings.

Methods

Overview

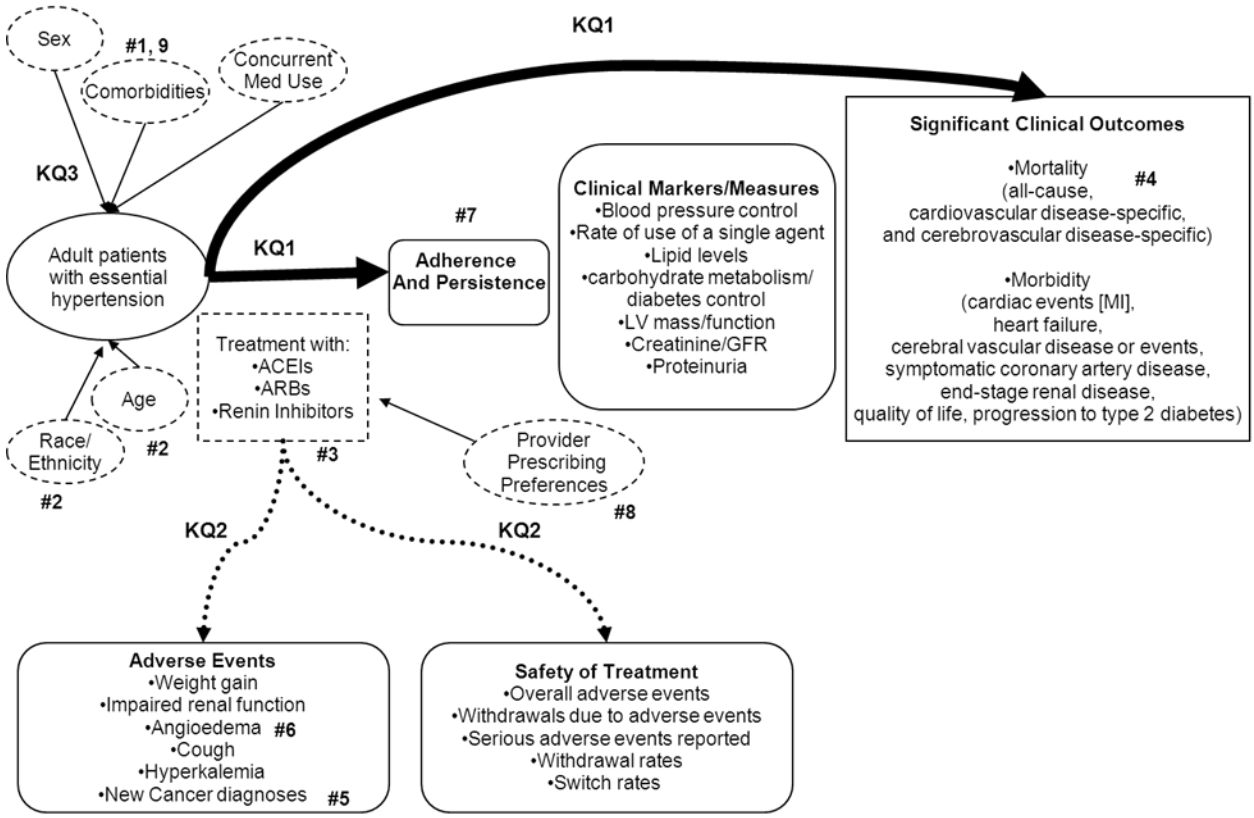
Our approach to identifying evidence gaps, prioritizing future research, and developing recommendations for stakeholders is outlined in the following steps. Further detail is provided below.

1. Develop an analytic framework from the original CER in order to understand the clinical and policy context of the review and its initial list of future research needs.
2. Create an initial list of evidence gaps based on the CER organized according to the population, interventions, comparators, and outcomes (PICO) framework.[9]
3. Form a stakeholder group representing appropriate clinician, policymakers, and patient perspectives.
4. Expand the list of evidence gaps based on stakeholder input.
5. Perform an updated review of published literature since the last CER (search last updated in December 2010) and a horizon scan for recently published and ongoing studies that may address the evidence gaps, but which are not included in the current CER.
6. Solicit stakeholder prioritization of the identified research gaps based on the updated literature review.
7. Determine the most appropriate study designs for the highest priority research areas.[10]

Analytic Framework

Figure 1 depicts the analytic framework for the CER. Future research areas are linked to the framework using numbers which link the research areas in Table 2, below. The Key Questions were organized within the context of the PICO. In general, the figure illustrates how ACEIs, ARBs, and DRIs may affect: (1) measures of blood pressure control, lipid levels, carbohydrate metabolism/diabetes control, measures of left ventricular mass/function, or measures of kidney disease (creatinine/glomerular filtration rate, proteinuria); and/or (2) clinically significant outcomes, such as mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific) or morbidity (especially major cardiovascular events [myocardial infarction, stroke], rates of progression to type 2 diabetes, and measures of quality of life). In addition, adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia) may occur at any point after ACEIs, ARBs, and/or DRIs are taken.

Figure 1. Analytic framework



Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction

Initial List of Research Needs

Results from the 2011 report suggest several evidence gaps for future research. These possibilities are neither exhaustive nor prioritized. The initial list generated by the study authors is provided in Table 2, organized according to the PICO format, with the addition of implementation gaps and methods for evidence synthesis.

Table 2. Initial list of evidence gaps

PICO Element	Evidence Gaps
Population	1. What is the comparative safety and effectiveness of treatment in subgroups of special importance, such as individuals with essential hypertension and at least one of the following: ischemic heart disease, diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia? 2. What is the comparative safety and effectiveness of specific subgroups such as the elderly and ethnic and racial minorities?
Interventions and comparators	3. Are there differential effects of specific ACEIs, ARBs, or DRIs that are not shared by other agents within their respective medication class?
Outcomes	4. What is the comparative effectiveness of these medications on cardiovascular and cerebrovascular events measured over several years? 5. What is the comparative effectiveness of these medications on cancer-related outcomes, which are infrequently reported in the existing literature? 6. What are the incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or DRIs?
Implementation gaps	7. Are there important differences in medication adherence and persistence with drug therapy across the different classes of drug?. 8. What are the provider patterns of prescribing these medications, and what interventions are used to support evidence-based decisionmaking about prescribing?
Methods for evidence synthesis	9. What are the best methods for synthesis of data across clinical conditions (e.g. congestive heart failure, ischemic heart disease, and chronic kidney disease) to better understand the comparative effectiveness of ACEIs, ARBs, and DRIs?

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); DRI(s) = direct renin inhibitor(s); PICO = population, interventions, comparators, and outcomes

Creation of Stakeholder Group

We selected stakeholders to include researchers involved in some of the primary randomized controlled trials (RCTs) included in the CER, other clinical experts and researchers in the content area, representatives from Federal and nongovernmental funding agencies, representatives from relevant professional societies, healthcare policymakers, and representatives from related consumer and patient advocacy groups (Table 3). This list included generalist and specialist physician perspectives and was solicited through the professional societies listed below. Within each group, we sought to identify an individual who was either familiar with the clinical area and its current uncertainties, or who brought a specific methodological area of expertise to the workgroup.

Table 3. Stakeholder organizations and roles

Organization	Purpose/Role
National Heart Lung and Blood Institute (NHLBI)	The NHLBI is one of the main funders of potential future studies of the comparative safety and effectiveness of ACEIs, ARBs, and DRIs in patients with hypertension; therefore, it was important to include their perspective in the prioritization of future research needs.
American College of Physicians (ACP)	ACP is the largest group representing internal medicine and its subspecialties. Most hypertension is managed by generalists or medicine subspecialists in the office setting and the ACP represents this broad group of stakeholders
Society of General Internal Medicine (SGIM)	Along with the AAFP below, SGIM represents generalist physicians who manage most patients with hypertension. These groups' members are most often the front line providers, managing the majority of patients with hypertension and representing important stakeholder groups.
American Heart Association (AHA)	The AHA funds clinical, outcomes, and health services research in cardiovascular disease and stroke. They are also a leading advocacy group for advancing science and improving the quality of cardiovascular care.
American Society of Hypertension (ASH)	ASH is the subspecialty group representing generalists and specialists with a focus on hypertension care. Their membership is comprised of generalists, cardiologists, and nephrologists and we sought a representative with content expertise in this area for representing future research needs.
American Academy of Family Physicians (AAFP)	Most hypertension medication prescriptions are written by primary care providers. The AAFP represented family physicians that were not otherwise included in any of the internal medicine stakeholder groups.
Payer	We sought a representative from a private payer and a representative from Blue Cross/Blue Shield of North Carolina participated. Although payers may not fund future research projects, we sought their opinion on the information needed to change their coverage decisions.
Patient Advocate	We identified a patient advocate to represent the research priorities and issues from the patient's perspective.
Centers for Medicare & Medicaid (CMS)	We sought a representative from CMS. Although CMS may not fund future research projects, like private insurers, they are important decisionmakers in prescription coverage.

Abbreviations: AAFP = American Academy of Family Physicians; ACEI(s) = angiotensin-converting enzyme inhibitor(s); ACP = American College of Physicians; AHA = American Heart Association; ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); ASH = American Society of Hypertension; CMS = Centers for Medicare & Medicaid Services; DRI(s) = direct renin inhibitor(s); NHLBI = National Heart Lung and Blood Institute; SGIM = Society of General Internal Medicine

We were able to recruit a representative from each of these nine groups. In addition, we identified a clinical pharmacist with expertise in ACEIs, ARBs, and experience in comparative effectiveness research. A total of 10 stakeholders were included in our final panel.

Stakeholder input was solicited and received through web-based survey techniques, email, and group discussions via teleconference. Group discussions were moderated by the EPC investigators to avoid domination of the discussion by any particular group and to ensure that all participants had an equal opportunity to ask questions and express their views. The AHRQ Task Order Officer was a participant in all group teleconferences and was included on all electronic communication with the stakeholder group.

Each potential stakeholder completed a statement of disclosure, was screened for apparent conflicts of interest, and approved by AHRQ prior to the first stakeholder call. Efforts were made to assemble a balanced group of individuals representing a wide range of perspectives.

Expansion of Research Gaps

We used the research priorities identified in the CER and also examined a complementary list of priorities taken from a related AHRQ-sponsored project entitled, "Future Research Needs for Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease."[11] Based on input from the stakeholder workgroup during the first call, we ultimately expanded the list of research priorities as shown in Table 4.

While most of these research areas were within the scope of the initial review, several raised by the stakeholder group were outside the scope of this review. These areas may represent important gaps in the knowledge base; however, we are less confident about the current state of the evidence since they were not included in the original report. These "out-of-scope" topics were included in our list, but were specifically noted so that the stakeholders were aware that these areas had not undergone the same level of systematic review and we, therefore, could not provide the same level of detail on the state of current evidence.

We have organized these gaps according to the PICO format and listed them in the table below. The areas determined to be out of scope from the original review are italicized in Table 4.

Table 4. Potential future research needs based on the CER and stakeholder input

PICO Element	Potential Future Research Need*
Population	1. Impact of **comorbidities** (such as ischemic heart disease, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multi-vessel coronary artery disease) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension 2. Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension 3. Impact of **genetic differences** (such as ACEI or angiotensin II receptor gene polymorphisms) on ACEI/ARB/DRI effectiveness or harms. 4. Impact of **health risk behaviors** such as diet, exercise, smoking, alcohol intake on ACEI/ARB/DRI effectiveness or harms
Intervention and comparator	5. Impact of the **dose response** (impact of medication dose or dosing interval) of ACEI/ARB/DRI on their effectiveness or harms 6. *Differential impact of **specific agents or subclasses** (based on tissue specificity, chemical properties, or pharmacokinetics) within each medication class on ACEI/ARB/DRI effectiveness or harms* 7. *The benefit of ACEI/ARB/DRI relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms* 8. *Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, diuretics, other antihypertensives) on ACEI/ARB/DRI effectiveness or harms* 9. *The impact of ACEI/ARB/DRI monotherapy compared to ACEI, ARB, and/or DRI **combination therapy** in essential hypertension* 10. *The impact of ACEI/ARB/DRI alone compared to ACEI/ARB/DRI combined with **aldosterone receptor antagonists*** 11. *The impact of ACEI/ARB/DRI alone compared to ACEI/ARB/DRI in combination with a **diuretic***

Table 4. Potential future research needs based on the CER and stakeholder input (continued)

PICO Element	Potential Future Research Need*
Outcome	12. Studies of **cardiovascular and cerebrovascular events** compared across the three medication classes thereby requiring evaluation of outcomes over several years 13. *Evaluation of **cancer-related outcomes**, which are infrequently reported in the existing literature.* 14. Evaluation of the incidence, timing, and clinical consequences of **angioedema** in patients treated with ACEIs, ARBs, or DRIs. 15. The impact of ACEI/ARB/DRI on incidence of **new cardiovascular or metabolic diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function) 16. The impact of ACEI/ARB/DRI on patient health status including **quality of life and functional capacity** 17. *The impact of ACEI/ARB/DRI on **utilization and cost** of therapy* 18. The impact of ACEI/ARB/DRI on progression of **renal insufficiency** or development of dialysis dependence 19. The impact of ACEI/ARB/DRI on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia) 20. *Impact of changing **trends in outcome event rates** over time on the comparative effectiveness of ACEI, ARBs, and DRIs.*
Implementation gaps	21. Relative medication **adherence and persistence** with drug therapy across the different classes of drugs. 22. *Studies of the **impact of health system** financing, delivery, and/or organization interventions on evidence based medication prescribing and patient adherence.* 23. **Practical clinical trials** or other or other external-validity-oriented studies that compare these medications in practice settings that better represent real-world practice.
Methods for evidence synthesis	24. *Methods for **synthesis of data across clinical conditions** (e.g., congestive heart failure, ischemic heart disease, and chronic kidney disease) to better understand the comparative effectiveness of ACEIs, ARBs, and DRIs.* 25. *Methods for **individual patient data meta-analysis**, to better examine subgroups in the absence of other confounders*

*Out-of-scope research topics are in italics.
Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; DRI(s) = direct renin inhibitor(s); LV = left ventricular); PICO = population, interventions, comparators, and outcomes

Review of the Current Literature

We performed three database searches to identify ongoing and recently published studies relevant to the identified evidence gaps. These searches included the following:

1. A search of ClinicalTrials.gov for ongoing studies. This search included the key words "ACEI OR ACE-I OR ARB OR DRI OR Angiotensin OR Renin" and was limited to open studies in adults received from 12/7/2007 to 12/7/2011.
2. An update of the MEDLINE® (via Ovid) search used in the original CER entitled,
3. "Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACE-Is) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension,"[6] to identify relevant RCT literature published since the last search date (12/23/10).
4. A search of PubMed® for relevant systematic reviews and meta-analyses published from 2008 to the present, which might address the out of scope evidence gaps.

The exact search strategies used are provided in Appendix A.

Search results were reviewed for applicability to the identified research gaps listed in Table 4. We included articles from each search if they met the following criteria: (1) included patients with hypertension; (2) reported original data or combined original data in a systematic review or decision analysis; (3) included a comparison between an ACEI, ARB, or DRI and either an alternative medication, another ACEI, ARB, DRI, or placebo; and (4) included outcomes that could be categorized according to our identified list of research priorities. The goal for this literature search was to provide the stakeholders an idea of which research areas had recent or ongoing literature to address these gaps. Since we did not intend to synthesize this data with the existing report, these articles did not undergo full article abstraction or reconciliation of differences between article reviewers.

The search of each database yielded the following list of articles:

Clinicaltrials.gov:

- 86 active protocols submitted since 12/2007
- 11 included as potentially relevant based on screening
- All RCTs
- Sample size: 60 patients to 720 patients

Updated MEDLINE/PubMed:

- 167 articles found on original search
- 31 included as potentially relevant based on abstract screening
- Duration of followup range: 12 weeks to 30 weeks

PubMed search of systematic reviews on out of scope topics:

- 356 articles identified
- 32 included and linked to an out of scope research gap

Based on these searches, we created a list of articles and clinical trials pertaining to the 25 identified evidence gaps. This document was provided to the stakeholders prior to their final prioritization and is reproduced in Appendix B.

Research Prioritization

Process Used

The stakeholders were provided the AHRQ Effective Health Care Program Selection Criteria and instructed to use these criteria as the basis for their decisions regarding research prioritization:

Appropriateness:

- Represents a health care drug, intervention, device, technology or health care system/setting available (or soon to be available) in the United States
- Relevant to 1013 enrollees (Medicare, Medicaid, Children's Health Insurance Program [CHIP], other Federal health care programs)
- Represents one of the priority conditions designated by the U.S. Department of Health and Human Services (HHS)

Importance:

- Represents a significant disease burden, large proportion or priority population
- Is of high public interest; affects health care decisionmaking, outcomes, or costs for a large proportion of the U.S. population or for a priority population in particular.
- Was nominated/strongly supported by one or more stakeholder groups
- Represents important uncertainty for decisionmakers
- Incorporates issues around both clinical benefits and potential clinical harms
- Represents important variation in clinical care, or controversy in what constitutes appropriate clinical care
- Represent high costs to consumers, patients, health care systems or payers; due to common use, high unit costs, or high associated costs

Desirability of new research/duplication:

- Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic reviews by AHRQ or others)

Feasibility:

- Effectively uses existing research and knowledge by considering adequacy of research for conducting a systematic review and newly available evidence

Potential impact:

- Potential for significant health impact, significant economic impact, potential change, potential risk from inaction, addressing inequities and vulnerable populations, and/or addressing a topic with clear implications for resolving important dilemmas in health and health care decisions made by one or more stakeholder groups.

Participants in our stakeholder group participated in two conference calls, each of which was followed by an online prioritization exercise. The first call (October 2011) was used to introduce the stakeholder group to the project's objective and to describe the key clinical questions, the original CER report and its findings, and the proposed methods for the prioritization process. During this meeting, the identified research priorities were introduced to the stakeholders, and the group was invited to share feedback regarding additional research priorities. Following this conference call (December 2011), the stakeholders were invited to perform an initial online ranking of the identified research priorities (including the additional priorities identified by the stakeholder team). This ranking utilized a forced-ranking prioritization method, whereby participants were given 9 votes, which could be allocated to any of the 25 research priorities, with a maximum of 3 votes per item.

Stakeholders then participated in a second conference call (December 2011), during which the Duke EPC team shared the search results for relevant ongoing and recently published studies, as well as the stakeholders' initial ranking of research priorities results. During this conference call, the majority of the time was dedicated to discussing prioritization. Following this second call, a final online ranking exercise was distributed to the stakeholder group. This exercise utilized the same prioritization method as the first ranking exercise, and produced the final ranked list of research priorities. Research needs were ranked into tiers; only those in the top tier moved on to the final stage of study design development.

Research Question Development and Research Design Considerations

For the top tier future research needs, we considered advantages and disadvantages of various potential study designs. We adapted a conceptual framework for recommending study designs based on our prior future research needs report on ACEI and ARBs in ischemic heart disease.[11] Our overall approach to recommending study designs for addressing specific evidence gaps was to emphasize the study design with the least risk of bias, but the greatest likelihood of completion. For areas outside of the original CER scope, we suggested specific study designs that may be appropriate, while remaining cognizant that without a comprehensive systematic review, one cannot determine with certainty the degree to which those evidence gaps have already been addressed. A thorough systematic review may be the most appropriate initial step before further original research is undertaken for the priorities out of scope from the CER. The figure depicting this framework and a discussion of different designs is included in Appendix C.

Results

Based on the 2011 hypertension CER, the related ACEI/ARB prioritization project in ischemic heart disease, and our discussion with stakeholders, we identified the 25 potential research areas listed in Table 4. Not all areas were considered within the scope of the 2011 CER; these out-of-scope areas are highlighted in italics. Since these areas were out of scope for the original review, it is unclear whether large evidence gaps exist for these areas; however, they were identified and deemed potentially important by the stakeholder panel. With regard to the final stakeholder ranking, 9 out of 10 stakeholders participated and ranked the research priorities. The final ranking is listed below in Table 5 and is divided into a top, middle, and lower tier, based on the overall score.

Table 5. Final ranking of future research needs for ACEIs, ARBs, and DRIs in hypertension

Question	Score
Top Tier	
Studies of cardiovascular and cerebrovascular events compared across the three medication classes thereby requiring evaluation of outcomes over several years	11
Impact of comorbidities (such as ischemic heart disease, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multi-vessel coronary artery disease) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension	10
Impact of demographic differences (such as age, race, sex) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension	8
Practical clinical trials or other or other external validity-oriented studies that compare these medications in practice settings that better represent real-world practice.	8
The impact of ACEI/ARB/DRI on incidence of new cardiovascular or metabolic diagnoses (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	5
The impact of ACEI/ARB/DRI on patient health status including quality of life and functional capacity	5
Relative medication adherence and persistence with drug therapy across the different classes of drugs.	5
Middle Tier	
The benefit of ACEI/ARB/DRI relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms	*4*
The impact of ACEI/ARB/DRI on utilization and cost of therapy	*4*
Impact of health risk behaviors such as diet, exercise, smoking, alcohol intake on ACEI/ARB/DRI effectiveness or harms	3
The impact of ACEI/ARB/DRI on progression of renal insufficiency or development of dialysis dependence	3
Impact of changing trends in outcome event rates over time on the comparative effectiveness of ACEI, ARBs, and DRIs	*3*
Better understanding of provider patterns of prescribing these medications, and of interventions used to support evidence-based decisionmaking about prescribing	*3*
Impact of class effect (impact of differences between specific agents within each class) of ACEI/ARB/DRI on their effectiveness or harms	2
The impact of ACEI/ARB/DRI on development of non-angioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	2

Table 5. Final ranking of future research needs for ACEIs, ARBs, and DRIs in hypertension (continued)

Question	Score
Lower Tier	
Impact of concurrent medications(such as antiplatelet agents, lipid-lowering medications, diuretics, other antihypertensives) on ACEI/ARB/DRI effectiveness or harms	*1*
Methods for synthesis of data across clinical conditions (e.g., CHF, ischemic heart disease, and chronic kidney disease) to better understand the comparative effectiveness of ACEI, ARBs, and DRIs	*1*
Methods for individual patient data meta-analysis, to better examine subgroups in the absence of other confounders	*1*
Impact of the dose response (impact of medication dose or dosing interval) of ACEI/ARB/DRI on their effectiveness or harms	0
Impact of genetic differences (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB/DRI effectiveness or harms	0
The impact of ACEI, ARB, or DRI monotherapy compared to ACEI, ARB, and/or DRI combination therapy in hypertension	*0*
The impact of ACEI/ARB/DRI alone compared to ACEI/ARB/DRI combined with aldosterone receptor antagonists	*0*
The impact of ACEI/ARB/DRI alone compared to ACEI/ARB/DRI in combination with a diuretic	*0*
Evaluation of cancer-related outcomes, which are infrequently reported in the existing literature	*0*
Evaluation of the incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or DRIs	0

Out-of-scope research topics are highlighted in italics.
Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; DRI(s) = direct renin inhibitor(s); LV = left ventricular

These final rankings were not significantly changed from the preliminary rankings provided by the stakeholders prior to the second call. Notably, none of the future research areas considered out of scope from the original review appeared in the top tier. Based on the stakeholder-identified top tier, the EPC team discussed potential study designs for each research area—these are listed in Table 6. While the proposed methods to address each area are not intended to be restrictive of potential study designs, this section is intended to discuss the benefits or limitations for each study design for answering these questions.

Table 6. High-priority research areas and possible study designs

Research area	RCT?	Meta-analysis or individual patient data analysis across RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
What is the comparative effectiveness of these medications on cardiovascular and cerebrovascular events measured over several years?	**Maybe:** Large number of studies recently completed or ongoing in patients with other comorbidities may make new RCTs unnecessary	**Maybe:** If recent data is not included in original CER or if it is methodologically valid to combine studies of medication impact across different conditions (such as hypertension, ischemic heart disease, chronic kidney disease)	**Maybe:** If sufficient number of studies available; adjustment for confounding could be an issue	**Maybe:** Most direct way to address long-term outcomes; however, resource requirements for longer-term studies are potential limitations	**Yes:** Most efficient method for evaluating long-term outcomes given the large number of existing studies; appropriate coding for covariates an issue	**Maybe:** Potential role for helping determine clinically important differences
What is the impact of comorbidities (such as ischemic heart disease, CHF, diabetes, peripheral arterial disease, chronic kidney disease) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension?	**Maybe:** May be feasible for common comorbidities; existing or ongoing studies might be sufficient for some	**Yes:** If individual patient data or separate subgroup data not reported in current trials could be obtained and pooled for analysis; would require cooperation from the multiple sponsors of RCTs in this area	**Yes:** If individual patient data or separate subgroup data not reported in current trials could be obtained and pooled for analysis; would require cooperation from the multiple sponsors; if available, could address less common comorbidities, long-term safety/ effectiveness	**Maybe:** Most direct way to address less common comorbidities; allows for adjustment for confounding; sample size and resources needed for longer follow-up are potential limitations	**Yes:** Most efficient method for evaluating less common comorbidities over longer time frames; appropriate coding of covariates a potential limitation	**No:** Except for potential role in defining clinically or economically meaningful differences

Table 6. High-priority research areas and possible study designs (continued)

Research area	RCT?	Meta-analysis or individual patient data analysis across RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
What is the impact of demographic differences (such as age, race, sex) on ACEI/ARB/DRIs effectiveness or harms in patients with hypertension?	**No:** Unlikely to be sufficient power in single RCT to determine differences among subgroups	**Maybe:** If individual patient data or separate subgroup data not reported in current trials could be obtained and pooled for analysis; would likely require cooperation from the multiple sponsors to combine data	**Yes:** If individual patient data or separate subgroup data not reported in current trials could be obtained and pooled for analysis; would likely require cooperation from the multiple sponsors to obtain unpublished information	**Yes:** If new data collection undertaken to address other questions, impact of demographic differences could be estimated in analysis	**Yes:** Most efficient method for evaluating demographic differences; appropriate coding of other covariates a potential limitation	**Maybe:** Model could help determine impact of subgroup differences on overall population effectiveness, cost-effectiveness
Do the results differ in practical clinical trials or other or other external validity-oriented studies that compare these medications in practice settings that better represent real-world practice?	**Yes:** New RCT could however be challenging and could have technical issues with generalizability, existing RCT data may not appropriately represent community setting and participation in study may influence provider practices	**Maybe:** May be appropriate if sufficient studies available, although not identified in initial review	**Maybe:** May be appropriate if sufficient studies available; could be difficult to combine observational data from different settings	**Yes:** Would minimize influence of study protocol on provider practices; sample size and resources needed for longer followup are potential limitations	**Maybe:** Comparison of existing studies in settings with different incentives and disincentives for evidence-based prescribing	**Maybe:** Potential role for modeling impact of different rates of outcomes that may be observed outside traditional clinical trial.
What is the impact of ACEI/ARB/DRI on incidence of new cardiovascular or metabolic diagnoses such as diabetes, atrial fibrillation, CHF with or without preserved LV function?	**Maybe:** Relatively large number of recent or ongoing studies, although not specifically in patients with hypertension; unclear what additional information new RCTs would provide	**Yes:** Sufficient number of studies, so would be an efficient method for evaluating incidence of new diagnoses; main potential issue is duration of follow-up	**Yes:** If sufficient observational data available, could efficiently address incidence of new diagnoses over long time frame	**Maybe:** Most direct way of addressing duration limitations; allows for adjustment for confounding; sample size and resources needed for longer-term follow-up are potential limitations.	**Yes:** May be most efficient method for evaluating new diagnosis incidence, given resources needed for new study; appropriate coding of covariates a potential limitation	**No:** Except for potential role in defining clinically or economically meaningful differences

Table 6. High-priority research areas and possible study designs (continued)

Research area	RCT?	Meta-analysis or individual patient data analysis across RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
What is the impact of ACEI/ARB/DRI on patient health status including quality of life and functional capacity?	**Yes:** Given that these outcomes are not frequently reported, incorporation of disease-specific and generic QOL instruments into new trials would be appropriate	**Maybe:** If additional evidence is available that was not included in the original CER, and if consistent instruments utilized to allow data synthesis	**No:** Validated QOL instruments rarely reported in observational studies, so likely not appropriate	**Yes:** Incorporation of QOL instruments into new observational studies would be appropriate and relatively low cost; cross-sectional studies for obtaining population-level utilities reasonable	**Maybe:** If validated QOL instrument reported in existing studies	**Maybe:** Potential role for helping determine clinically important differences
Are there important differences in medication adherence and persistence with drug therapy across the different classes of drug?	**Maybe:** If sufficient data on impact on non-adherence (e.g., difference in outcomes between ITT and adherent populations); major limitation is that RCT subjects may not be generalizable to overall patient population.	**Maybe:** If additional evidence is available that was not included in the original CER, and if sufficient data reported on impact on non-adherence (e.g., difference in outcomes between ITT and adherent populations); major limitation is that RCT subjects may not be generalizable to overall population	**Maybe:** If additional evidence available not previously included in the original CER and if data on adherence collected consistently across studies	**Yes:** Most reliable way to track adherence, but sample size and resources needed for longer follow-up are potential limitations	**Maybe:** Technical issues with measuring adherence from administrative data	**Maybe:** Potential role for helping determine clinically important differences

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); DRI(s) = direct renin inhibitor(s); ITT = intention-to-treat; QOL = quality of life; RCT = randomized controlled trial

Discussion

The 2011 update of the 2007 CER of ACEIs, ARBs, and DRIs in essential hypertension clearly demonstrated that this is an active area of research with 59 percent more studies than the 2007 report. However, data from these new studies have not significantly changed the conclusions or the strength of evidence from the original report. These studies reported additional data on blood pressure lowering, adverse events, and cough, but with little added precision for our estimates of effect which were known with a high level of certainty. Conversely, the new evidence reported did not significantly add to our understanding of long-term outcomes, quality of life, renal outcomes, medication adherence, or differences in key patient subgroups. This emphasized that new studies are not appropriately targeting the remaining areas of uncertainty[7] and emphasizes the need to clearly define future research priorities. The recommendations for future research on ACEI, ARBs, and DRIs found in this report represent a broad range of stakeholder perspectives including those of general physicians, physician specialists, researchers, policymakers, and patients. The prioritized areas represent three primary foci: (1) heterogeneity in treatment response (i.e., impact of comorbidities and demographic differences); (2) long-term clinical outcomes (i.e., cardiovascular and cerebrovascular events, incident diabetes or cardiovascular diagnoses, quality of life); and (3) implementation and generalizability (i.e., practical research designs and medication adherence/persistence).

Notably, these three areas are very similar to the highest future research priorities identified during a recent Future Research Needs project on ACEI and ARBs in ischemic heart disease. Six of the top seven future research priorities in the hypertension report are also represented in the top seven future research priorities in the ischemic heart disease report.[11] The similarities between the research priorities for these medications in ischemic heart disease and hypertension may be explained in part by the overlap of two stakeholders who participated in the ischemic heart disease and hypertension prioritization projects. Nevertheless, given the complete group of 10 stakeholders within the hypertension project and 9 within the ischemic heart disease project, these 2 stakeholders who participated in both projects constituted a minority and were, therefore, not excessively influential in the discussion. This commonality has important implications for how CERs of common comparators are designed. These pharmacotherapies have been compared in large studies and in systematic reviews for multiple related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease.[8,12,13] These systematic reviews, like the one used for the basis of our report, have limited inclusion to studies conducted in patients with the target condition; however, they examine an overlapping set of efficacy and safety outcomes. Combining studies which report identical outcomes in different target populations may potentially yield important new information that could address the identified research gaps. This approach may be particularly useful for infrequent outcomes such as vascular events, new diagnoses, or mortality where greater statistical power is needed.[14]

Given the limited time the stakeholders have to review the existing evidence, it is also possible that their prioritization represent their general research priorities, rather than the state of evidence for this specific topic. The tendency to view a scientific problem through the prism of one's preconceived ideas or personal research agenda is well known. As AHRQ prepares further prioritization reports, it would be interesting to examine recurrent themes that arise in the top tier of research priorities.

The stakeholder group included several topics that were out-of-scope for the original review. The expansion of topics promotes consideration of new areas of research that have not been adequately explored; however, the original CER did not comment on the state of current research in these out-of-scope areas, and they should only be promoted with the caveat that existing literature may already adequately address these areas. We identified recent systematic reviews on these out-of-scope topics, but we cannot summarize the state of evidence with the same rigor as in-scope topics included in the original CER. Among our highest rated research priorities, there were no topics clearly out of the scope of the original review, but a formal means of guiding the prioritization of in- and out-of-scope topics would be helpful for future projects.

Conclusions

A workgroup of 10 stakeholders identified the following seven research areas as the highest priority for future research for the comparative effectiveness of ACEIs, ARBs, or DRIs in patients with hypertension.

1. What is the comparative effectiveness of these medications on cardiovascular and cerebrovascular events measured over several years?
    a. Recommended study design: if able to combine with chronic conditions other than hypertension, then a systematic review with broader inclusion criteria could provide additional information not included in the CER, which was restricted to patients with hypertension. If not, then large long-term clinical trial or observational study would be preferable
2. What is the impact of comorbidities (such as ischemic heart disease, CHF, diabetes, peripheral arterial disease, or chronic kidney disease) on ACEI/ARB/DRI effectiveness or harms in patients with hypertension?
    a. Recommended study design: if patient-level data are available from relevant trials, then a patient-level meta-analysis may be the most efficient approach.
3. What is the impact of demographic differences (such as age, race, or sex) on the effectiveness or harms of ACEI/ARB/DRIs in patients with hypertension?
    a. Recommended study design: if patient-level data are available from relevant trials, then a patient-level meta-analysis is most appropriate.
4. Do the results differ in practical clinical trials or other or other external validity-oriented studies that compare these medications in practice settings that better represent real-world practice?
    a. Recommended study designs: either a large clinical trial with broader inclusion criteria to maximize generalizability, or an observational study of patients in typical community practice.
5. What is the impact of ACEI/ARB/DRI on incidence of new cardiovascular or metabolic diagnoses such as diabetes, atrial fibrillation, or CHF with or without preserved LV function?
    a. Recommended study design: if patients can be combined across clinical conditions (i.e., not exclusively hypertension), then a systematic review of existing studies is most appropriate.
6. What is the impact of ACEI/ARB/DRI on patient health status including quality of life and functional capacity?
    a. Recommended study design: randomized controlled trials (RCTs) with the inclusion of validated quality of life measures as an outcome.
7. Are there important differences in medication adherence and persistence with drug therapy across the different classes of drug?
    a. Recommended study design: new observational studies with a focus on the longitudinal measurement of adherence and persistence.

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
CER	comparative effectiveness review
DRI	direct renin inhibitors
HHS	Department of Health and Human Services
EPC	Evidence-based Practice Center
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PICO	population, interventions, comparators, and outcomes
RAS	renin-angiotensin system
RCT	randomized controlled trial
CHIP	Children's Health Insurance Program

Appendix A. Exact Search Strings

The exact search strings used for this project are given below.

MEDLINE® via Ovid (update of search done for original CER)

Search date: November 14, 2011

Set	Terms	Results
1	(losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp.	12976
2	losartan/	5301
3	exp angiotensin II type 1 receptor blockers/ or exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]	11741
4	(cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp.	130
5	or/1-4	16740
6	(quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril or saralasin or teprotide).mp.	25618
7	angiotensin-converting enzyme inhibitors/ or captopril/ or cliazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or saralasin/ or teprotide/	37922
8	6 or 7	41516
9	5 and 8	6538
10	limit 9 to yr="2010 - current"	544
11	limit 10 to english language	496
12	exp hypertension/dt	53251
13	11 and 12	128
14	randomized controlled trial.pt.	321519
15	controlled clinical trial.pt.	83947
16	Randomized Controlled Trials/	77891
17	Random Allocation/	73587
18	Double-Blind Method/	113895
19	Single-Blind Method/	15743
20	or/14-19	540647
21	Animal/ not Human/	3621311
22	20 not 21	500390
23	clinical trial.pt.	469975
24	exp Clinical Trial/	667855
25	(clinic$ adj25 trial$).tw.	201771
26	((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.	111399
27	Placebos/	30695
28	placebo$.tw.	134423

Set	Terms	Results
29	random$.tw.	544924
30	Research Design/	65156
31	(Latin adj square).tw.	2982
32	or/23-31	1152741
33	32 not 21	1062417
34	Comparative Study/	1567956
35	exp Evaluation Studies/	160340
36	Follow-up Studies/	437364
37	Prospective Studies/	310272
38	(control$ or prospectiv$ or volunteer$).tw.	2455249
39	Cross-Over Studies/	29081
40	or/34-39	4117015
41	40 not 21	3181350
42	22 or 33 or 41	3671587
43	13 and 42	70
44	limit 43 to abstracts	67
45	(aliskiren or tekturna).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	523
46	(renin inhibitor or renin inhibitors).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	1099
47	renin/ai	1507
48	or/45-47	1913
49	5 and 48	311
50	49 and 42 and 12	78
51	8 and 48	545
52	51 and 42 and 12	94
53	50 or 52	123
54	limit 53 to english language	110
55	43 or 54	167

PubMed® via Ovid (search for systematic reviews)

Search date: December 16, 2011

Set #	Terms	Results
#1	(("losartan"[MeSH Terms] OR "losartan"[tw]) OR ("valsartan"[Supplementary Concept] OR "valsartan"[tw]) OR ("telmisartan"[Supplementary Concept] OR "telmisartan"[tw]) OR ("eprosartan"[Supplementary Concept] OR "eprosartan"[tw]) OR ("candesartan"[Supplementary Concept] OR "candesartan"[tw]) OR ("irbesartan"[Supplementary Concept] OR "irbesartan"[tw]) OR ("olmesartan"[Supplementary Concept] OR "olmesartan"[tw]) OR ("angiotensin ii type 1 receptor blockers"[MeSH Terms] OR "angiotensin ii type 1 receptor blockers"[tw] OR "angiotensin ii type 1 receptor blockers"[Pharmacological Action]) OR ("losartan"[MeSH Terms] OR "losartan"[tw] OR "cozaar"[tw]) OR ("telmisartan"[Supplementary Concept] OR "telmisartan"[tw] OR "micardis"[tw]) OR ("candesartan cilexetil"[Supplementary Concept] OR "candesartan cilexetil"[tw] OR "atacand"[tw]) OR ("eprosartan"[Supplementary Concept] OR "eprosartan"[tw] OR "teveten"[tw]) OR ("irbesartan"[Supplementary Concept] OR "irbesartan"[tw] OR "avapro"[tw]) OR ("olmesartan medoxomil"[Supplementary Concept] OR "olmesartan medoxomil"[tw] OR "benicar"[tw]) OR ("valsartan"[Supplementary Concept] OR "valsartan"[tw] OR "diovan"[tw])	16858
#2	("quinapril"[Supplementary Concept] OR "quinapril"[tw]) OR ("perindopril"[MeSH Terms] OR "perindopril"[tw]) OR ("ramipril"[MeSH Terms] OR "ramipril"[tw]) OR ("captopril"[MeSH Terms] OR "captopril"[tw]) OR ("enalapril"[MeSH Terms] OR "enalapril"[tw]) OR ("benazepril"[Supplementary Concept] OR "benazepril"[tw]) OR ("trandolapril"[Supplementary Concept] OR "trandolapril"[tw]) OR ("fosinopril"[MeSH Terms] OR "fosinopril"[tw]) OR ("moexipril"[Supplementary Concept] OR "moexipril"[tw]) OR ("enalaprilat"[MeSH Terms] OR "enalaprilat"[tw]) OR ("cilazapril"[MeSH Terms] OR "cilazapril"[tw]) OR ("saralasin"[MeSH Terms] OR "saralasin"[tw]) OR ("teprotide"[MeSH Terms] OR "teprotide"[tw]) OR ("angiotensin-converting enzyme inhibitors"[MeSH Terms] OR ("angiotensin-converting"[tw] AND "enzyme"[tw] AND "inhibitors"[tw]) OR "angiotensin-converting enzyme inhibitors"[tw] OR ("angiotensin"[tw] AND "converting"[tw] AND "enzyme"[tw] AND "inhibitors"[tw]) OR "angiotensin converting enzyme inhibitors"[tw] OR "angiotensin-converting enzyme inhibitors"[Pharmacological Action]) OR ("captopril"[MeSH Terms] OR "captopril"[tw]) OR ("cilazapril"[MeSH Terms] OR "cilazapril"[tw]) OR ("enalapril"[MeSH Terms] OR "enalapril"[tw]) OR ("enalaprilat"[MeSH Terms] OR "enalaprilat"[tw]) OR ("fosinopril"[MeSH Terms] OR "fosinopril"[tw]) OR ("lisinopril"[MeSH Terms] OR "lisinopril"[tw]) OR ("perindopril"[MeSH Terms] OR "perindopril"[tw]) OR ("ramipril"[MeSH Terms] OR "ramipril"[tw]) OR ("saralasin"[MeSH Terms] OR "saralasin"[tw]) OR ("teprotide"[MeSH Terms] OR "teprotide"[tw])	47412
#3	OR ("aliskiren"[Supplementary Concept] OR "aliskiren"[tw]) OR ("aliskiren"[Supplementary Concept] OR "aliskiren"[tw] OR "tekturna"[tw]) OR (("renin"[MeSH Terms] OR "renin"[tw]) AND inhibitor[tw]) OR (("renin"[MeSH Terms] OR "renin"[All Fields]) AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[tw] AND "inhibitors"[tw]) OR "antagonists and inhibitors"[tw] OR "inhibitors"[tw])) OR ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin-Converting Enzyme Inhibitors"[Pharmacological Action]) OR ("Angiotensin Receptor Antagonists"[Mesh] OR "Angiotensin Receptor Antagonists"[Pharmacological Action] OR "Angiotensin II Type 2 Receptor Blockers"[Mesh] OR "Angiotensin II Type 1 Receptor Blockers"[Mesh]) OR "Renin/antagonists and inhibitors"[Mesh] OR "direct renin inhibitors"[tw] OR "DRI"[tw] OR "DRIs"[tw]	53191
#4	AND (English[lang] AND systematic[sb] NOT ("infant"[MeSH Terms] OR ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms] OR ("animals"[MeSH Terms:noexp])) AND ("2008"[PDAT] : "2011"[PDAT])) AND English[lang] AND systematic[sb] AND ("2008"[PDAT] : "2011"[PDAT]))	51550
#5	(#1 OR #2 OR #3) AND#4	356

Appendix B. Table of Research Priorities Linked to Recent Publications and Ongoing Studies

Priority	Details
1	**Impact of comorbidities (such as ischemic heart disease, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multi-vessel coronary artery disease) on ACE-I/ARB/DRI effectiveness or harms in patients with hypertension** **MEDLINE:** Krone W, Hanefeld M, Meyer HF, et al.. 2011. Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome. Journal of Human Hypertension 25 (Mar) 186-95 **ClinicalTrials.gov:** The Study of Novel Dual Renin Angiotensin Aldosterone System (RAAS) Blockade; Valsartan/Aliskiren in African American Patients With Hypertension and the Metabolic Syndrome, NCT01432106; RCT of 100 pts Shiga Microalbuminuria Reduction Trial-2 in Patients with Diabetes (Drug: Aliskiren and any angiotensin receptor blockers), NCT0146199; RCT of 320 pts Antiproteinuric Effect of Imidapril Versus Ramipril in Type 2 Diabetic and Hypertensive Patients With Microalbuminuria, NCT012300034, RCT of 206 pts Aliskiren Versus Ramipril on Antiproteinuric Effect in Hypertensive, Type 2 Diabetic Patients With Microalbuminuria, NCT01038895, RCT of 120 pts Aliskiren and Valsartan vs Valsartan Alone in Patients With Stage II Systolic Hypertension and Type II Diabetes Mellitus, NCT00927394, RCT of 422 pts
2	**Impact of demographic differences (such as age, race, sex) on ACE-I/ARB/DRIs effectiveness or harms in patients with hypertension** **MEDLINE:** Duprez DA, Munger MA, Botha J, et al.. 2010. Aliskiren for geriatric lowering of systolic hypertension: a randomized controlled trial. Journal of Human Hypertension 24 (Sep) 600-8 Mallion J-M, Omboni S, Barton J, et al.. 2011. Antihypertensive efficacy and safety of olmesartan and ramipril in elderly patients with mild to moderate systolic and diastolic essential hypertension. Blood Pressure 20 Suppl 1 (Apr) 3-11 Malacco E, Omboni S, Volpe M, et al.. 2010. Antihypertensive efficacy and safety of olmesartan medoxomil and ramipril in elderly patients with mild to moderate essential hypertension: the ESPORT study. Journal of Hypertension 28 (Nov) 2342-50 Verdecchia P, Calvo C, Mockel V, et al.. 2007. Safety and efficacy of the oral direct renin inhibitor aliskiren in elderly patients with hypertension. Blood Pressure 16 (#date#) 381-91 **ClinicalTrials.gov:** The Study of Novel Dual Renin Angiotensin Aldosterone System (RAAS) Blockade; Valsartan/Aliskiren in African American Patients With Hypertension and the Metabolic Syndrome, NCT01432106; RCT of 100 pts

Priority	Details
3	**Impact of genetic differences (such as ACE or angiotensin II receptor gene polymorphisms) on ACE-I/ARB/DRI effectiveness or harms** **MEDLINE:** Moore N, Dicker P, O'Brien JK, et al.. 2007. Renin gene polymorphisms and haplotypes, blood pressure, and responses to renin-angiotensin system inhibition. Hypertension 50 (Aug) 340-7 **ClinicalTrials.gov:** Ocsaar and CYP2C9 Ploymorphism, Is There a Connection Between Pharmacokinetics, Pharmacodynamics and Pharmacogenetics?, NCT00732966, RCT of 30 pts
4	**Impact of health risk behaviors such as diet, exercise, smoking, alcohol intake on ACE-I/ARB/DRI effectiveness or harms** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
5	**Impact of the dose response (impact of medication dose or dosing interval) of ACE-I/ARB/DRI on their effectiveness or harms** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
6	**Differential impact of specific agents or subclasses (based on tissue specificity, chemical properties, or pharmacokinetics) within each medication class on ACE-I/ARB/DRI effectiveness or harms** **MEDLINE:** Ohishi M, Takeya Y, Tatara Y, et al.. 2010. Strong suppression of the renin-angiotensin system has a renal-protective effect in hypertensive patients: high-dose ARB with ACE inhibitor (Hawaii) study. Hypertension Research - Clinical & Experimental 33 (Nov) 1150-4 **ClinicalTrials.gov:** The Clinical Study to Evaluate the Efficacy and Safety of Fimasartan in Patients With Mild to Moderate Essential Hypertension (Fimasartan vs. Candesartan), NCT01135212, RCT of 288 pts Antiproteinuric Effect of Imidapril Versus Ramipril in Type 2 Diabetic and Hypertensive Patients With Microalbuminuria, NCT012300034, RCT of 206 pts Ocsaar and CYP2C9 Ploymorphism, Is There a Connection Between Pharmacokinetics, Pharmacodynamics and Pharmacogenetics?, NCT00732966, RCT of 30 pts Valsartan and Amlodipine Compared to Losartan and Amlodipine in Hypertensive Patients, NCT00716950, RCT of 187 pts

Priority	Details
7	**The benefit of ACE-I/ARB/DRI relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms** **MEDLINE:** Jordan J, Engeli S, Boye SW, et al.. 2007. Direct Renin inhibition with aliskiren in obese patients with arterial hypertension. Hypertension 49 (May) 1047-55 **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Bangalore S, Kumar S, Wetterslev J, et al.. 2011. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 342 (#date#) d2234 Petrella R and Michailidis P. 2011. Retrospective analysis of real-world efficacy of angiotensin receptor blockers versus other classes of antihypertensive agents in blood pressure management. Clin Ther 33 (Sep) 1190-203 Sciarretta S, Palano F, Tocci G, et al.. 2011. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. Arch Intern Med 171 (Mar 14) 384-94 Van Bortel LM, Fici F and Mascagni F. 2008. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs 8 (#date#) 35-44 Vijan S. 2009. Diabetes: treating hypertension. Clin Evid (Online) 2009 (#date#) #pages# Wald DS, Law M, Morris JK, et al.. 2009. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 122 (Mar) 290-300 Webb AJ, Fischer U, Mehta Z, et al.. 2010. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 375 (Mar 13) 906-15 Wright JM and Musini VM. 2009. First-line drugs for hypertension. Cochrane Database Syst Rev #volume# (#date#) CD001841

Priority	Details
8	**Impact of concurrent medications(such as antiplatelet agents, lipid-lowering medications, diuretics, other antihypertensives) on ACE-I/ARB/DRI effectiveness or harms** **MEDLINE:** O'Brien E, Barton J, Nussberger J, et al.. 2007. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. Hypertension 49 (Feb) 276-84 Vaidyanathan S, Valencia J, Kemp C, et al.. 2006. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. International Journal of Clinical Practice 60 (Nov) 1343-56 **ClinicalTrials.gov:** Comparison of Sevikar® and the Combination of Perindopril/Amlodipine on Central Blood Pressure (ACE + CCB vs. ARB + CCB), NCT 01101009, RCT of 720 pts **Systematic reviews:** Wald DS, Law M, Morris JK, et al.. 2009. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 122 (Mar) 290-300
9	**The impact of ACE I, ARB, or DRI monotherapy compared to ACE I, ARB, and/or DRI combination therapy in essential hypertension** **MEDLINE:** Persson F, Lewis JB, Lewis EJ, et al.. 2011. Aliskiren in combination with losartan reduces albuminuria independent of baseline blood pressure in patients with type 2 diabetes and nephropathy. Clinical Journal of The American Society of Nephrology: CJASN 6 (May) 1025-31 Geiger H, Barranco E, Gorostidi M, et al.. 2009. Combination therapy with various combinations of aliskiren, valsartan, and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone. Journal of Clinical Hypertension 11 (Jun) 324-32 Solomon SD, Appelbaum E, Manning WJ, et al.. 2009. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. Circulation 119 (Feb 3) 530-7 Yarows SA, Oparil S, Patel S, et al.. 2008. Aliskiren and valsartan in stage 2 hypertension: subgroup analysis of a randomized, double-blind study. Advances in Therapy 25 (Dec) 1288-302 Parving H-H, Persson F, Lewis JB, et al.. 2008. Aliskiren combined with losartan in type 2 diabetes and nephropathy.[Reprint in Ugeskr Laeger. 2009 Mar 9;171(11):881-4; PMID: 19291865]. New England Journal of Medicine 358 (Jun 5) 2433-46 Uresin Y, Taylor AA, Kilo C, et al.. 2007. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. Journal of the Renin-Angiotensin-Aldosterone System 8 (Dec) 190-8 Oparil S, Yarows SA, Patel S, et al.. 2007. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial.[Erratum appears in Lancet. 2007 Nov 3;370(9598):1542]. Lancet 370 (Jul 21) 221-9 Pool JL, Schmieder RE, Azizi M, et al.. 2007. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. American Journal of Hypertension 20 (Jan) 11-20

Priority	Details
	ClinicalTrials.gov: The Study of Novel Dual Renin Angiotensin Aldosterone System (RAAS) Blockade; Valsartan/Aliskiren in African American Patients With Hypertension and the Metabolic Syndrome, NCT01432106; RCT of 100 pts Aliskiren and Valsartan vs Valsartan Alone in Patients With Stage II Systolic Hypertension and Type II Diabetes Mellitus, NCT00927394, RCT of 422 pts **Systematic reviews:** Arici M and Erdem Y. 2009. Dual blockade of the renin-angiotensin system for cardiorenal protection: an update. Am J Kidney Dis 53 (Feb) 332-45 Baker WL, Coleman CI, Kluger J, et al.. 2009. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med 151 (Dec 15) 861-71 Dusing R and Sellers F. 2009. ACE inhibitors, angiotensin receptor blockers and direct renin inhibitors in combination: a review of their role after the ONTARGET trial. Curr Med Res Opin 25 (Sep) 2287-301 Probstfield J. 2009. Defining the role of renin/angiotensin-targeted antihypertensive therapy in decreasing cardiovascular risk: evidence, guideline evolution, and questions to be resolved. J Fam Pract 58 (Jun) S1-8 Zhenfeng Z, Huilan S, Junya J, et al.. 2011. A systematic review and meta-analysis of aliskiren and angiotension receptor blockers in the management of essential hypertension. J Renin Angiotensin Aldosterone Syst 12 (Jun) 102-12
10	**The impact of ACE-I/ARB/DRI alone compared to ACE-I/ARB/DRI combined with aldosterone receptor antagonists** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Bomback AS, Kshirsagar AV, Amamoo MA, et al.. 2008. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis 51 (Feb) 199-211 Navaneethan SD, Nigwekar SU, Sehgal AR, et al.. 2009. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 4 (Mar) 542-51

Priority	Details
11	**The impact of ACE-I/ARB/DRI alone compared to ACE-I/ARB/DRI in combination with a diuretic** **MEDLINE:** O'Brien E, Barton J, Nussberger J, et al.. 2007. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. Hypertension 49 (Feb) 276-84 Pool JL, Schmieder RE, Azizi M, et al.. 2007. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. American Journal of Hypertension 20 (Jan) 11-20 **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Morimoto S, Takahashi N, Morita T, et al.. 2010. Critical appraisal and pooled analysis of telmisartan alone or in combination with hydrochlorothiazide for achieving blood pressure goals. Integr Blood Press Control 3 (#date#) 73-9 Wald DS, Law M, Morris JK, et al.. 2009. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 122 (Mar) 290-300
12	**Studies of cardiovascular and cerebrovascular events compared across the three medication classes thereby requiring evaluation of outcomes over several years** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found

Priority	Details
13	**Evaluation of cancer-related outcomes, which are infrequently reported in the existing literature** **MEDLINE:** Collaboration ARBT. 2011. Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138,769 individuals. Journal of Hypertension 29 (Apr) 623-35 **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Bangalore S, Kumar S, Kjeldsen SE, et al.. 2011. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol 12 (Jan) 65-82 Chang CH, Lin JW, Wu LC, et al.. 2011. Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. J Clin Oncol 29 (Aug 1) 3001-7 Coleman CI, Baker WL, Kluger J, et al.. 2008. Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials. J Hypertens 26 (Apr) 622-9 Mc Menamin UC, Murray LJ, Cantwell MM, et al.. 2011. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cancer progression and survival: a systematic review. Cancer Causes Control #volume# (Nov 25) #pages# Sipahi I, Chou J, Mishra P, et al.. 2011. Meta-analysis of randomized controlled trials on effect of angiotensin-converting enzyme inhibitors on cancer risk. Am J Cardiol 108 (Jul 15) 294-301 Sipahi I, Debanne SM, Rowland DY, et al.. 2010. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol 11 (Jul) 627-36 Yoon C, Yang HS, Jeon I, et al.. 2011. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and cancer risk: a meta-analysis of observational studies. CMAJ 183 (Oct 4) E1073-84
14	**Evaluation of the incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or DRIs** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found

Priority	Details
15	**The impact of ACE-I/ARB/DRI on incidence of new cardiovascular or metabolic diagnoses (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)** **MEDLINE:** Fogari R, Zoppi A, Salvadeo SAT, et al.. 2011. Fibrinolysis and insulin sensitivity in imidapril and candesartan (FISIC study) recipients with hypertension. Hypertension Research - Clinical & Experimental 34 (Apr) 509-15 Al-Mallah M, Khawaja O, Sinno M, et al.. 2010. Do angiotensin converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis. Cardiology Journal 17 (#date#) 448-56 Shariff N, Zelenkofske S, Eid S, et al.. 2010. Demographic determinants and effect of pre-operative angiotensin converting enzyme inhibitors and angiotensin receptor blockers on the occurrence of atrial fibrillation after CABG surgery. BMC Cardiovascular Disorders 10 (#date#) 7 Schaer BA, Schneider C, Jick SS, et al.. 2010. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study.[Summary for patients in Ann Intern Med. 2010 Jan 19;152(2):I-16; PMID: 20083810]. Annals of Internal Medicine 152 (Jan 19) 78-84 **ClinicalTrials.gov:** Imidapril and Candesartan on Fibrinolysis and Insulin-Sensitivity in Patients With Mild to Moderate Hypertension, NCT00644475, RCT of 60 pts
16	**The impact of ACE-I/ARB/DRI on patient health status including quality of life and functional capacity** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
17	**The impact of ACE-I/ARB/DRI on utilization and cost of therapy** **MEDLINE:** Chang J, Yang W, Kahler KH, et al.. 2011. Compliance, persistence, healthcare resource use, and treatment costs associated with aliskiren plus ARB versus ACE inhibitor plus ARB combination therapy: in US patients with hypertension. American Journal of Cardiovascular Drugs 11 (#date#) 21-32 **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Lang CD, Arora RR, Saha SA, et al.. 2008. Bayesian meta-analysis of tissue angiotensin-converting enzyme inhibitors for reduction of adverse cardiovascular events in patients with diabetes mellitus and preserved left ventricular function. J Cardiometab Syndr 3 (Winter) 45-52 Tavakoli M, Pumford N, Woodward M, et al.. 2009. An economic evaluation of a perindopril-based blood pressure lowering regimen for patients who have suffered a cerebrovascular event. Eur J Health Econ 10 (Feb) 111-9 Theodoratou D, Maniadakis N, Fragoulakis V, et al.. 2009. Analysis of published economic evaluations of angiotensin receptor blockers. Hellenic J Cardiol 50 (Mar-Apr) 105-18

Priority	Details
18	**The impact of ACE-I/ARB/DRI on progression of renal insufficiency or development of dialysis dependence** **MEDLINE:** Persson F, Lewis JB, Lewis EJ, et al.. 2011. Aliskiren in combination with losartan reduces albuminuria independent of baseline blood pressure in patients with type 2 diabetes and nephropathy. Clinical Journal of The American Society of Nephrology: CJASN 6 (May) 1025-31 Wong J, Molyneaux L, Constantino M, et al.. 2010. Beyond ONTARGET: angiotensin-converting enzyme inhibition and angiotensin II receptor blockade in combination, a lesser evil in some?. Diabetes, Obesity & Metabolism 12 (Dec) 1072-8 Ohishi M, Takeya Y, Tatara Y, et al.. 2010. Strong suppression of the renin-angiotensin system has a renal-protective effect in hypertensive patients: high-dose ARB with ACE inhibitor (Hawaii) study. Hypertension Research - Clinical & Experimental 33 (Nov) 1150-4 Persson F, Rossing P, Reinhard H, et al.. 2009. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. Diabetes Care 32 (Oct) 1873-9 Parving H-H, Persson F, Lewis JB, et al.. 2008. Aliskiren combined with losartan in type 2 diabetes and nephropathy.[Reprint in Ugeskr Laeger. 2009 Mar 9;171(11):881-4; PMID: 19291865]. New England Journal of Medicine 358 (Jun 5) 2433-46 **ClinicalTrials.gov:** The Study of Novel Dual Renin Angiotensin Aldosterone System (RAAS) Blockade; Valsartan/Aliskiren in African American Patients With Hypertension and the Metabolic Syndrome, NCT01432106; RCT of 100pts Shiga Microalbuminuria Reduction Trial-2 in Patients with Diabetes (Drug: Aliskiren and any angiotensin receptor blockers), NCT0146199; RCT of 320 pts Antiproteinuric Effect of Imidapril Versus Ramipril in Type 2 Diabetic and Hypertensive Patients With Microalbuminuria, NCT012300034, RCT of 206 pts Aliskiren Versus Ramipril on Antiproteinuric Effect in Hypertensive, Type 2 Diabetic Patients With Microalbuminuria, NCT01038895, RCT of 120 pts ALiskiren or Losartan Effects on bioMARKers of Myocardial Remodeling, NCT01176032, RCT of 296 pts
19	**The impact of ACE-I/ARB/DRI on development of non-angioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)** **MEDLINE:** Duprez DA, Munger MA, Botha J, et al.. 2010. Aliskiren for geriatric lowering of systolic hypertension: a randomized controlled trial. Journal of Human Hypertension 24 (Sep) 600-8 Mallion J-M, Omboni S, Barton J, et al.. 2011. Antihypertensive efficacy and safety of olmesartan and ramipril in elderly patients with mild to moderate systolic and diastolic essential hypertension. Blood Pressure 20 Suppl 1 (Apr) 3-11 Malacco E, Omboni S, Volpe M, et al.. 2010. Antihypertensive efficacy and safety of olmesartan medoxomil and ramipril in elderly patients with mild to moderate essential hypertension: the ESPORT study. Journal of Hypertension 28 (Nov) 2342-50

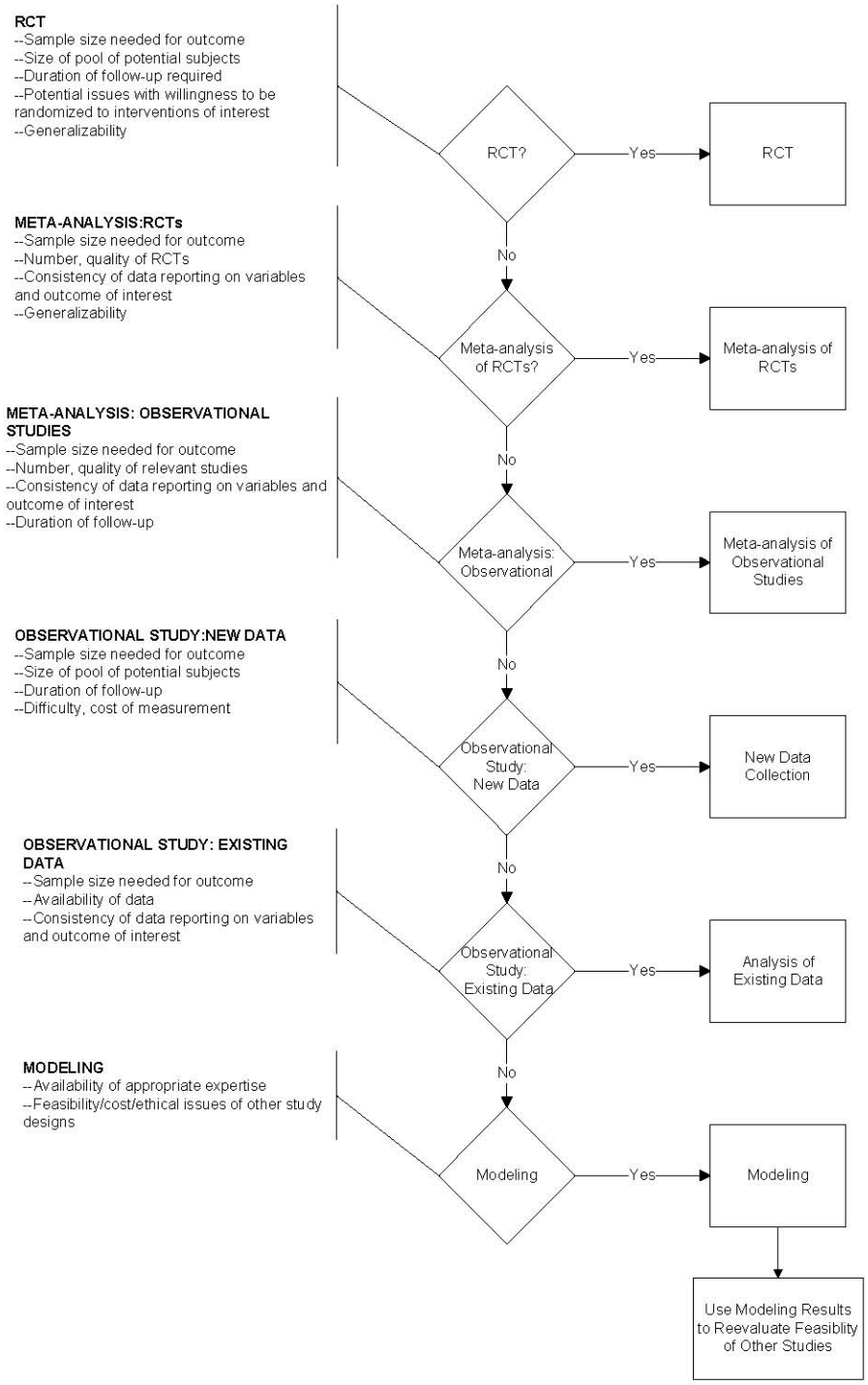
Priority	Details
	Spinar J, Vitovec J, Soucek M, et al.. 2010. CORD: COmparison of Recommended Doses of ace inhibitors and angiotensin II receptor blockers. International Journal of Cardiology 144 (Oct 8) 293-4 Stanton AV, Gradman AH, Schmieder RE, et al.. 2010. Aliskiren monotherapy does not cause paradoxical blood pressure rises: meta-analysis of data from 8 clinical trials. Hypertension 55 (Jan) 54-60 Geiger H, Barranco E, Gorostidi M, et al.. 2009. Combination therapy with various combinations of aliskiren, valsartan, and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone. Journal of Clinical Hypertension 11 (Jun) 324-32 Parving H-H, Persson F, Lewis JB, et al.. 2008. Aliskiren combined with losartan in type 2 diabetes and nephropathy.[Reprint in Ugeskr Laeger. 2009 Mar 9;171(11):881-4; PMID: 19291865]. New England Journal of Medicine 358 (Jun 5) 2433-46 Andersen K, Weinberger MH, Egan B, et al.. 2008. Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. Journal of Hypertension 26 (Mar) 589-99 Uresin Y, Taylor AA, Kilo C, et al.. 2007. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. Journal of the Renin-Angiotensin-Aldosterone System 8 (Dec) 190-8 Verdecchia P, Calvo C, Mockel V, et al.. 2007. Safety and efficacy of the oral direct renin inhibitor aliskiren in elderly patients with hypertension. Blood Pressure 16 (#date#) 381-91 Strasser RH, Puig JG, Farsang C, et al.. 2007. A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension. Journal of Human Hypertension 21 (Oct) 780-7 Oparil S, Yarows SA, Patel S, et al.. 2007. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial.[Erratum appears in Lancet. 2007 Nov 3;370(9598):1542]. Lancet 370 (Jul 21) 221-9 Pool JL, Schmieder RE, Azizi M, et al.. 2007. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. American Journal of Hypertension 20 (Jan) 11-20 Mallion J-M, Omboni S, Barton J, et al.. 2011. Antihypertensive efficacy and safety of olmesartan and ramipril in elderly patients with mild to moderate systolic and diastolic essential hypertension. Blood Pressure 20 Suppl 1 (Apr) 3-11 **ClinicalTrials.gov:** Aliskiren and Valsartan vs Valsartan Alone in Patients With Stage II Systolic Hypertension and Type II Diabetes Mellitus, NCT00927394, RCT of 422 pts ALiskiren or Losartan Effects on bioMARKers of Myocardial Remodeling, NCT01176032, RCT of 296 pts

Priority	Details
20	**Relative medication adherence and persistence with drug therapy across the different classes of drugs** **MEDLINE:** Chang J, Yang W, Kahler KH, et al.. 2011. Compliance, persistence, healthcare resource use, and treatment costs associated with aliskiren plus ARB versus ACE inhibitor plus ARB combination therapy: in US patients with hypertension. American Journal of Cardiovascular Drugs 11 (#date#) 21-32 Malacco E, Omboni S, Volpe M, et al.. 2010. Antihypertensive efficacy and safety of olmesartan medoxomil and ramipril in elderly patients with mild to moderate essential hypertension: the ESPORT study. Journal of Hypertension 28 (Nov) 2342-50 Strasser RH, Puig JG, Farsang C, et al.. 2007. A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension. Journal of Human Hypertension 21 (Oct) 780-7 Mallion J-M, Omboni S, Barton J, et al.. 2011. Antihypertensive efficacy and safety of olmesartan and ramipril in elderly patients with mild to moderate systolic and diastolic essential hypertension. Blood Pressure 20 Suppl 1 (Apr) 3-11 **ClinicalTrials.gov:** No relevant citations found
21	**Studies of the impact of health system financing, delivery, and/or organization interventions on evidence based medication prescribing and patient adherence.** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Austin PC, Tu JV, Ko DT, et al.. 2008. Factors associated with the use of evidence-based therapies after discharge among elderly patients with myocardial infarction. CMAJ 179 (Oct 21) 901-8 Austin PC, Tu JV, Ko DT, et al.. 2008. Use of evidence-based therapies after discharge among elderly patients with acute myocardial infarction. CMAJ 179 (Oct 21) 895-900 Kagoma YK, Weir MA, Iansavichus AV, et al.. 2011. Impact of estimated GFR reporting on patients, clinicians, and health-care systems: a systematic review. Am J Kidney Dis 57 (Apr) 592-601 Khan SS, Gheorghiade M, Dunn JD, et al.. 2008. Managed care interventions for improving outcomes in acute heart failure syndromes. Am J Manag Care 14 (Dec) S273-86; quiz S287-91 Schneider PJ, Murphy JE and Pedersen CA. 2008. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. J Am Pharm Assoc (2003) 48 (Jan-Feb) 58-63

Priority	Details
22	**Practical clinical trials or other or other external-validity-oriented studies that compare these medications in practice settings that better represent real-world practice** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Petrella R and Michailidis P. 2011. Retrospective analysis of real-world efficacy of angiotensin receptor blockers versus other classes of antihypertensive agents in blood pressure management. Clin Ther 33 (Sep) 1190-203
23	**Methods for synthesis of data across clinical conditions (e.g. congestive heart failure, ischemic heart disease, and chronic kidney disease) to better understand the comparative effectiveness of ACE-I, ARBs and DRIs** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Petrella R and Michailidis P. 2011. Retrospective analysis of real-world efficacy of angiotensin receptor blockers versus other classes of antihypertensive agents in blood pressure management. Clin Ther 33 (Sep) 1190-203 Verdecchia P, Angeli F, Repaci S, et al.. 2009. Comparative assessment of angiotensin receptor blockers in different clinical settings. Vasc Health Risk Manag 5 (#date#) 939-48
24	**Methods for individual patient data meta-analysis, to better examine subgroups in the absence of other confounders** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** No relevant citations found
25	**Impact of changing trends in outcome event rates over time on the comparative effectiveness of ACE-I, ARBs, and DRIs.** **MEDLINE:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** No relevant citations found

Appendix C. Criteria for Research Prioritization

Figure C1. Framework for suggesting study designs for future research needs pertaining to the comparative effectiveness of angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers and direct renin inhibitors for treatment of hypertension



We explore below in more detail the potential study designs represented in the Figure above and their specific considerations:

Randomized Controlled Trials (RCTs)

Ideally, all evidence gaps would be filled by conducting effectiveness RCTs that specifically address the area of interest; however, especially for many questions of interest for comparative effectiveness research, RCTs are rarely the most practical option. Considerations include:

- Sample size required for a particular outcome and to include a representative sample of patients: Many outcomes of interest, particularly those involving safety, are relatively uncommon, requiring an inordinately large sample size to achieve adequate power.
- Size of the pool of potential subjects: Some conditions may be relatively uncommon, or the subpopulation of interest relatively small, adversely affecting the sample size.
- Alternatively, comorbidities may be common among patients with the condition in question, creating potential difficulties with inclusion/exclusion criteria for an RCT.
- Duration of followup required: Minimizing loss to followup within the context of a trial, particularly if blinding must be maintained, is both expensive and difficult the longer the duration of followup, but for some outcomes lengthy followup is required.
- Issues with willingness to be randomized: Patient and provider beliefs about effectiveness, side effects, or other factors can make it difficult to recruit subjects into trials for some interventions.
- Generalizability: Inclusion/exclusion criteria often mean that subjects who participate in
- RCTs rarely reflect the full spectrum of either disease severity or co-morbidity that exists in the real world.

Meta-Analysis of RCTs

If a new RCT is not feasible, then a meta-analysis of existing RCTs may provide the next most valid answer to the question if studies are available; however, all of the potential difficulties with a new RCT are potential problems with existing RCTs. Given sufficient numbers and quality of existing RCTs, some questions may be addressable through meta-analysis. The main issue is whether data on the variables and outcomes of interest have been collected and reported consistently by enough RCTs to warrant a meta-analysis.

Meta-analysis of RCTs may be particularly appropriate for research gaps outside the scope of the initial CER; however, as highlighted by the authors of the original CER in their discussion of future research needs, this method may also be able answer key questions included in the original CER. Depending on the volume of ongoing research, existing reviews may quickly become out of date, particularly in cardiovascular research. In addition, when insufficient evidence exists for particular key questions, modifying the study inclusion/exclusion criteria from the initial review may allow broader inclusion of studies that can address these research gaps. This may be particularly true when a specific clinical condition, such as hypertension, has significant clinical overlap with related conditions such as ischemic heart disease, peripheral vascular disease, diabetes, chronic kidney disease, or congestive heart failure. When the outcomes of interest are common to all conditions (e.g., medication side effects, quality of life) then meta-analysis across clinical conditions may provide additional useful information. In meta-analyses of clinical trials, clinicians are often interested in examining subset effects, yet study-level analyses can lead to biased assessments and have some limitations in explaining heterogeneity. A meta-analysis of

individual patient data offers several advantages for this purpose, but may not always be feasible given the multiple different sources of data and the proprietary nature of industry-sponsored research.

Meta-Analysis of Observational Studies

If a meta-analysis of RCTs is not feasible, the next most valid and feasible alternative would be a meta-analysis of observational studies. Many of the same issues inherent in meta-analyses of RCTs (both study-level and patient-level data) are also present, including:

- Heterogeneity in study design, inclusion, and exclusion criteria;
- Consistency in variable definitions and collection; and
- Varying duration of followup.

In addition, control of confounding can be especially challenging at the study level. Here, patient-level meta-analysis may be particularly appropriate, since it facilitates adjustment. The main challenge here is accessibility to the appropriate data, which may be difficult, especially with industry-sponsored studies.

Observational Study—Collection of New Data

If there is not sufficient literature available for a meta-analysis of observational data, then design of a new study would be the next most valid and feasible study design. Ideally, a prospective study with subject recruitment, data collection, and data analysis specifically intended to address the question of interest would be designed and carried out. Challenges to feasibility of a new observational study include:

- Duration of followup and retention: Many of the most important evidence gaps may require data on outcomes over a longer period of time. Subject retention is crucial both to maximize study power and minimize bias to differential dropout, but the resources required to maintain high retention over a long study period are substantial.
- Recruitment: Depending on the outcomes being assessed, participation in an ongoing observational study may be burdensome. Especially for patients treated with already approved treatments and whose clinical care is not affected by participation in a study, assuring maximal recruitment can be difficult. This may be a special problem in some populations with historically low levels of participation in research.

Observational Study—Analysis of Existing Data

If a new observational study is not feasible, there may be existing data available that address the relevant question. Major issues here include:

- Ease of access to data, particularly proprietary data from industry-sponsored trials or private health plans
- Extracting useful data from administrative or clinical records. ICD-9 (*International Classification of Diseases, Ninth Revision*) and CPT (*Current Procedural Terminology*) codes are not sensitive to many relevant factors in a patient's clinical history, or to disease severity within conditions. Paper records are difficult to abstract because of issues relating to legibility, consistency in diagnostic language, and the human resources required to convert clinical records into useful analytic data. Electronic medical records are more useful, but are not universally used, and systems may not be compatible. For

any of these sources, data on the variables of greatest interest may not have been consistently collected.

- Generalizability: Patients enrolled in Medicare, Medicaid, or private health plans may differ in a number of respects, such as income and employment history, that may be relevant, but which may be difficult to adjust for given the available data.

Modeling

Finally, if none of the above options is feasible, simulation modeling may be able to address some questions. Modeling is particularly helpful for addressing questions that involve very long durations of followup, or options that cannot feasibly be included in an RCT, such as the comparative impact of different screening frequencies on cancer incidence, mortality, and life expectancy. The main limitation here is the availability of appropriate expertise in both modeling and the clinical conditions being studied.