Effective Health Care Program

Future Research Needs Paper
Number 8

Future Research Needs for Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

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. 290-2007-10066-I). The findings and conclusions in this document are those of the author(s), 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.

This report may be used, in whole or in part, as the basis for research design or funding opportunity announcements. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This information does not represent and should not be construed to represent a determination or policy of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

This project was funded under Contract No. 290-2007-10066-I from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS).

Future Research Needs Paper

Number 8

Future Research Needs for Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease

Identification of Future Research Needs from Comparative Effectiveness Review No. 18

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10066-I

Prepared by:
Duke Evidence-based Practice Center
Durham, NC

Investigators
Gillian D. Sanders, Ph.D.
Benjamin Powers, M.D.
Matthew Crowley, M.D.
Evan Myers, M.D., M.P.H.
Amanda McBroom, Ph.D.
Michael Musty, B.A.
Rebecca Gray, D.Phil.

AHRQ Publication No. 10-EHC006-EF
November 2010

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

Suggested citation: Sanders GD, Powers B, Crowley M, Myers E, McBroom A, Musty M, Gray R. Future Research Needs for Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. Future Research Needs Paper No. 8. (Prepared by Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 11-EHC006-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2010. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

As part of a new effort in 2010, AHRQ has supported EPCs to work with various stakeholders, including patients, to further develop and prioritize the future research needed by decisionmakers. The Future Research Needs products are intended to inform and support researchers and those who fund research to ultimately enhance the body of comparative effectiveness evidence so that it is useful for decisionmakers.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative effectiveness reviews will be updated regularly.

Acknowledgments

The Duke Evidence-Based Practice Center thanks investigators William Baker, Pharm.D., B.C.P.S., and C. Michael White, Pharm.D., F.C.P., F.C.C.P., for valuable discussions regarding the comparative effectiveness review *Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease* prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center.

Stakeholder Group

Javed Butler, M.D., M.P.H., F.A.C.C., F.A.H.A.; Emory University; Atlanta, GA
Joanne Foody, M.D., F.A.C.C., F.A.H.A.; Brigham and Women's Hospital; Boston, MA
David Gordon, M.D., Ph.D., M.P.H.; National Heart Lung and Blood Institute; Bethesda, MD
Michael Ho, M.D., Ph.D.; Denver VA Medical Center; Denver, CO
Newell McElwee, Pharm.D., M.P.H.; Merck & Co., Inc.; North Wales, PA
Allison Rosen, M.D., M.P.H., ScD.; University of Massachusetts; Worcester, MA
Lawrence Sadwin, B.S.; Patient Advocate, Warren, RI
David Sugano, Dr.P.H.; Novartis; East Hanover, NJ
Jed Weissberg, M.D.; Kaiser Permanente; Oakland, CA

AHRQ Contacts

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality

Elisabeth U. Kato, M.D., M.R.P.
Task Order Officer
Evidence-based Practice Program
Agency for Healthcare Research and Quality

Contents

Tables

Figures

Appendixes

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its comparative effectiveness reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Background

Despite advances in therapy, ischemic heart disease (IHD) remains the most common cause of morbidity and mortality in the United States. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers/antagonists (ARBs) have been shown to improve clinical outcomes for some patients, including those with heart failure and those with both myocardial infarction and ventricular dysfunction. However, the comparative effectiveness of ACE inhibitors and ARBs alone or in combination for patients with IHD remains uncertain.

A comparative effectiveness review (CER) published by the University of Connecticut Evidence-based Practice Center (EPC) in 2009 found strong evidence that ACE inhibitors reduced total mortality and nonfatal myocardial infarction (MI) in comparison to placebo among adults with stable IHD and preserved ventricular function, but increased the risk for syncope and cough. There was low to moderate evidence that ARBs reduced a composite of cardiovascular endpoints compared to placebo, and these agents were well-tolerated. The one available study directly comparing the impact of ACE inhibitors and ARBs on cardiovascular outcomes in patients with IHD revealed no significant difference between the classes in the rate of cardiovascular outcomes, but demonstrated higher rates of cough and angioedema among patients treated with ACE inhibitors, and higher rates of hypotensive symptoms among patients treated with ARBs.

A list of research gaps is a common component of CERs and is an important step in outlining a future research agenda; however, such lists do not always clearly suggest how future research should be prioritized, or which projects are in fact feasible. In this pilot project, we sought to expand on the work done by the University of Connecticut EPC to identify and prioritize gaps in the evidence supporting the comparative effectiveness of ACE inhibitor and ARB therapy in patients with IHD. The prioritization process we used combined a review of recently published and ongoing studies, engagement of nine stakeholders, and participation of these stakeholders in both qualitative and quantitative exercises of research needs prioritization.

Methods

As part of the pilot project we (1) expanded the list of categories for possible future research based on discussions with the University of Connecticut EPC and review of a related CER on ACE inhibitors and ARBs for hypertension, (2) reviewed recently published and ongoing studies relevant to ACE inhibitor and ARB therapy in IHD, (3) performed three

prioritization exercises with a group of nine stakeholders, and (4) developed a conceptual framework for recommending study designs.

Ongoing Studies

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

(1) A search of ClinicalTrials.gov for ongoing studies.
(2) An update (via PubMed®) of the MEDLINE® search used in the original CER to identify relevant randomized clinical trial literature published since the last search date (July 2009).
(3) A search of PubMed for relevant systematic reviews and meta-analyses published since July 2009.

Research Area Prioritization

Project stakeholders participated in three conference calls and three prioritization exercises. Each prioritization exercise built off the findings of the previous exercise. The call and prioritization exercises occurred in the following order:

- Conference Call 1: Introduced stakeholders to the project's objectives and described the key clinical questions, the original CER report and its findings, and proposed methods for the prioritization process, including use of a decision model and value-of-information analyses to quantitatively prioritize future research needs.
- Prioritization Exercise 1: Stakeholders were asked to rate the importance of future research exploring various characteristics using a five-point Likert scale via an online tool. They were also asked to rank their top five research priorities from the complete list.
- Conference Call 2: Used to review and discuss the results of the initial exercise.
- Prioritization Exercise 2: We distributed additional material to stakeholders, including a list of potential priority setting criteria to use when considering the appropriate priority for the research questions, the results of the initial survey prioritization, and summary evidence tables from the original CER report. Each stakeholder was then asked to rank the 16 research areas from 1 to 16 in order of importance.
- Conference Call 3: Reviewed the findings of the second prioritization exercise, detailed our search of recently published literature and ongoing trials, described the decision analytic model and its key assumptions and data, discussed the model's findings, and then provided an opportunity for the group to discuss the existing ranking.
- Prioritization Exercise 3: Further material was distributed to stakeholders, including the qualitative ranking results and the recently published literature and ongoing trials in each research area. Each stakeholder was then asked to rank the areas from 1 to 16. This final step produced our final ranking.

Study Design Recommendations

We developed a conceptual framework for recommending study designs. Our overall approach to recommending specific study designs for addressing specific evidence gaps emphasized the study design with the least risk of bias and the greatest likelihood of completion. For areas out of scope of the original CER, we suggest specific study designs that may be

appropriate, although without the benefit of a comprehensive systematic review, cannot ascertain whether some of these studies have already been completed.

Stakeholder Engagement and Handling Conflicts of Interest

Nine stakeholders were selected for participation in this project from a variety of backgrounds and perspectives. They included physicians affiliated with academic institutions, representatives of professional societies with a cardiovascular focus or expertise in comparative effectiveness research, a payer institution, industry representatives, the National Heart Lung and Blood Institute, and a patient representative. In selecting members of the stakeholder group, efforts were made to assemble a balanced group of individuals representing a range of perspectives. Efforts were also made to avoid inclusion of researchers whose participation in the prioritization process might result in an unfair advantage in the development of future research proposals.

Results

Table A describes the final prioritized list of research areas with recommended study designs. The top six research areas were consistently ranked highly and deemed most important; these six areas are enclosed within broad borders for emphasis in Table A. As described in our methods, we expanded the list of research gaps to include five areas outside the scope of the original CER but deemed to be of high priority based on discussions with the University of Connecticut EPC team, our related work on the comparative effectiveness of ACE inhibitors and ARBs in patients with essential hypertension, and feedback from our stakeholders. These additional five research areas from outside the scope of the original CER are shaded in gray in Table A. For these five gaps identified as important by the stakeholders, we did perform a literature search and a search of ongoing trials to identify duplication and assess feasibility; however without a comprehensive systematic review, we cannot be certain that some of these studies have not already been done.

Table A. Ranked research area prioritization and recommended study designs for addressing evidence gaps

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
1	E: Strategies to enhance greater **evidence-based use** of ACEIs/ ARBs	**Maybe:** Need to consider whether issues related to evidence-based medication use are unique to ACEIs/ ARBs. In addition there may be technical issues with generalizability of RCT on practitioner behavior—practitioners willing to participate in RCT may be more likely to practice evidence-based medicine (EBM).	**Maybe:** If issues related to evidence-based practice are generic and sufficient studies on specific strategies available, meta-analysis might be feasible	**Maybe:** If issues related to evidence-based practice are generic, and sufficient studies on specific strategies are available, meta-analysis might be feasible. Technical issues with ability to adjust for wide range of potential confounders.	**Maybe:** If able to prospectively follow outcomes after implementation of new strategy for enhancing evidence-based use	**Yes:** Comparison of different settings with different incentives/ disincentives for evidence-based prescribing	**Maybe:** Potential role for modeling impact of different strategies, including use of newer techniques such as agent-based modeling. Could inform future study design.
2	F: The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	**Maybe:** If sufficient data on impact on nonadherence (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 available was not previously included in the original CER and if sufficient data on impact on nonadherence (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 available not previously included in the original CER and if data on adherence collected consistently across studies	**Yes:** Most reliable way to track adherence	**Maybe:** Technical issues with measuring adherence from administrative data	**Maybe:** Model could help determine clinically important differences

Table A. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
3	A: Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD	**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. 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 of RCTs in this area. If available, could address less common comorbidities, longer term safety/ effectiveness	**Maybe:** Most direct way of addressing less common methods; allows for adjustment for confounding. Sample size and resources needed for longer followup are potential limitations.	**Yes:** Most efficient method for 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
4	K: The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**	**Yes:** Incorporation of disease-specific and generic QOL instruments into new trials	**Maybe:** If additional evidence available not previously included in the original CER with consistent use of instruments to allow data synthesis	**No:** Validated QOL instruments rarely reported in observational studies	**Yes:** Relatively low cost. Cross-sectional studies for obtaining population-level utilities reasonable.	**Maybe:** If validated QOL instrument collected	**Maybe:** Model could help determine clinically important differences

Table A. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
5	B: Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD	**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 obtain unpublished information.	**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. Appropriate coding of other covariates a potential limitation.	**Maybe:** Model could help determine impact of subgroup differences on overall population effectiveness, cost-effectiveness
6	J: The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	**No:** Relatively large number of recent or ongoing studies; unclear what additional information new RCTs would provide	**Yes:** Sufficient number of studies. Main potential issue is duration of followup.	**Yes:** If available, could address less common outcomes over longer time frame	**Maybe:** Most direct way of addressing duration limitations; allows for adjustment for confounding. Sample size and resources needed for longer followup are potential limitations.	**Yes:** May be most efficient method, 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
7	I: The benefit of ACEIs/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	**Yes:** Especially for shorter term outcomes	**Yes:** Especially for shorter term outcomes	**Maybe:** If sufficient number of studies available; adjustment for confounding an issue	**Maybe:** Most appropriate for longer term outcomes; resource requirements for longer term studies a major issue	**Yes:** Appropriate coding for covariates an issue	**Yes:** Model could help determine clinically important differences

Table A. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
8	M: The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy	**Maybe:** Could collect cost/ utilization data as part of RCT; major issue is generalizability	**Maybe:** If sufficient number of studies available	**Maybe:** If sufficient number of studies available	**Maybe:** Adding costs/utilization to planned observational study reasonable	**Yes:** Appropriate coding for covariates an issue	**Yes:** Model helpful for determining meaningful differences
9	L: The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	**Maybe:** Large number of studies recently completed or ongoing	**Maybe:** if additional evidence available not previously included in the original CER s	**Maybe:** If sufficient number of studies available; adjustment for confounding an issue	**Maybe:** Most appropriate for longer term outcomes; resource requirements for longer term studies a major issue	**Yes:** Appropriate coding for covariates an issue	**Maybe:** Model could help determine clinically important differences
10	C: Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	**No:** Unlikely to be sufficient power within single trial	**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 obtain unpublished information.	**Maybe:** If individual patient data or separate subgroup data not reported in current studies could be obtained and pooled for analysis. Would likely require cooperation from the multiple sponsors to obtain unpublished information.	**Yes:** May be required for longer term outcomes	**Yes:** Appropriate coding for covariates an issue	**Maybe:** Model could help determine clinically meaningful differences

Table A. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
11	N: The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	**Maybe:** If existing or ongoing studies unlikely to answer question	**Yes:** Likely to be sufficient number of studies	**Maybe:** If sufficient number of studies available	**Yes:** May be required for longer term outcomes	**Yes:** Appropriate coding for covariates an issue	**Maybe:** Model could help determine clinically meaningful differences
12	D: Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	**Maybe:** Sample size is major issue	**Maybe:** If sufficient number of studies. Patient-level meta-analysis of RCT data would be particularly useful.	**Maybe:** If sufficient number of studies	**Yes:** Most feasible way to ensure that genetic material available	**Maybe:** If genetic data available, or reasonable options for obtaining	**Yes:** Model could help determine potential clinical utility of identifying genetic differences
13	G: Impact of the **dose response** (impact of medication dose or dosing interval) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	**Yes:** Most straightforward way to obtain estimate of impact on different dosing	**Maybe:** If sufficient number of studies	**No:** Dose response difficult to measure in observational data	**No:** Dose response difficult to measure in observational data	**No:** Dose response difficult to measure in observational data	**Maybe:** Model could be useful for determining clinically meaningful differences

Table A. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
14	H: Impact of **class effect** (impact of differences between specific agents within each class) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	**Yes:** Ideal for unbiased estimate; if equivalence study, could require large sample size	**Maybe:** If sufficient number of studies	**Maybe:** If sufficient number of studies	**Maybe:** RCT would be preferable	**Maybe:** RCT would be preferable; appropriate coding for covariates is an issue. Could be useful for preliminary estimates.	**Maybe:** Model could be useful for determining clinically meaningful differences
15	O: The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	**No:** Reasonable number of studies, power of individual studies limited	**Maybe:** If additional evidence available not previously included in the original CER	**Maybe:** If additional evidence available not included in the original CER.	**Maybe:** Observational design more practical for longer term outcomes	**Maybe:** Coding of covariates main issue	**Maybe:** Model potentially useful for determining clinically meaningful differences
16	P: The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**	**No:** Reasonable number of studies, power of individual studies limited	**Maybe:** If additional evidence available not previously included in the original CER.	**Maybe:** if additional evidence available not previously included in the original CER	**Maybe:** Observational design more practical for longer term outcomes	**Maybe:** Coding of covariates main issue	**Maybe:** Model potentially useful for determining clinically meaningful differences

Abbreviations in Table A: ACEI(s)=angiotensin-converting enzyme inhibitor(s), ARB(s)=angiotensin II receptor blocker(s)/antagonist(s), CHF=congestive heart failure, CVA=cerebrovascular accident, IHD=ischemic heart disease, ITT=intention-to-treat, LV=left ventricular, MI=myocardial infarction, PICO=population, interventions, comparators of interest, and outcomes, QOL=quality of life

Conclusions

In addition to prioritizing future research areas specific to ACEI and ARB therapy in patients with IHD, this pilot study provided several insights into the future research needs assessment process within the broader EPC program. Overall, our experience suggests that the results of stakeholder prioritization exercises performed cold (i.e., without provision of basic information about the status of current research, etc.), are likely to be unstable and may vary greatly depending on what instrument is used. However, provision and discussion of such data appear to lead to greater consensus and more stable ranking of stakeholder preferences. The following specific recommendations are based both on the experience of the investigative team and on explicit feedback received from the stakeholder group.

- The EPC's review of the recently published literature and ongoing studies was performed and shared with stakeholders between Prioritization Exercises 2 and 3. It was widely agreed by stakeholders that this information was very helpful in their understanding of the evidence gaps and importance of future research. We therefore suggest that this step be performed before engagement of the stakeholder group so that results can be shared with them early in the process. Note that depending on when the future research needs report is developed in the CER process, this information may come directly from the CER and therefore not require an additional step
- Several of the stakeholders felt that they had expertise in related fields (cardiovascular trials, medical decisionmaking, patient advocacy) but were not particularly well-qualified in the specific domain of ACEI and ARB therapy in IHD. Although the breadth of expertise and perspectives in the stakeholder group was intentional, it would have been helpful to the group for the EPC team to provide additional background material and time for the stakeholder group to become familiar with the existing evidence and specific clinical domain. Again, developing the future research needs report as part of the CER process would allow the evidence report to serve as the source of this background material.
- A face-to-face meeting was suggested by both stakeholders and the investigative team. Although such a meeting would have required both time and resources, it would have allowed a more global presentation of the available evidence, the decision analytic model, and, most importantly, an opportunity for the stakeholders to discuss amongst themselves (with the guidance of the EPC team) the reasons for their specific rankings.
- The optimal size of the stakeholder group is unclear. In addition to considerations regarding appropriate representation of all potential stakeholders, the time and resources available for meetings and conference calls, and establishing processes to ensure that all stakeholders have the opportunity to contribute, there are sample size issues raised by using methods such as mean ranking scores—a larger number of rankings might have allowed a greater spread of scores, or sufficient variation in the distribution of scores, to assist in discriminating between different research areas.
- Because the pilot projects were, by necessity, both exploring potential prioritization methods and a specific clinical domain, it is unclear whether specific tools or processes were challenging because of their methodology or because of the specific evidence base (or lack thereof) for the clinical domain. It will therefore be important to look across the entire set of pilot projects for broad themes that can be incorporated into the global EPC program.

Background

Clinical Context

Despite advances in therapy, ischemic heart disease (IHD) remains the most common cause of morbidity and mortality in the United States. The prevalence of IHD is estimated at 16.8 million adults, and the death rate is 278.9 per 100,000 people, with IHD responsible for over 35 percent or all deaths nationwide.[1]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers/antagonists (ARBs) have been shown to improve clinical outcomes for some patients, including those with heart failure and those with myocardial infarction (MI) and ventricular dysfunction.[2-9] However, the comparative effectiveness of ACE inhibitors and ARBs alone or in combination for patients with IHD remains uncertain. Their potential role in the management of the broader population of patients with known IHD or at high risk for IHD is also unclear.

To address this area of uncertainty, a comparative effectiveness review (CER) project sponsored by the Agency for Healthcare Research and Quality (AHRQ) was awarded to the University of Connecticut Evidence-based Practice Center (EPC). The subsequent CER reviewed data available through July of 2009 comparing the benefits and harms of adding ACE inhibitors, ARBs, or both to standard medical therapy in adults with stable IHD or IHD risk equivalents.[10-11] The report specifically addressed the following seven key questions:

Key Question 1. In patients with stable IHD or IHD risk equivalents who have preserved left ventricular (LV) systolic function, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal MI, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality-of-life measures?

Key Question 2. In patients with stable IHD or IHD risk equivalents who have preserved LV systolic function and are receiving standard medical therapy, what is the comparative effectiveness of combining ACE inhibitors and ARBs vs. either an ACE inhibitor or ARB alone in terms of total mortality, cardiovascular mortality, nonfatal MI, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality-of-life measures?

Key Question 3. In patients with IHD and preserved LV function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal MI, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?

Key Question 4. In patients with stable IHD or IHD risk equivalents who have preserved LV systolic function, what are the comparative harms of adding ACE inhibitors or ARBs to standard medical therapy when compared to standard medical therapy alone?

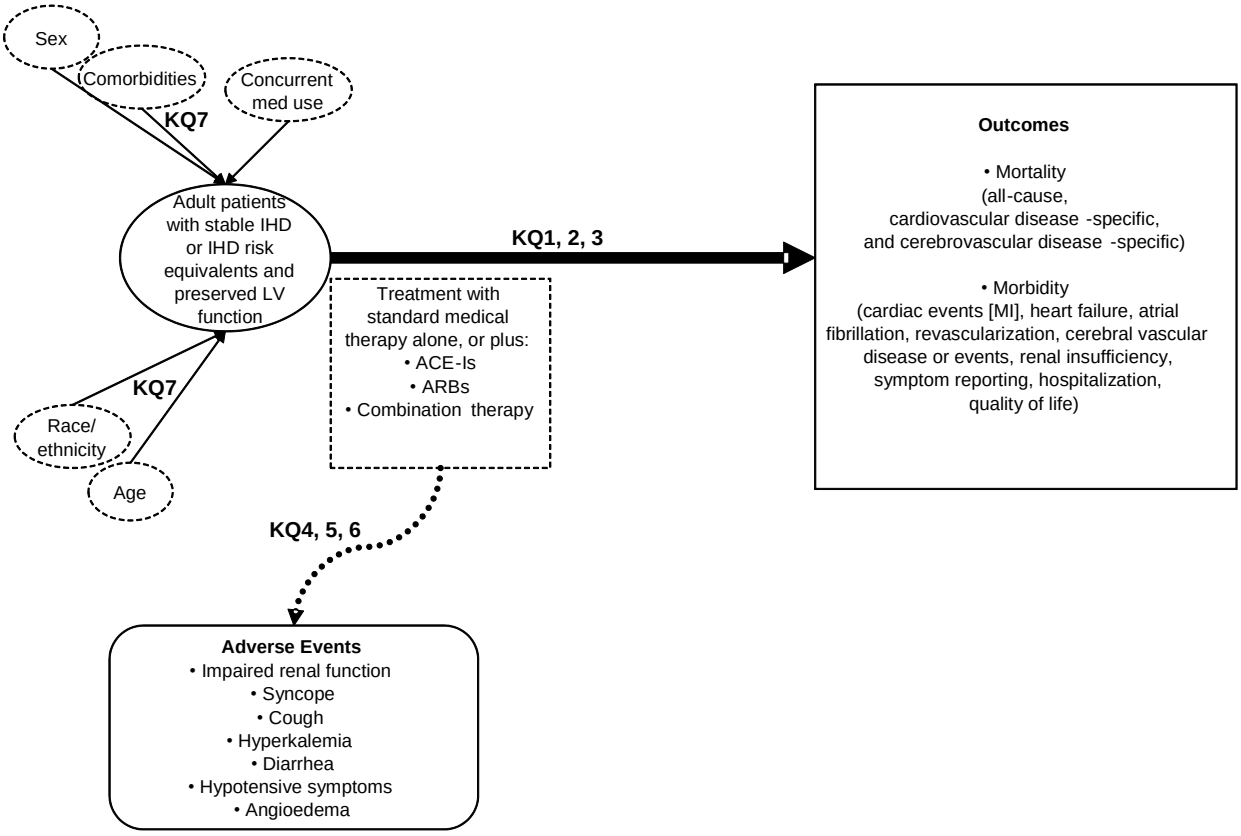
Key Question 5. In patients with stable IHD who have preserved LV systolic function and are receiving standard medical therapy, what is the evidence of comparative harms of combination ACE inhibitor and ARB therapy vs. use with either an ACE inhibitor or ARB alone?

Key Question 6. In patients with IHD and preserved LV systolic function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what are the comparative harms of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone?

Key Question 7. What is the evidence that benefits or harms differ by subpopulations, including: demographics [sex, age, ethnicity, left ventricular ejection fraction (LVEF)], clinical course (previous treatment with a stent or coronary artery bypass surgery, degree and location of lesion, presence and pattern of symptoms), dose of the ACE inhibitor or ARB used, comorbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid-lowering drugs, beta-blockers, antiplatelet agents)?

These seven key questions are graphically displayed in Figure 1 through an analytic framework.

Figure 1. Analytic framework



The CER found strong evidence that ACE inhibitors reduced total mortality and nonfatal MI in comparison to placebo among adults with stable IHD and preserved ventricular function, but increased the risk for syncope and cough. There was low to moderate evidence that ARBs reduced a composite of cardiovascular endpoints compared to placebo and were well-tolerated.

The one available study directly comparing the impact of ACE inhibitors and ARBs on cardiovascular outcomes in patients with IHD revealed no significant difference between the classes in the rate of cardiovascular outcomes, but demonstrated higher rates of cough and angioedema among patients treated with ACE inhibitors, and higher rates of hypotensive symptoms among patients treated with ARBs.[12] The same study compared combination therapy with ACE inhibitors and ARBs to monotherapy with each class of agents and found no difference in vascular outcomes, but a higher discontinuation rate in the combination therapy group due to medication side effects.

Research Gaps

Although 41 studies including over 64,000 randomized patients were evaluated in this CER, the authors identified multiple areas where insufficient evidence existed to answer the key questions regarding the comparative effectiveness of ACE inhibitors and ARBs. While there was a high strength of evidence for ACE inhibitors compared to placebo for total mortality, the evidence was insufficient, low, or moderate for the impact of ACE inhibitors or ARBs on several cardiovascular outcomes, including cardiovascular mortality, nonfatal myocardial infarction, or stroke, suggesting that future research on the impact of ACE inhibitors or ARBs on cardiovascular outcomes may influence their conclusions. In addition, the report highlighted the potential utility of an individual patient data meta-analysis of major ACE inhibitor or ARB trials or future trials to provide insight into the impact of ACE inhibitors and ARBs on the following areas:

- Comparative benefits and harms in minority groups, including Asians, African Americans and Latinos.
- Comparative benefits and harms in patients with single- vs. multi-vessel disease and specifically with left anterior descending artery disease.
- Comparative benefits and harms in patients with a baseline ejection fraction (EF) between 40 percent and 70 percent.
- Comparative benefits and harms in patients taking adenosine diphosphate drugs vs. those taking no antiplatelet therapy.
- Comparative benefits and harms in patients with a history of revascularization.
- Comparative benefits and harms associated with adding ACE inhibitors or ARBs to standard medical therapy in patients with stable IHD and preserved left ventricular function vs. adding other cardiovascular drugs such as calcium channel blockers.
- Comparative benefits and harms associated with adding ACE inhibitors or ARBs to standard medical therapy in patients without proven stable IHD but with IHD risk equivalents.
- Comparative benefits and harms relating to dosing intensity of ACE inhibitors or ARBs.
- Comparative benefits and harms in patients with genetic polymorphisms within the ACE gene or the angiotensin II type 1 receptor.

The above evidence gaps represented areas where the EPC thought there was an underlying pharmacological rationale for suspecting potential differences; given the large number of clinical trials that have already been conducted, the University of Connecticut team thought that meta-analysis of individual patient data was the most efficient method to begin to address these gaps.

In addition to the priorities identified in the IHD CER, there are other evidence gaps which need to be addressed by future research in order to inform decisionmaking and resource

allocation with respect to use of ACE inhibitors and ARBs. These include differences in treatment- and outcome-associated costs; the incidence of rare but serious side effects such as angioedema; differential impact on quality of life; and variation in observed population outcomes due to differences in patient selection, treatment adherence, or the uptake of evidence-based recommendations. Based on discussions with the University of Connecticut EPC, review of a recent draft update of a related CER of ACE inhibitors and ARBs in hypertension,[13-14] and discussions with our stakeholder group, we expanded the list of categories for future research. This expanded list included five research areas that were outside the scope of the original CER report, but for which the University of Connecticut EPC investigators, the Duke EPC team, and the stakeholder group felt that additional research was needed.

The decision to expand the list of research gaps beyond those identified in the original CER was based on two different rationales. The first was based on clinical overlap between our target condition, IHD, and other conditions for which ACE inhibitors and ARBs have an indication and a strong evidence base, such as hypertension, congestive heart failure, and chronic kidney disease. These conditions are interrelated and share several risk factors and clinical outcomes, yet are typically separated in comparative effectiveness trials and systematic reviews of the literature. We expanded our list of potential research gaps based on this literature to include outcomes of interest not included in the initial review (e.g. renal insufficiency, new diagnosis of heart failure) and research questions that have been raised in systematic reviews of these conditions (such as medication class effect, dose response, and alternative comparisons) that may span across these clinical conditions. The second rationale was reflected in the comments of several stakeholders who believed the clinical efficacy of ACE-inhibitors and ARBs was sufficiently well known and the most pressing challenge was improving the implementation of this evidence base for patients likely to benefit. Based on this input, medication adherence and enhanced evidence based use were added as important research gaps for consideration.

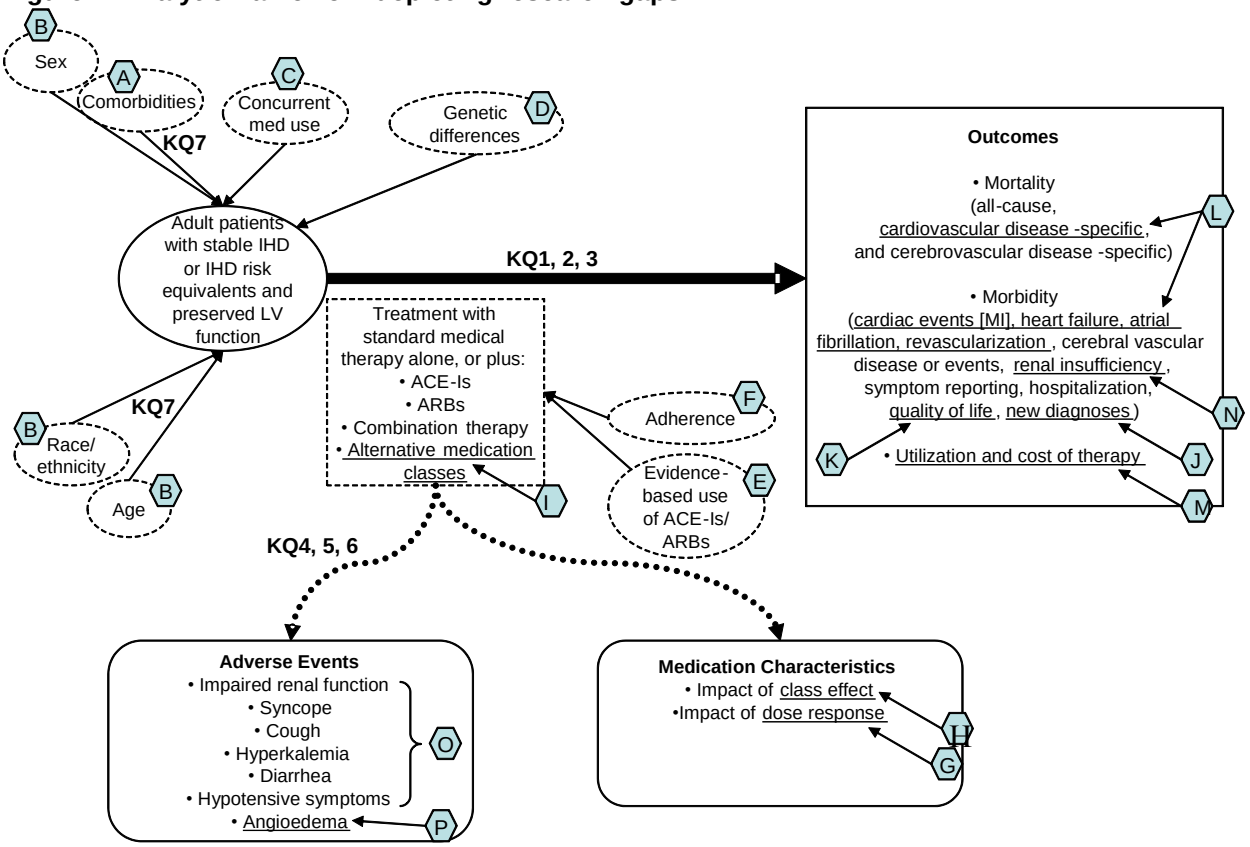
This initial list of future research priorities is summarized below in Table 1 according to the PICO (population, interventions, comparators of interest, and outcomes) format. The identified research gaps are also identified on our analytic framework in Figure 2 with letter coding. Those research gaps that were outside the scope of the original CER are shaded in gray in Table 1 and throughout the report.

Table 1. Research gaps organized by PICO format

Research gaps	Letter code (*see* Figure 2)
PATIENT POPULATION:	
Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD	A
Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD	B
Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	C
Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	D
INTERVENTION:	
Strategies to enhance greater **evidence-based use** of ACEIs/ARBs	E
The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	F
Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD	G
Impact of **class effec**t (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD	H
COMPARATOR:	
The benefit of ACEIs/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	I
OUTCOME:	
The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	J
The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**	K
The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	L
The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy	M
The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	N
The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	O
The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**	P

Abbreviations in Table 1: ACEI(s)=angiotensin-converting enzyme inhibitor(s), ARB(s)=angiotensin II receptor blocker(s)/antagonist(s), CHF=congestive heart failure, CVA=cerebrovascular accident, IHD=ischemic heart disease, LV=left ventricular, MI=myocardial infarction, PICO=population, interventions, comparators of interest, and outcomes

Figure 2. Analytic framework depicting research gaps



A list of research gaps is a common component of CERs and is an important step in outlining a future research agenda; however, such lists do not always clearly suggest how future research should be prioritized, or what research projects are in fact feasible. In this pilot project, we sought to expand on the work done by the University of Connecticut EPC in the original CER to identify and prioritize gaps in the evidence supporting the comparative effectiveness of ACE inhibitor and ARB therapy in patients with IHD. This prioritization process combined a review of recently published and ongoing studies, engagement of nine stakeholders, and participation of these stakeholders in both qualitative and quantitative exercises of research needs prioritization.

Methods

Identifying Ongoing Studies

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.
(2) An update (via PubMed®) of the MEDLINE® search used in the original CER, "Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease,"[10] and the associated *Annals of Internal Medicine* publication[11] to identify relevant randomized controlled trial (RCT) literature published since the last search date (July 2009).
(3) A search of PubMed for relevant systematic reviews and meta-analyses published since July 2009.

The exact search strategies used are provided in Appendix A.

Search results were reviewed for applicability to the identified research gaps listed in Table 1. We included articles from each search if they met the following criteria: (1) included patients with known IHD or at high risk for IHD based on risk factors of hypertension, diabetes, peripheral arterial disease, or chronic kidney disease, but excluding congestive heart failure (CHF); (2) reported original data or combined original data in a systematic review or decision analysis; (3) included a comparison between either an ACE inhibitor or ARB and either an alternative medication, another ACE inhibitor or ARB, or placebo; and (4) included outcomes that could be categorized according our identified list of research priorities.

Prioritizing Research

We used multiple methods to prioritize the identified research needs. These included both a qualitative prioritization exercise and then further ranking of the research areas after a quantitative ranking of the areas using a decision analytic framework. A more formal comparison of these different methods (specifically, a comparison of the qualitative and quantitative processes) will be discussed in our upcoming report on "Future Research Methods Project: Determining Appropriate Use of Modeling or Value of Information." In the present pilot report we instead describe the prioritization tools and process, but then focus on the findings as they specifically relate to the evidence gaps in the comparative effectiveness of ACE inhibitor and ARB therapy in patients with IHD.

Participants in our stakeholder group (described below) participated in three prioritization exercises and three conference calls. Each prioritization exercise included a group discussion of the previous exercise's findings and built on the previous exercise's ranking of research areas. The ranking from the third prioritization exercise was therefore considered to be cumulative and to represent the final order of research areas. The results of each prioritization exercise are summarized in Appendix D.

The first conference call (June 2010) 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 proposed methods for the prioritization process, including the use of a decision model and value-of-information analyses to quantitatively prioritize the research needs.

Stakeholders were then asked to rate the importance of further research exploring various characteristics using a 5-point Likert scale via an online tool (Appendix B). They were also asked to rank their top five research priorities from the complete list. We used these two ranking exercises to look for internal consistency by individual stakeholders in their ranking and to help us identify any confusion with the prioritization exercise.

Stakeholders then participated in a second conference call (July 2010), in which the results of the initial exercise were reviewed with the group and discussed. During this conference call it became clear to the Duke EPC investigative team that several components of the exercise needed to be clarified—both in terms of the criteria the stakeholders should be considering when prioritizing research needs, and the current evidence base of the comparative effectiveness of ACE inhibitor and ARB therapy in patients with IHD.

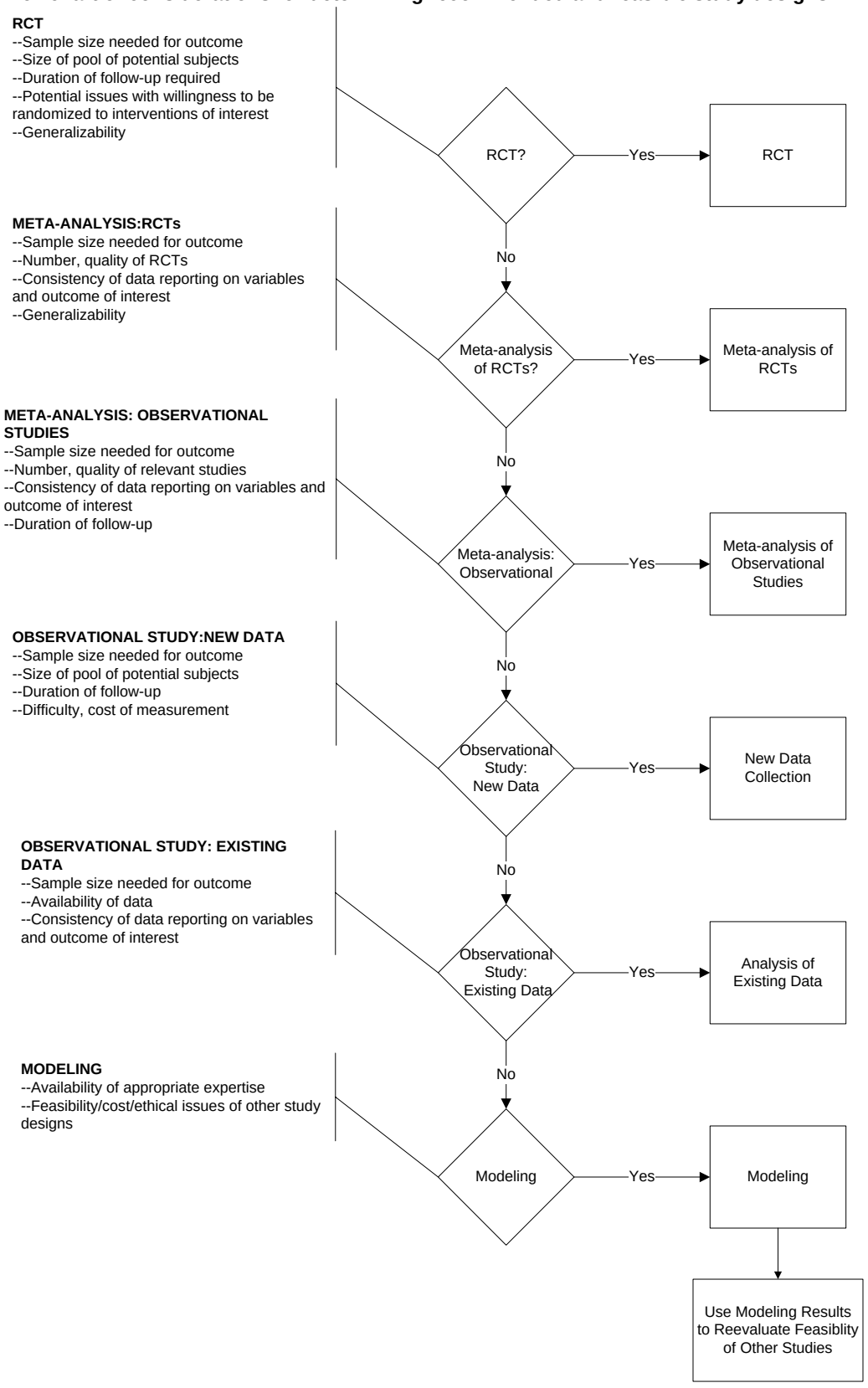
Although we had planned only one prioritization exercise using the qualitative survey, based on our second conference call and the need for clarification, we distributed to the stakeholder group additional material (Appendix B) including a list of potential priority setting criteria that could be used when considering the appropriate priority for the research questions, the results of the initial survey prioritization, and summary evidence tables from the original CER report and resulting publication. We then asked each stakeholder to rank the 16 research areas from 1 to 16 in order of importance. The final conference call (September 2010, Appendix B) reviewed the findings of the second prioritization exercise, detailed the Duke EPC's search of recently published literature and ongoing trials, described the decision analytic model and its key assumptions and data, discussed the model's findings, and, finally, provided an opportunity for the group to discuss the existing ranking. As planned a priori, this final conference call focused on the quantitative findings from the decision analytic model. After this call, a final survey was distributed to the stakeholder group (Appendix B) that included the qualitative ranking results and the recently published literature and ongoing trials in each research area. Stakeholders were again asked to rank the areas from 1 to 16. This final exercise produced our final ranking.

Determining Appropriate and Feasible Study Designs

In addition to exploring the prioritization of research needs, we sought to determine appropriate and feasible study designs for the identified priorities. Our overall approach to recommending specific study designs for addressing specific evidence gaps is depicted in Figure 3. In an ideal world, an effectiveness randomized controlled trial (RCT) would be conducted to address evidence gaps, since this design has the least risk of bias. However, for many evidence gaps, RCTs are not feasible for a variety of reasons, including the need for large sample sizes to adequately power for a representative population, the need for long duration of followup for some long-term outcomes, patient and provider reluctance to participate, and a variety of other factors. Our overall approach to study design recommendation starts with the premise that one should choose the least biased design that is feasible and affordable. If, for example, an RCT is not feasible, then a meta-analysis of RCTs (or a patient-level meta-analysis from RCTs) may be most appropriate and feasible. If meta-analysis of RCTs is not feasible, then meta-analysis (again, including patient-level analysis) of observational studies could provide valuable information to answer the research question. This somewhat hierarchical approach considers the feasibility and validity of the study to answer the question and assumes that the question is not answered by current research. However, questions that were identified as gaps in a systematic review presumably may not have sufficient evidence for a meta-analysis, although an individual patient data meta-analysis may still be valuable. For questions that were out of scope of the

original systematic review, it may be appropriate to consider a systematic review to identify if trials or observational studies have already been conducted.

Figure 3. Flowchart of considerations for determining recommended and feasible study designs



We explore below in more detail the potential study designs represented in Figure 3 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; for example, RCTs of treatments for conditions where hysterectomy is a potential therapy have historically had extreme difficulty meeting recruitment goals.
- Generalizability: Inclusion/exclusion criteria often mean that subjects who participate in RCTs rarely reflect the full spectrum of either disease severity or comorbidity that exist 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.[15] 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 IHD, has significant clinical overlap with related conditions such as hypertension, 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. However, study-level analyses, such as those conducted for the recent CER report of ACE inhibitors and ARBs by the University of Connecticut EPC, 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. We provide an example of one use of modeling here; more detailed discussions of the potential uses for models in addressing evidence gaps will be included in upcoming reports both by our group and by other EPCs.

As an example of determining the recommended study design for a given evidence gap, we describe here the process we used for the gap exploring the impact of demographic differences (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD. We first considered whether an RCT would be feasible. Unfortunately, it was determined that an ECT would be unlikely to have sufficient power in a single RCT to determine differences among subgroups and therefore would not be recommended. We next considered if a meta-analysis of RCTs would be feasible. We classified this study design as being possible but dependent on individual patient data or separate subgroup data not reported in current trials being obtained from the original authors and pooled for analysis. Such a meta-analysis of RCT data would likely require cooperation from the multiple sponsors to obtain unpublished information. The use of a meta-analysis of observational studies was believed to be more feasible though still most likely has the requirements of obtaining the needed data from multiple sponsors. Obtaining new data through an observational study was considered feasible. If new data collection was undertaken to address other questions, the impact of demographic differences could be estimated in the analysis. We felt that the most efficient method for exploring this evidence gap would be an observational study using existing data. Appropriate coding of other covariates is a potential limitation. Finally, modeling could help determine the impact of subgroup differences on overall population effectiveness or cost-effectiveness.

Engaging Stakeholders, Researchers, and Funders

The authors developed this working document with input from a group of interested stakeholders. Nine stakeholders were selected for participation in this project from a variety of backgrounds and perspectives. The group included physicians affiliated with academic institutions, representatives of professional societies with a cardiovascular focus or expertise in comparative effectiveness research (American Heart Association, American College of Cardiology, American College of Physicians, Society for Medical Decision Making), a payer institution, industry representatives, the National Heart Lung and Blood Institute, and a patient representative.

Input was solicited from the stakeholders in reviewing and developing the list of research gaps, reviewing the structure of the decision analytic model, informing model assumptions and sources for data inputs, and identifying important outcomes for consideration in modeling. Once the list of research gaps was established, stakeholders were asked to participate in the three prioritization exercises described above.

Stakeholder input was solicited and received through web- and paper-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.

Handling Conflicts of Interest

In selecting members of the stakeholder group, efforts were made to assemble a balanced group of individuals representing a range of perspectives. The group included individuals with experience in cardiology, as well as individuals with expertise in decision modeling and comparative effectiveness research.

Efforts were also made to avoid inclusion of researchers whose participation in the prioritization process might result in an unfair advantage in the development of future research proposals. Stakeholders were provided with the results of the first two qualitative prioritization exercises during the course of their participation in the project. The final recommended list of prioritized areas incorporating the final ranking of future research needs were not made available to the stakeholder group until public posting of the draft report.

Results

Recently Published and Ongoing Studies

The findings from our review of the recently published literature and ongoing studies are summarized in Appendix C.

The PubMed search updating the original CER identified 309 articles. These were reviewed, and 25 met our inclusion criteria. The majority of large studies reporting cardiovascular outcomes reported secondary outcomes or subgroup analyses from previously published large clinical trials.[12,16-19] There was no recently published research for several of the research areas, including strategies to enhance greater evidence-based use, impact of ACE inhibitors or ARBs on quality of life, impact of ACE inhibitor/ARB adherence, and dose-response relationship between ACE inhibitors and ARBs. The largest number of recently published research focused on the outcomes of cardiovascular events (10 studies) and development of new diagnoses (6 studies). One large clinical trial published after the CER report found no impact of the ARB valsartan vs. placebo on cardiovascular outcomes.[20]

The search of Clinicaltrials.gov identified 207 registered trials, of which 60 were still open at the time of the search. From these, we included 25 studies based on our review criteria.

The search of PubMed for relevant systematic reviews identified 134 articles, of which only 3 were included after review. The majority of articles were excluded because they represented expert narrative reviews rather than systematic reviews to answer a particular research question.

Recommended Research Prioritization

We describe here the findings of our three prioritization exercises. As described above, prioritization was designed as an iterative process with each successive exercise built on the previous exercise and its findings. Each step was followed by a conference call, during which stakeholders were provided with the prioritization results and had an opportunity to discuss the findings and the relative merits of each research priority. This process occurred in three distinct steps:

(1) After compiling the list of potential future research areas, stakeholders were asked to:
   a. Rate the importance of each research area using a 5-point Likert scale
   b. Rank their top five priority research areas

(2) Following review and discussion of these initial results, we asked individual stakeholders to rank all 16 research areas in order of importance.

(3) We provided the stakeholders with an updated literature review of recent and ongoing research for each priority and presented a decision analytic model identifying areas of uncertainty in this field. Following this, we asked each stakeholder to re-rank all 16 research areas in order of importance.

Prioritization Exercise 1

Table D1 (Appendix D) provides the Likert scale data for the first step in the research prioritization. Of note, this method of prioritization did not allow the 16 research areas to be

broadly distributed in terms of importance and resulted in numerous areas receiving the same average score. Table D2 (Appendix D) lists the research areas grouped by average score.

Table D3 (Appendix D) demonstrates the results when stakeholders were asked to explicitly rank the top five research areas. Table D4 (Appendix D) summarizes these findings and when compared with Table D2 (Appendix D) demonstrates that the prioritization of these research areas differs depending on the prioritization method used.

Prioritization Exercise 2

Our second prioritization exercise had individual stakeholders rank the 16 research areas in order of importance. Table D5 (Appendix D) provides the results of this ranking by stakeholder and then summary statistics of these rankings. Of note is that 14 of 16 research areas were ranked by at least one stakeholder as being in the top four research areas, while simultaneously being ranked by a second stakeholder as being in the bottom four research areas in terms of importance. Five of the research priorities (evidence-based use, comorbidities, adherence, cardiovascular outcomes, and class effect) were ranked by at least one stakeholder as being most important area for future research.

Table D6 (Appendix D) displays the prioritized list of research areas using the average rank score. The overall ranking of the list did not differ substantially when it was prioritized using the median score. Prioritizing based on the 1st quartile would have increased the importance of evaluating ACE inhibitor/ARB adherence (from a rank of 6th to 2nd).

Prioritization Exercise 3

Our final prioritization exercise had stakeholders re-rank the research areas from 1 to 16 after reviewing the findings of the decision analytic model, discussing as a group the rankings from the second prioritization exercise, and reviewing the status of recently published and ongoing studies by research area (see Appendix C).

Table D7 (Appendix D) presents the individual rankings and summary statistics for this final prioritization exercise. Of note, most of the rankings remained consistent between the second and third exercises. Notable exceptions included the ranking of research into the incidence of new diagnoses (such as diabetes, atrial fibrillation, or CHF with or without preserved LV function), which fell from being ranked second to being ranked sixth. It was instead replaced by an emphasis on research into medication adherence. This change could potentially have been influenced by the relatively large number of recently published studied (n=6) and ongoing clinical trials (n=5) related to new diagnoses and the scarcity of research (no new studies, and one potentially relevant clinical trial) related to medication adherence. Of interest, the decision analytic model of ACE inhibitor and ARB therapy in IHD patients indicated that uncertainty related to new diagnoses had a significant impact on the model's findings.

Although the overall ranking did not change substantially from the second to the third prioritization exercise, the consensus among the stakeholders in their rankings did improve. The variance in the rankings was greatly reduced, and although one stakeholder still ranked the top research area (evidence-based use) as 12th, there was much more consistency among the stakeholders and their rankings of the top and bottom five areas.

Table 2 lists the final prioritization of the 16 research areas using the average score from Prioritization Exercise 3. Gray shading indicates gaps identified by the stakeholders that were not part of the scope of the original CER.

Table 2. Final ranking of 16 research areas

Ranking	Research area
1	Strategies to enhance greater **evidence-based use** of ACEIs/ARBs
2	The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
3	Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD
4	The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD
6	The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
7	The benefit of ACEIs/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy
9	The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
10	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD
11	The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
12	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD
13	Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of **class effec**t (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**

Abbreviations in Table 2: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes

Appropriate and Feasible Study Designs

Table 3 depicts our final ranked research areas and specific recommendations for addressing the 16 identified evidence gaps. For each potential research area, we provide our rationale for why each higher level of study design is not feasible or appropriate. The top six research areas were consistently ranked highly and deemed most important; these six areas are enclosed within broad borders for emphasis in Table 3. Again, those research areas that were outside the scope of the original CER are shaded in gray. While these gaps were clearly identified as important by the stakeholders, we have some caveats concerning recommended study designs. We did perform a literature search and a search of ongoing trials to identify

duplication and assess feasibility; however our choice of study design is less well grounded for these gaps than for the other gaps which are backed up by a full systematic review

Table 3. Ranked research area prioritization and recommended study designs for addressing evidence gaps

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
1	E: Strategies to enhance greater **evidence-based use** of ACEIs/ ARBs	**Maybe:** Need to consider whether issues related to evidence-based medication use are unique to ACEIs/ ARBs. In addition there may be technical issues with generalizability of RCT on practitioner behavior—practitioners willing to participate in RCT may be more likely to practice evidence-based medicine (EBM).	**Maybe:** If issues related to evidence-based practice are generic and sufficient studies on specific strategies available, meta-analysis might be feasible	**Maybe:** If issues related to evidence-based practice are generic, and sufficient studies on specific strategies are available, meta-analysis might be feasible. Technical issues with ability to adjust for wide range of potential confounders.	**Maybe:** If able to prospectively follow outcomes after implementation of new strategy for enhancing evidence-based use	**Yes:** Comparison of different settings with different incentives/ disincentives for evidence-based prescribing	**Maybe:** Potential role for modeling impact of different strategies, including use of newer techniques such as agent-based modeling. Could inform future study design.
2	F: The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	**Maybe:** If sufficient data on impact on nonadherence (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 available was not previously included in the original CER and if sufficient data on impact on nonadherence (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 available not previously included in the original CER and if data on adherence collected consistently across studies	**Yes:** Most reliable way to track adherence	**Maybe:** Technical issues with measuring adherence from administrative data	**Maybe:** Model could help determine clinically important differences

Table 3. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
3	A: Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD	**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. 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 of RCTs in this area. If available, could address less common comorbidities, longer term safety/ effectiveness	**Maybe:** Most direct way of addressing less common methods; allows for adjustment for confounding. Sample size and resources needed for longer followup are potential limitations.	**Yes:** Most efficient method for 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
4	K: The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**	**Yes:** Incorporation of disease-specific and generic QOL instruments into new trials	**Maybe:** If additional evidence available not previously included in the original CER with consistent use of instruments to allow data synthesis	**No:** Validated QOL instruments rarely reported in observational studies	**Yes:** Relatively low cost. Cross-sectional studies for obtaining population-level utilities reasonable.	**Maybe:** If validated QOL instrument collected	**Maybe:** Model could help determine clinically important differences

Table 3. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
5	B: Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD	**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 obtain unpublished information.	**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. Appropriate coding of other covariates a potential limitation.	**Maybe:** Model could help determine impact of subgroup differences on overall population effectiveness, cost-effectiveness
6	J: The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	**No:** Relatively large number of recent or ongoing studies; unclear what additional information new RCTs would provide	**Yes:** Sufficient number of studies. Main potential issue is duration of followup.	**Yes:** If available, could address less common outcomes over longer time frame	**Maybe:** Most direct way of addressing duration limitations; allows for adjustment for confounding. Sample size and resources needed for longer followup are potential limitations.	**Yes:** May be most efficient method, 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
7	I: The benefit of ACEIs/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	**Yes:** Especially for shorter term outcomes	**Yes:** Especially for shorter term outcomes	**Maybe:** If sufficient number of studies available; adjustment for confounding an issue	**Maybe:** Most appropriate for longer term outcomes; resource requirements for longer term studies a major issue	**Yes:** Appropriate coding for covariates an issue	**Yes:** Model could help determine clinically important differences

Table 3. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
8	M: The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy	**Maybe:** Could collect cost/ utilization data as part of RCT; major issue is generalizability	**Maybe:** If sufficient number of studies available	**Maybe:** If sufficient number of studies available	**Maybe:** Adding costs/utilization to planned observational study reasonable	**Yes:** Appropriate coding for covariates an issue	**Yes:** Model helpful for determining meaningful differences
9	L: The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	**Maybe:** Large number of studies recently completed or ongoing	**Maybe:** if additional evidence available not previously included in the original CER s	**Maybe:** If sufficient number of studies available; adjustment for confounding an issue	**Maybe:** Most appropriate for longer term outcomes; resource requirements for longer term studies a major issue	**Yes:** Appropriate coding for covariates an issue	**Maybe:** Model could help determine clinically important differences
10	C: Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	**No:** Unlikely to be sufficient power within single trial	**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 obtain unpublished information.	**Maybe:** If individual patient data or separate subgroup data not reported in current studies could be obtained and pooled for analysis. Would likely require cooperation from the multiple sponsors to obtain unpublished information.	**Yes:** May be required for longer term outcomes	**Yes:** Appropriate coding for covariates an issue	**Maybe:** Model could help determine clinically meaningful differences

Table 3. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
11	N: The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	**Maybe:** If existing or ongoing studies unlikely to answer question	**Yes:** Likely to be sufficient number of studies	**Maybe:** If sufficient number of studies available	**Yes:** May be required for longer term outcomes	**Yes:** Appropriate coding for covariates an issue	**Maybe:** Model could help determine clinically meaningful differences
12	D: Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	**Maybe:** Sample size is major issue	**Maybe:** If sufficient number of studies. Patient-level meta-analysis of RCT data would be particularly useful.	**Maybe:** If sufficient number of studies	**Yes:** Most feasible way to ensure that genetic material available	**Maybe:** If genetic data available, or reasonable options for obtaining	**Yes:** Model could help determine potential clinical utility of identifying genetic differences
13	G: Impact of the **dose response** (impact of medication dose or dosing interval) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	**Yes:** Most straightforward way to obtain estimate of impact on different dosing	**Maybe:** If sufficient number of studies	**No:** Dose response difficult to measure in observational data	**No:** Dose response difficult to measure in observational data	**No:** Dose response difficult to measure in observational data	**Maybe:** Model could be useful for determining clinically meaningful differences

Table 3. Ranked research area prioritization and recommended study designs for addressing evidence gaps (continued)

Rank	Research area	RCT?	Meta-analysis of RCTs?	Meta-analysis of observational studies?	New observational study?	Analysis of existing data?	Model?
14	H: Impact of **class effect** (impact of differences between specific agents within each class) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	**Yes:** Ideal for unbiased estimate; if equivalence study, could require large sample size	**Maybe:** If sufficient number of studies	**Maybe:** If sufficient number of studies	**Maybe:** RCT would be preferable	**Maybe:** RCT would be preferable; appropriate coding for covariates is an issue. Could be useful for preliminary estimates.	**Maybe:** Model could be useful for determining clinically meaningful differences
15	O: The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	**No:** Reasonable number of studies, power of individual studies limited	**Maybe:** If additional evidence available not previously included in the original CER	**Maybe:** If additional evidence available not included in the original CER.	**Maybe:** Observational design more practical for longer term outcomes	**Maybe:** Coding of covariates main issue	**Maybe:** Model potentially useful for determining clinically meaningful differences
16	P: The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**	**No:** Reasonable number of studies, power of individual studies limited	**Maybe:** If additional evidence available not previously included in the original CER.	**Maybe:** if additional evidence available not previously included in the original CER	**Maybe:** Observational design more practical for longer term outcomes	**Maybe:** Coding of covariates main issue	**Maybe:** Model potentially useful for determining clinically meaningful differences

Abbreviations in Table 3: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, ITT = intention-to-treat, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes, QOL = quality of life

Discussion

In addition to prioritizing future research areas specific to ACE inhibitor and ARB therapy in patients with IHD, this pilot study provided several insights into the future research needs assessment process within the broader EPC program. The following discussion points and recommendations are based both on the experience of the investigative team and on explicit feedback received from the stakeholder group.

The discussions with stakeholders and research prioritization revealed two distinct perspectives on future research priorities. All stakeholders agreed that the extensive body of literature evaluating ACE inhibitors and ARBs in patients with or at high risk for IHD had definitively answered many of the key questions posed in the CER on a large population level; however, they viewed the subsequent priorities differently. The first perspective placed the highest value on understanding heterogeneity of treatment effects so that therapy could move from being based on broad population categories (i.e., patients with IHD) to a more individually tailored approach. From this perspective, understanding differential treatment effects according to baseline demographics, comorbidities, genetics, or concurrent medications represents a logical step toward a more personalized approach to treatment. This perspective is shared by many, and a substantial amount of research in several areas is focused on extending evidence-based medicine to personalized medicine.

The second perspective acknowledges that while traditional research on clinical efficacy or harms may be worthwhile, its value would be small relative to focusing on improving the application of this research to high-risk populations who are likely to benefit from these medications. This perspective recognizes the suboptimal quality of care and unexplained treatment variations and seeks to improve the broader implementation of ACE inhibitors and ARBs to the population likely to benefit. From this health services perspective, stakeholders would place particular value on research to improve evidence-based use, treatment adherence, and cost and utilization of therapy.

The importance of improved evidence-based use of these therapies was specifically highlighted by several members of the stakeholder group in the first conference call. The emphasis on this point could be interpreted two ways. It could be understood as a prioritization of dissemination and implementation of the current research findings which were felt to have answered the key questions with sufficient precision. This interpretation views the value of advancing current knowledge about ACE inhibitors or ARBs as significantly lower than the value of maximizing the fidelity with which current knowledge is implemented; however, it may not necessarily specify the methods by which this is achieved. To some this may be considered a vote against continued research on the comparative effectiveness of ACE inhibitors or ARBs. However, prioritizing greater evidence-based use could alternatively be viewed as a vote for greater funding of the science of implementation. This may include interventions such as prescriber decision support, financial incentives, or other means to promote evidence-based use of ACE inhibitors or ARBs. While we tried to distinguish gaps in implementation from gaps in implementation science with the stakeholder group, we cannot be certain which is most represented in our current prioritization. This issue would be worth exploring in future research prioritization, especially as it is not unique to our content area.

There were likely other underlying perspectives; these were not explicitly discussed during the prioritization process, but became more apparent as the stakeholder discussion

unfolded. An explicit discussion of broader viewpoints may have provided greater transparency for the perspective reflected in this prioritization.

In terms of the prioritization methods used, the investigative team and stakeholder group had several recommendations. Overall, our experience suggests that the results of stakeholder prioritization exercises performed cold (that is, without provision of basic information about the status of current research, etc.), are likely to be unstable and may vary greatly depending on what instrument is used. However, provision and discussion of such data appear to lead to greater consensus and more stable ranking of stakeholder preferences. Specifically, we make the following recommendations:

- The EPC's review of the recently published literature and ongoing studies was performed and shared with stakeholders between Prioritization Exercises 2 and 3. It was widely agreed by stakeholders that this information was very helpful in their understanding of the evidence gaps and importance of future research. We therefore suggest that this step be performed before engagement of the stakeholder group so that results can be shared with them early in the process. Note that depending on when the Future Research Needs report is developed in the CER process, this information may come directly from the CER and therefore not require an additional step
- Several of the stakeholders felt that they had expertise in related fields (cardiovascular trials, medical decisionmaking, patient advocacy) but were not particularly well-qualified in the specific domain of ACE inhibitor and ARB therapy in IHD. Although the breadth of expertise and perspectives in the stakeholder group was intentional, it would have been helpful to the group for the EPC team to provide additional background material and time for the stakeholder group to become familiar with the existing evidence and specific clinical domain. Again, developing the Future Research Needs report as part of the CER process would allow the evidence report to serve as the source of this background material.
- A face-to-face meeting was suggested by both stakeholders and the investigative team. Although such a meeting would have required both time and resources, it would have allowed a more global presentation of the available evidence, the decision analytic model, and, most importantly, an opportunity for the stakeholders to discuss amongst themselves (with the guidance of the EPC team) the reasons for their specific rankings.
- The optimal size of the stakeholder group is unclear. In addition to considerations regarding appropriate representation of all potential stakeholders, the time and resources available for meetings and conference calls, and establishing processes to ensure that all stakeholders have the opportunity to contribute, there are sample size issues raised by using methods such as mean ranking scores—a larger number of rankings might have allowed a greater spread of scores, or sufficient variation in the distribution of scores, to assist in discriminating between different research areas.
- Because the pilot projects were, by necessity, both exploring potential prioritization methods and a specific clinical domain, it is unclear whether specific tools or processes were challenging because of their methodology or because of the specific evidence base (or lack thereof) for the clinical domain. It will therefore be important to look across the entire set of pilot projects for broad themes that can be incorporated into the global EPC program.

Note that we did not explicitly engage our stakeholder group in two components of our study, namely, (1) determination of recommended study design for the identified research areas, and (2) a discussion of the criteria by which the research areas should be ranked. Although both of these steps are important components of ranking future research priorities, the time and interaction available with the stakeholder group was limited. In future prioritization exercises, engagement of the stakeholders in these steps is encouraged.

Conclusions

The Duke EPC used a three-step prioritization process to engage stakeholders in the evaluation of future research needs in the use of ACE inhibitors and ARBs in patients with IHD. The prioritization process combined qualitative surveys of stakeholders and quantitative analysis of research uncertainties. Through this cumulative process we determined that six research areas were consistently ranked highly and deemed most important. These research areas, and our recommended study designs for these future projects, are:

- Strategies to enhance greater evidence-based use of ACE inhibitors/ARBs
    - Recommended study design: Analysis of existing observational data (note that evidence from other clinical domains may be appropriate here, since there is no reason to suspect that the barriers to evidence-based use of ACE inhibitors/ARBs are unique to these drugs or specific patient populations)
    - Note that although ranked as top priority consistently by our stakeholder group, this research area is outside the scope of the original CER report.
- The impact of ACE inhibitor/ARB adherence (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
    - Recommended study design: New observational study
- Impact of comorbidities (such as hypertension, 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 inhibitor/ARB effectiveness or harms in patients with stable IHD
    - Recommended study design: Meta-analysis of RCTs (patient-level analysis would be particularly useful)
- The impact of ACE inhibitor/ARB in patients with stable IHD on patient quality of life
    - Recommended study design: Incorporation of quality-of-life metrics into new RCT or observational studies
- Impact of demographic differences (such as age, race, sex) on ACE inhibitor/ARB effectiveness or harms in patients with stable IHD
    - Recommended study design: Analysis of existing observational data, or if patient-level data from existing RCTs are available, a meta-analysis of these data would allow exploration of heterogeneity in treatment effects
- The impact of ACE inhibitor/ARB in patients with stable IHD on incidence of new diagnoses (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
    - Recommended study design: Meta-analysis of RCTs (patient-level analysis would be particularly useful)
    - Note that although consistently highly ranked by our stakeholder group, this research area is outside the scope of the original CER report.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):e21-181.
2. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med 1995;332(2):80-85.
3. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333(25):1670-1676.
4. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273(18):1450-1456.
5. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355(9215):1582-1587.
6. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667-1675.
7. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362(9386):759-766.
8. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362(9386):767-771.
9. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349(20):1893-1906.
10. Coleman CI, Baker WL, Kluger J, et al. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. October 2009. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 7, 2010.
11. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med 2009;151(12):861-871.
12. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358(15):1547-1559.
13. Matchar DB, McCrory DC, Orlando LA, et al. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension. Comparative Effectiveness Review No. 10. (Prepared by Duke Evidence-based Practice Center under Contract No. 290-02-0025.) Rockville, MD: Agency for Healthcare Research and Quality. November 2007. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 10, 2010.
14. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med 2008;148(1):16-29.
15. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007;147(4):224-233.
16. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372(9644):1174-1183.

17. Major outcommes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertenisve and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT) . JAMA 2002;288(23):2981-2997.
18. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358(9287):1033-41
19. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362(9386):782-788.
20. McMurray JJ, Holman RR, Haffner SM, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362(16):1477-1490.

Abbreviations

ACE	Angiotensin-converting enzyme
ACEI(s)	Angiotensin-converting enzyme inhibitor(s) [used in tables only]
AHRQ	Agency for Healthcare Research and Quality
ARB(s)	Angiotensin II receptor blocker(s)/antagonist(s)
CER	Comparative Effectiveness Review
CHF	Congestive heart failure
CPT	*Current Procedural Terminology*
CVA	Cerebrovascular accident
EPC	Evidence-based Practice Centers
ICD-9	*International Classification of Diseases, Ninth Revision*
IHD	Ischemic heart disease
ITT	Intention-to-treat
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
PICO	Population, interventions, comparators of interest, and outcomes
PICOTS	Population, interventions, comparators of interest, outcomes, timing, and settings
QOL	Quality of life
RCT	Randomized controlled trial

Appendix A. Exact Search Strategies

We ran three separate searches of electronic databases to identify ongoing and recently published studies potentially relevant to the evidence gaps identified in this report:

(1) A search of ClinicalTrials.gov for ongoing studies.
(2) An update of the PubMed® search used in the Comparative Effectiveness Review (CER) on "Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease."[1]
(3) A search of PubMed for systematic reviews and meta-analyses.

Exact search strings used in the three searches are given below.

Search of ClinicalTrials.gov (last search date September 2, 2010)

(Ischemic Heart Disease OR coronary Artery Disease OR Diabetes OR Chronic Kidney Disease OR Peripheral Artery Disease) [DISEASE] AND (ACEI OR ACE-I OR ARB OR Angiotensin) [TREATMENT] AND ("Adult" OR "Senior") [AGE-GROUP]

Update of PubMed Search Used in CER on "Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease" (last search date August 23, 2010)

((coronary artery disease[mesh] OR coronary disease[mesh] OR myocardial ischemia[mesh] OR angina pectoris[mesh] OR angina, unstable[mesh] OR arterial occlusive diseases[mesh] OR peripheral vascular diseases[mesh] OR vascular diseases[mesh] OR atherosclerosis[mesh] OR cardiovascular diseases[mesh] OR carotid artery diseases[mesh]) OR ("preserved left" OR "stable CAD" OR "stable chd" OR "stable coronary" OR "preserved coronary" OR "preserved systolic" OR "preserved ventricular" OR "preserved lvef" OR "preserved ef" OR "preserved ejection" OR "intact left" OR "intact systolic" OR "intact ventricular" OR "intact lvef" OR "intact ef" OR "normal systolic" OR "intact ventricular" OR "intact lvef" OR "intact ef" OR "normal systolic" OR "normal ventricular" OR "normal lvef" OR "normal ef")) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh] OR randomly[tiab] OR trial[ti]) AND humans[mesh]) AND (alacepril OR benazepril OR captopril OR ceronapril OR cilazapril OR delapril OR enalapril OR fosinopril OR imidapril OR libenzapril OR lisinopril OR moexipril OR moveltipril OR pentopril OR perindopril OR quinapril OR ramipril OR spirapril OR temocapril OR teprotide OR trandolapril OR zofenopril OR losartan OR olmesartan OR telmisartan OR valsartan OR eprosartan OR candesartan OR tasosartan OR irbesartan OR angiotensin-converting enzyme inhibitors[mesh] OR angiotensin II type 1 receptor blockers[mesh] OR ACEI OR ARB) AND (("2009/07/01"[PDat] : "3000"[PDat])) AND English[lang]

Search of PubMed for systematic reviews and meta-analyses (last search date August 31, 2010)

(((coronary artery disease[mesh] OR coronary disease[mesh] OR myocardial ischemia[mesh] OR angina pectoris[mesh] OR angina, unstable[mesh] OR arterial occlusive diseases[mesh] OR peripheral vascular diseases[mesh] OR vascular diseases[mesh] OR atherosclerosis[mesh] OR cardiovascular diseases[mesh] OR carotid artery diseases[mesh]) OR ("preserved left" OR "stable CAD" OR "stable chd" OR "stable coronary" OR "preserved coronary" OR "preserved systolic" OR "preserved ventricular" OR "preserved lvef" OR "preserved ef" OR "preserved ejection" OR "intact left" OR "intact systolic" OR "intact ventricular" OR "intact lvef" OR "intact ef" OR "normal systolic" OR "intact ventricular" OR "intact lvef" OR "intact ef" OR "normal systolic" OR "normal ventricular" OR "normal lvef" OR "normal ef")) AND (alacepril OR benazepril OR captopril OR ceronapril OR cilazapril OR delapril OR enalapril OR fosinopril OR imidapril OR libenzapril OR lisinopril OR moexipril OR moveltipril OR pentopril OR perindopril OR quinapril OR ramipril OR spirapril OR temocapril OR teprotide OR trandolapril OR zofenopril OR losartan OR olmesartan OR telmisartan OR valsartan OR eprosartan OR candesartan OR tasosartan OR irbesartan OR angiotensin-converting enzyme inhibitors[mesh] OR angiotensin II type 1 receptor blockers[mesh] OR ACEI OR ARB) AND (("2009/07/01"[PDat] : "3000"[PDat])) AND English[lang]) AND (review[pt] OR "meta-analysis"[pt] OR meta-analysis OR meta-analy* OR metaanaly* OR metanaly* OR review OR (overview AND systematic) OR (review AND systematic))

Reference

1. Coleman CI, Baker WL, Kluger J, et al. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. October 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 7, 2010.

Appendix B. Prioritization Tools

The material presented below represents the tools used in each of three prioritization exercises conducted with the stakeholder group.

Prioritization Exercise 1

The following survey was administered to stakeholders electronically on July 19, 2010, using SurveyMonkey™ software. In this survey, stakeholders were asked to use a 5-point Likert scale to rate the importance of further research in the areas of the 16 identified research gaps. Possible responses ranged from "Not at all important" to "Very important." A free text field was offered to allow stakeholders to enter additional research areas for consideration. Stakeholders were also asked to rank their top five research priorities from the complete list of options, including any additional considerations entered into the free text field.

Page #1

1. Participant Information

1. Please provide your name

Name:

Page #2

2. Patient/Population Subgroup Differences

2. With respect to impact on modulating ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease, to what extent do the following patient/population characteristics warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Demographic differences (such as age, race, gender)	○	○	○	○	○
Co-morbidities (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial	○	○	○	○	○

disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease)					
Concurrent medications (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives)					
Genetic differences (such as ACE or Angiotensin II receptor gene polymorphisms)					

Page #3

3. Medication Characteristics

3. With respect to impact on modulating ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease, to what extent do the following ACE-I/ARB characteristics warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Dose-response (impact of medication dose or dosing interval)					
Class effect (impact of differences between specific agents within each class)					
Benefit relative to alternative					

medication classes (calcium channel blocker, diuretic, or beta-blocker)					

Page #4

4. Health Care Delivery

4. With respect to impact on modulating ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease, to what extent do the following issues warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Adherence (including differential adherence within and between medication classes)	○	○	○	○	○
Strategies to enhance greater evidence-based use of ACE-I/ARBs	○	○	○	○	○

Page #5

5. Outcomes/Adverse Effects

5. With respect to impact on choice of ACE-I/ARB in patients with stable ischemic heart disease, to what extent do the following outcomes warrant further research?

Please indicate your rating of each characteristic below.

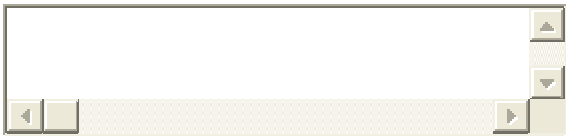
	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Cardiovascular outcomes (such as	○	○	○	○	○

cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)					
Incidence of new diagnoses (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)	○	○	○	○	○
Progression of renal insufficiency or development of dialysis dependence	○	○	○	○	○
Development of angioedema	○	○	○	○	○
Development of nonangioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	○	○	○	○	○
Patient quality of life	○	○	○	○	○
Utilization and cost of therapy	○	○	○	○	○

6. If there are other outcomes or adverse effects that in your opinion should be considered in Question #5 above, please list them here and include your rating of each outcome or adverse effect using the following

scale:

1 - Not at all important
2 - Somewhat unimportant
3 - Neutral
4 - Somewhat important
5 - Very important



Page #6

6. Ranking of Top Selections

7. Please list your top 5 selections for further research from the options presented in previous questions (including question #6) in order from #1 to #5. In your ranking, consider #1 to be the most important. The options from previous questions are reproduced below.

	1 - Most Important	2	3	4	5
Demographic differences (such as age, race, gender)	○	○	○	○	○
Co-morbidities (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease)	○	○	○	○	○
Concurrent medications (such as anti-platelet	○	○	○	○	○

agents, lipid lowering medications, other anti-hypertensives)					
Genetic differences (such as ACE or Angiotensin II receptor gene polymorphisms)	○	○	○	○	○
Dose-response (impact of medication dose or dosing interval)	○	○	○	○	○
Class effect (impact of differences between specific agents within each class)	○	○	○	○	○
Benefit relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker)	○	○	○	○	○
Adherence (including differential adherence within and between medication classes)	○	○	○	○	○
Strategies to enhance greater evidence-based use of ACE-I/ARBs	○	○	○	○	○
Cardiovascular outcomes (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure	○	○	○	○	○

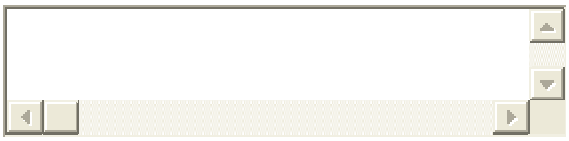
control, measures of atherosclerosis, etc.)					
Incidence of new diagnoses (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)					
Progression of renal insufficiency or development of dialysis dependence					
Development of angioedema					
Development of nonangioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)					
Patient quality of life					
Utilization and cost of therapy					
Other outcomes or adverse effects (specify from your response to question #6)					

If Other was selected above, specify the selection here.

Page #7

7. Additional Comments

8. Please use the space below to add any additional comments you would like to share as part of this survey or for discussion during the Stakeholder teleconference on 22Jul2010.



Page #8

8. Thank You

Thank you for your time in completing this survey -- we will be discussing the responses with the group during our next Stakeholder teleconference on July 22nd at 2pm ET.

We look forward to your continued participation in this project.

Prioritization Exercise 2

The following qualitative prioritization exercise was conducted with stakeholders on July 28, 2010. In this exercise, stakeholders were provided with a PDF document including the results of Prioritization Exercise 1 and a list of priority setting criteria that could be used when considering the appropriate priority for the research questions. Summary tables describing the evidence base regarding the comparative effectiveness of ACE inhibitor and ARB therapy in patients with IHD[1-2] or hypertension[3-4] were also distributed to the group. Stakeholders were asked to prioritize each research area in order from 1 to 16.

References

1. Coleman CI, Baker WL, Kluger J, et al. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. October 2009. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 7, 2010.
2. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med 2009;151(12):861-871.
3. Matchar DB, McCrory DC, Orlando LA, et al. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension. Comparative Effectiveness Review No. 10. (Prepared by Duke Evidence-based Practice Center under Contract No. 290-02-0025.) Rockville, MD: Agency for Healthcare Research and Quality. November 2007. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 10, 2010.
4. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med 2008;148(1):16-29.

1) Please consider the information provided with respect to the following hypothetical scenario:

You have been asked to serve on a national advisory panel for an organization interested in funding research on the comparative effectiveness of ACEIs or ARBs for patients with ischemic heart disease.

The organization has a limited research budget and has tasked you with prioritizing the ***most important areas for future research.*** *You are to use your own judgment based on your knowledge and experience as to which topics would have the greatest impact on patient outcomes.*

Please rank the following 16 areas of future research from 1 to 16, with 1 indicating the highest priority, and 16 the lowest priority.

Research Area	**Ranking (1 = Most Important, 16 = Least Important)**
Impact of demographic differences (such as age, race, gender) on ACEI/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)	
Impact of co-morbidities (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease) on ACEI/ARB effectiveness or harms in patients with stable IHD	
Impact of concurrent medications (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	
Impact of genetic differences (such as ACE or Angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	
Impact of the dose response (impact of medication dose or dosing interval) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	
Impact of class effect (impact of differences between specific agents within each class) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	

Research Area	Ranking (1 = Most Important, 16 = Least Important)
The benefit of ACEI/ARBs relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	
The impact of ACEI/ARB adherence (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	
Strategies to enhance greater evidence-based use of ACEI/ARBs	
The impact of ACEI/ARB in patients with stable IHD on cardiovascular outcomes (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	
The impact of ACEI/ARB in patients with stable IHD on incidence of new diagnoses (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)	
The impact of ACEI/ARB in patients with stable IHD on progression of renal insufficiency or development of dialysis dependence	
The impact of ACEI/ARB in patients with stable IHD on development of angioedema	
The impact of ACEI/ARB in patients with stable IHD on development of nonangioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	
The impact of ACEI/ARB in patients with stable IHD on patient quality of life	
The impact of ACEI/ARB in patients with stable IHD on utilization and cost of therapy	

2) List of potential priority setting criteria that may be used when considering the appropriate priority for the research questions*

1. Disease burden
   The proposed research will reduce disease burden (Prevalence, mortality, morbidity) on afflicted individuals and their families, caretakers, and communities.

2. Cost
   The proposed research has potential to lead to substantial cost efficiencies or cost savings for patients, health plans, or public health programs, through reduction of unnecessary or excessive costs.

3. Variation in care
   The proposed research will reduce unexplained variations (overuse, underuse, misuse) in prevention, diagnosis, access, and/or treatment protocols.

4. Appropriateness
   The proposed research involves a healthcare drug, intervention, device, or technology available (or soon to be available) in the US and is relevant to Section 1013 enrollees (Medicare, Medicaid, SCHIP, other federal healthcare programs)

5. Information gaps and duplication
   The proposed research will fill substantial gaps in the current body of evidence, and there is no other research planned or in progress that will answer the research question, thereby contributing to reduced clinical uncertainties, changes in use and/or coverage of a technology or set of technologies (i.e., improvability of evidence or value of information).

6. Gaps in translation
   The proposed research is likely to improve translation of research findings or existing recommendations into clinical practice or identify improved strategies for research translation.

*Reference: Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: Institute of Medicine, 2009.

3) For information only

The results of the initial ranking of these priorities by the stakeholder group using:

(a) The Likert scale

Comorbidities subgroups
Progression of renal insufficiency or development of dialysis dependence
Utilization and cost of therapy
Demographic differences
Concurrent medications
Benefit relative to alternative medication classes
Strategies to enhance greater evidence-based use
Cardiovascular outcomes
Incidence of new diagnoses
Genetic differences
Adherence
Patient quality of life
Dose-response
Class effect
Development of nonangioedema adverse effects
Development of angioedema

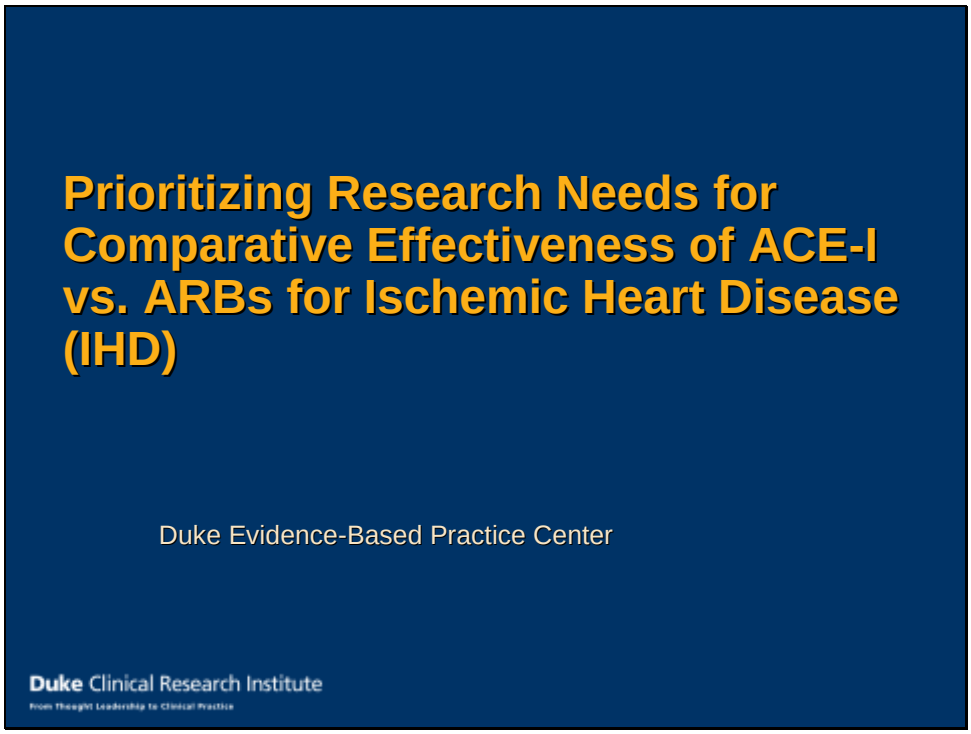
(b) Top 5 ranking

Cardiovascular outcomes
Incidence of new diagnoses
Benefit relative to alternative medication classes
Strategies to enhance greater evidence-based use
Demographic differences
Adherence
Patient quality of life
Comorbidities
Class effect
Genetic differences
Utilization and cost of therapy
Concurrent medications
Progression of renal insufficiency or development of dialysis dependence
Dose-response
Development of angioedema
Development of nonangioedema adverse effects

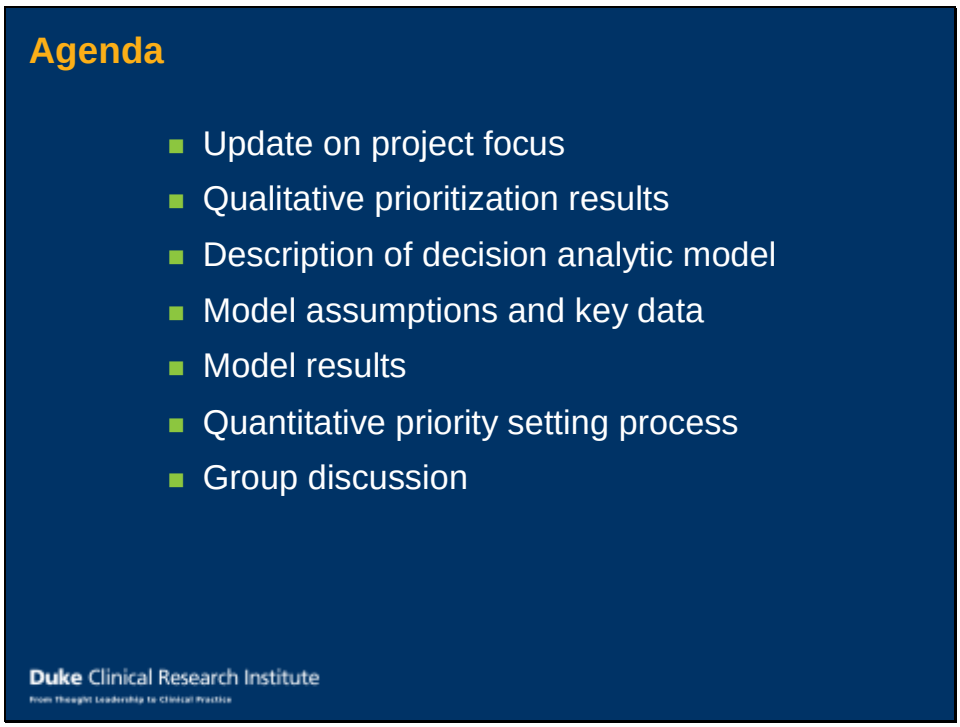
Prioritization Exercise 3

The following PowerPoint slideshow was presented during a conference call held with stakeholders on September 3, 2010. During this call, the group discussed the results of Prioritization Exercise 2, findings from the Duke EPC's search of recently published literature and ongoing trials, findings from the decision analytic model analysis, and potential changes to the existing ranking based on the body of newly available information.

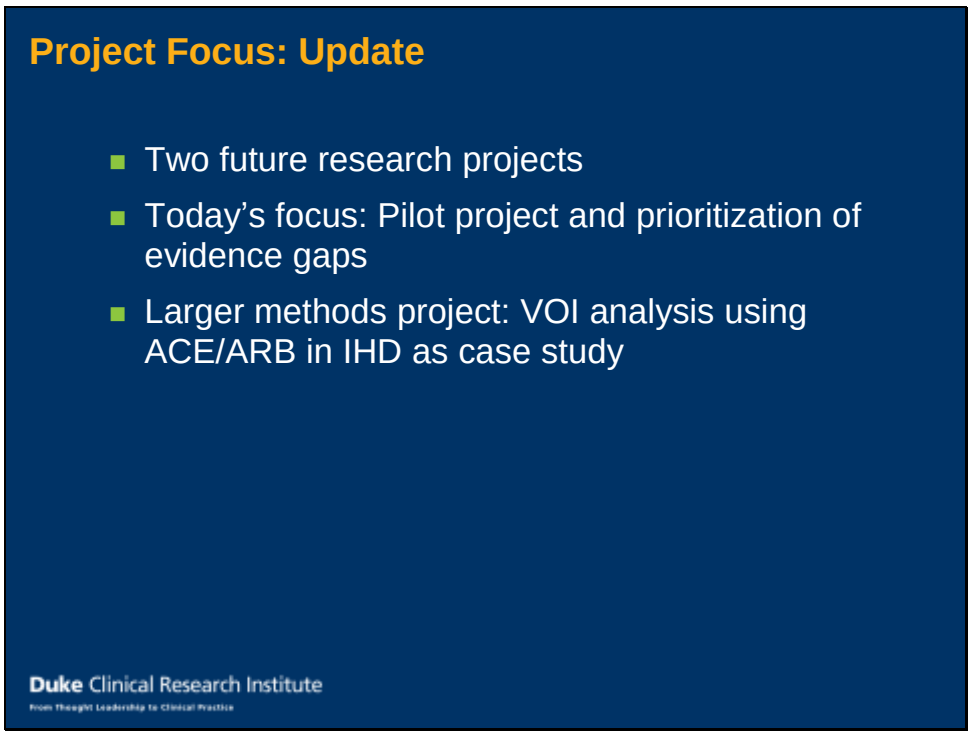
Slide 1



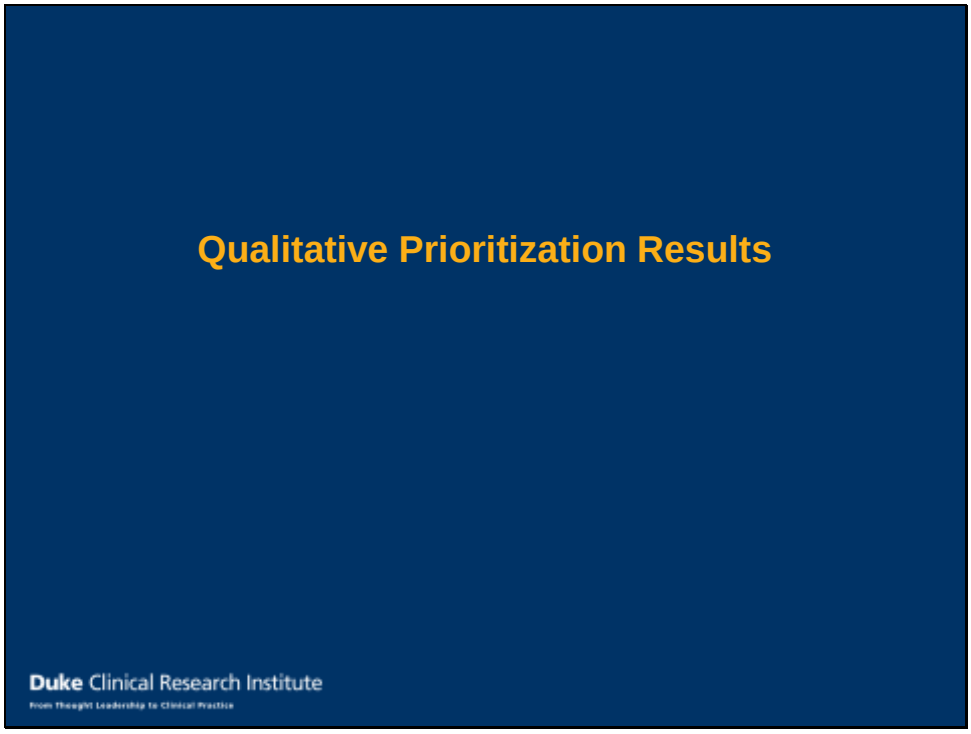
Slide 2



Slide 3



Slide 4



Slide 5

#	RESEARCH AREA
1	Strategies to enhance greater **evidence-based use** of ACE-I/ARBs
2	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)
3	Impact of **co-morbidities** on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, gender) on ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)
6	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
7	The benefit of ACE-I/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes**
9	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost** of therapy
10	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
11	Impact of **concurrent medications** (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
12	Impact of **genetic differences** (such as ACE or Angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
13	Impact of **class effect** (impact of differences between specific agents within each class) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**

Slide 6

Prioritization Descriptive Statistics

	Evidence-based use	New diagnoses	Co-morbidities	Quality of life	Demographic differences	Adherence	Alternative medication	Cardiovascular outcomes	Utilization and cost	Renal insufficiency	Concurrent medications	Genetic differences	Class effect	Dose response	Non-angioedema adverse effects	Angioedema
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Average	5.8	5.9	6.3	6.8	6.9	6.9	7.6	7.6	8.4	8.5	9.0	9.9	10.5	11.4	11.6	13.1
Minimum	1	2	1	3	4	1	2	1	3	2	4	3	1	8	4	6
Maximum	16	15	12	13	12	15	13	16	15	14	12	16	16	15	16	16
StDev	6.5	4.5	4.0	3.3	2.5	5.2	3.3	6.3	4.7	4.7	2.6	4.7	4.8	2.5	3.9	3.5
Variance	42.2	20.7	15.6	10.8	6.4	27.3	11.1	40.0	22.3	22.0	6.9	21.8	22.6	6.3	14.8	12.1
Median	3	4	5	6	7	6.5	7.5	6.5	8	9.5	9.5	11	12	11	13	14.5
1st Quart	1.0	2.8	3.8	4.8	5.5	2.0	6.0	1.8	4.5	4.5	7.8	7.0	8.5	9.8	9.8	12.3
3rd Quart	7.8	8.3	9.5	7.8	7.3	10.0	8.8	13.5	12.3	11.8	11.0	12.0	13.3	13.3	14.0	15.3

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 7

Ongoing/New Studies of Evidence Gaps?

#	RESEARCH AREA	Ongoing Trials	New Published Studies
1	Evidence-based use	1	2
2	New diagnoses	5	8
3	Co-morbidities	1	7
4	Quality of life	0	3
5	Demographic differences	0	2
6	Adherence	1	1
7	Alternative medication	5	3
8	Cardiovascular outcomes	7	18
9	Utilization and cost	1	1
10	Renal insufficiency	12	7
11	Concurrent medications	2	1
12	Genetic differences	1	3
13	Class effect	1	4
14	Dose response	0	2
15	Non-angioedema adverse effects	4	2
16	Angioedema	0	1

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

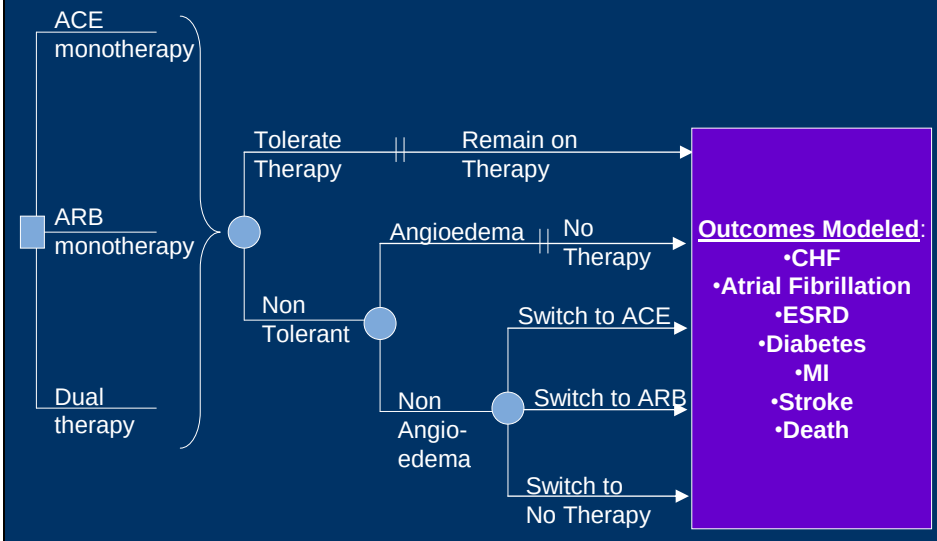
Slide 8

Decision Analytic Framework for Research Prioritization

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 9

Model Schematic



Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 10

Key Model Assumptions

- Assume all therapies are equally effective in reducing MI, stroke, ESRD, diabetes, atrial fibrillation, and development of CHF compared to standard medical therapy
- No difference in BP for any health state (many paths to BP lowering)
- Class effect for all ACE-I and ARBs
- Intolerance to one class (ACE-I or ARB) results in switching therapies
- Angioedema with either class disqualifies a patient from switching to the other class

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 11

Key Data Estimates

- Risk reduction of ACE/ARB compared with standard medical therapy
  - MI = 0.83
  - Stroke = 0.79
  - ESRD = 0.75
  - Diabetes = 0.90
  - CHF = 0.85
- Non tolerance (first year)
  - ACE = 7.8%
  - ARB = 6.1%
  - Dual therapy = 14.5%
- Angiodema risk (first month)
  - ACE = 0.062%
  - ARB = 0.008%
  - Dual therapy = 0.062%

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 12

PRELIMINARY Results

Strategy	Cost, $	Incr Cost, $	LY	Incr LY	ICER, $/LY	QALY	Incr QALY	ICER, $/QALY
ACE	1721		17.985			16.747		
ARB	1998	277	17.990	.0049	56,198	16.752	0.0054	51,456
Dual	2726	728	17.966	(0.023)	Dominated	16.727	(0.025)	Dominated

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

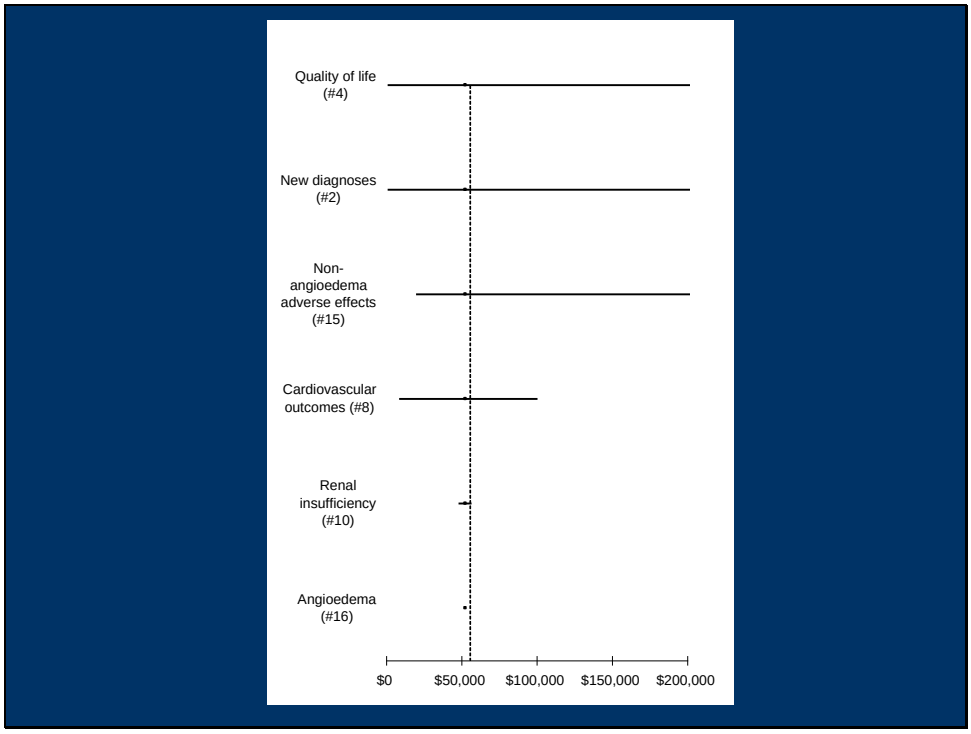
Slide 13

Impact of Evidence Gaps?

- How sensitive are our findings to uncertainty in the evidence?
- Initial modeling exploring impact of uncertainty of
  - New diagnoses
  - Quality of life
  - Cardiovascular outcomes
  - Renal insufficiency
  - Non-angioedema adverse events
  - Angioedema

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 14



Slide 15

Next Steps: Value of Information Analysis

- Include distributions for model parameters
- Model will give distributions of results
- Allows quantification of uncertainty
- Can then (formally) identify relative importance of different sources of uncertainty
- Value of information
  - Expected value of perfect information (reduce all uncertainty)
  - Expected value of partial perfect information (reduce particular sources of information)

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 16

Slide 17

#	RESEARCH AREA
1	Strategies to enhance greater **evidence-based use** of ACE-I/ARBs
2	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)
3	Impact of **co-morbidities** on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, gender) on ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)
6	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
7	The benefit of ACE-I/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes**
9	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost** of therapy
10	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
11	Impact of **concurrent medications** (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
12	Impact of **genetic differences** (such as ACE or Angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
13	Impact of **class effect** (impact of differences between specific agents within each class) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**

The following prioritization exercise was conducted with stakeholders on September 7, 2010. In this final survey, stakeholders were provided with a Word document including 1) the qualitative rankings as established in Prioritization Exercise 2 and 2) summaries of the recently published literature and ongoing trials that might inform each research area. Stakeholders were asked to consider these findings and then complete a final ranking of the research areas, again assigning priorities from 1 to 16.

Prioritized Future Research Needs for Comparative Effectiveness of ACEI vs. ARBs for Ischemic Heart Disease:

Summary of Recently Published Research and Active Clinical Trials

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
1	**Research Need:** Strategies to enhance greater **evidence-based use** of ACEI/ARBs **Recently Published Research:** none **Active Clinical Trials:** (1) Clinical trial of copayment reduction/elimination for post MI therapy **(**Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).)	
2	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function) **Recently Published Research:** (1) Comparison of Afib incidence in ALLHAT (lisinopril vs. chlorthalidone vs. amlodipine). No difference in incidence between different classes of medication. J Am Coll Cardiol, 2009; 54(22):2023-31 (2) Effect of valsartan vs. placebo in 9306 pts with impaired fasting glucose on the incidence of diabetes and cardiovascular events. 14% risk reduction for incident diabetes; no effect on CV outcomes. N Engl J Med, 2010; 362(16):1477-90 (3) Small trial of 26 pts on perindopril vs. placebo on outcome of LV structure and function measured by Doppler tissue echocardiography. Found slightly improved LV systolic/diastolic performance on perindopril J Cardiovasc Med (Hagerstown), 2009; 10(10):781-6 (4) Olmesartan vs. Irbesartan vs. telmisartan effects on glucose metabolism in 151 patients with hypertension and impaired fasting glucose. Found less insulin resistence in telmisartan group compared to other two. Clin Ther, 2010; 32(3):492-505 (5) Meta-analysis of 23 trials evaluating ACEI or ARB for prevention of AFib. Overall found odds ratio for afib reduced 33%, but significant heterogeneity between trials. J Am Coll Cardiol, 2010; 55(21):2299-307 (6) Evaluation of ramipril, telmisartan, both, or placebo on development of left ventricular hypertrophy or regression of LVH in patients with this at baseline (subanalysis from Ontarget/Transcend). Less incident LVH and greater LVH regression in telmisartan group compared to placebo. No benefit of dual therapy compared to either alone. Circulation, 2009; 120(14):1380-9 **Active Clinical Trials:** (1) Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Small mechanistic study looking at glucose metabolism. ClinicalTrials.gov	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	(ID:NCT00574834). (2) Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). Evaluates new diagnosis of Afib and DM as secondary outcomes. ClinicalTrials.gov (ID:NCT00149227). (3) Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). New dx of Diabetes is secondary outcome. ClinicalTrials.gov (ID:NCT00863980). (4) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233). (5) Prevention of Diabetes and Hypertension (PHIDIAS). Randomize ~6000 pts to different medication and diet interventions (including ACEI and ARB arms) to prevent development of hypertension or diabetes. ClinicalTrials.gov (ID:NCT00456963).	
3	**Research Need:** Impact of **co-morbidities** (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease) on ACEI/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Subgroup analysis of ONTARGET/TRANSCEND (ramipril, telmisartan, or both) looking at outcomes in patients with or without erectile dysfunction. Found ED predicted CV events, but no interaction between treatment effect and ED. Circulation, 2010; 121(12):1439-46 (2) Subgroup analysis of Survival of MI Long Term Eval study (zofenopril vs. placebo in 1400 pts) comparing RR with ACEI for patients with high baseline and low baseline cholesterol. Possible increased benefit of zofenopril in patients with higher baseline cholesterol. Fundam Clin Pharmacol, 2009; 23(5):641-8 (3) In patients with impaired glucose tolerance trial of valsartan vs. placebo for new onset DM or cardiovascular outcomes (n=9300pts). No difference in CV events. N Engl J Med, 2010; 362(16):1477-90 (4) Subgroup analysis of PROGRESS (perindopril vs. placebo) examining interaction between treatment effect and BMI. Found comparable risk reduction across entire range of BMIs. Hypertension, 2010; 55(5):1193-8 **Active Clinical Trials:** (1) Angiotensin Converting Enzyme (ACE) Inhibition and Peripheral Arterial Disease. Ramipril vs. placebo in ~264 pts with PAD. ClinicalTrials.gov (ID:NCT00681226)	
4	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on patient **quality of life** **Recently Published Research:** none **Active Clinical Trials:** none	
5	**Research Need:** Impact of **demographic differences** (such as age, race, gender) on ACEI/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	Recently Published Research: (1) Subgroup analysis of PROGRESS study (perindopril vs. placebo in ~ 6100 pts) comparing effects between Asian and Western participants . Found possible greater RRR in Asian participants compared to Western. J Hypertens, 2010; 28(2):395-400 **Active Clinical Trials:** none	
6	**Research Need:** The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD **Recently Published Research:** none **Active Clinical Trials:** (1) Clinical trial of copayment reduction/elimination for post MI therapy **(**Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).)	
7	**Research Need:** The benefit of ACEI/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Renal effects of aliskiren compared with and in combination with irbesartan in 26 patients with type 2 diabetes, hypertension, and albuminuria. Found similar albuminuria reduction with aliskiren and irbesartan. Diabetes Care, 2009; 32(10):1873-9 (2) Cost-utility analysis of ARB compared to ACEI in primary prevention and nitrendipine (CCB) in secondary prevention in Europe--the HEALTH model. Found eprosartan to be cost effective compared to ACEI (~25,000Euro/Qualy) and CCB (~9300Euro/Qualy) Value Health, 2009; 12(6):857-71 **Active Clinical Trials:** (1) Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Comparison of ramipril and hctz in approx 48 pts. ClinicalTrials.gov (ID:NCT00574834) (2) Aliskiren Versus Ramipril on Antiproteinuric Effect in Hypertensive, Type 2 Diabetic Patients With Microalbuminuria. Approx 120 total patients. ClinicalTrials.gov (ID:NCT01038895). (3) Rationale and Design for Shiga Microalbuminuria Reduction Trial. Valsartan vs. amlodipine in approx 160 pts. ClinicalTrials.gov (ID:NCT00202618). (4) A Study on Ca Blocker Versus AII Antagonists in Hypertension With Type 2 Diabetes. Approx 300pts included. ClinicalTrials.gov (ID:NCT00144144). (5) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. Approx 1150 enrolled. ClinicalTrials.gov (ID:NCT00129233).	
8	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	atherosclerosis, etc.) **Recently Published Research:** (1) Subgroup analysis of PROGRESS study (perindopril vs. placebo) comparing effects between Asian and Western participants. Found 20%RRR for composite of vascular events in Western pts; 38% RRR in Asian participants. J Hypertens, 2010; 28(2):395-400 (2) Subgroup analysis of EUROPA study (perindopril vs. placebo) looking at CV outcomes in patients already on calcium channel blocker. Addition of perindopril to CCB reduced total mortality by 46% compared to CCB alone. Am Heart J, 2010; 159(5):795-802 (3) Subgroup analysis of ONTARGET/TRANSCEND (ramipril, telmisartan, or both) looking at outcomes in patients with or without erectile dysfunction. Found similar results in patients with or without ED. Circulation, 2010; 121(12):1439-1446 (4) Subgroup analysis of Survival of MI Long Term Eval study (zofenopril vs. placebo) comparing RR with ACEI for patients with high baseline and low baseline cholesterol. In 6-week outcomes, found zofenopril provided RRR of 43% for death and CHF in high cholesterol pts; 25% RRR in low cholesterol pts. No difference at 1yr. Fundam Clin Pharmacol, 2009; 23(5):641-8 (5) Subgroup analysis of PROGRESS (perindopril vs. placebo) examining interaction between treatment effect and BMI. Perindopril reduced vascular events similarly across BMI range (average RRR ~22%). Hypertension, 2010; 55(5):1193-8 (6) Small trial (86 pts) post-PCI randomized to quinapril or placebo to evaluate impact on in-stent restenosis. Found quinapril reduced in-stend restnosis from 25.6% (placebo) to 9.3% (quinapril). Am J Cardiol, 2010; 105(1):54-8 (7) Trial (n=247pts) comparing olmesartan vs. placebo for coronary atherosclerosis progression as measured by Intravascular ultrasound. Olmesartan reduced total atheroma volume at 14months compared to placebo from 5.4% vs. 0.6%. J Am Coll Cardiol, 2010; 55(10):976-82 (8) Trial of valsartan vs. placebo for new onset DM or cardiovascular outcomes (n=9300pts). No difference in CV events. N Engl J Med, 2010; 362(16):1477-90 (9) Small trial of 26 pts on perindopril vs. placebo on outcome of LV structure and function measured by Doppler tissue echocardiography. Perindopril improved LV systolic/diastolic performance compared to placebo. J Cardiovasc Med (Hagerstown), 2009; 10(10):781-6 (10) Secondary outcome from ONTARGET/TRANSCEND (ramipril, telmisartan, or both) on development of LVH. Less incident LVH and greater LVH regression in telmisartan group compared to placebo. No benefit of dual therapy compared to either alone. Circulation, 2009; 120(14):1380-9 **Active Clinical Trials:** (1) Left Ventricular Function After Acute Myocardial Infarction (AMI). Treatment With Angiotensin 2-Receptor Blockade (GLOBAL-Study). ClinicalTrials.gov (ID:NCT00125645) (2) Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). ClinicalTrials.gov (ID:NCT00149227) (3) Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	Hypertensive Patients (KCPS). ClinicalTrials.gov (ID:NCT00863980). (4) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233). (5) A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov (ID:NCT01075698). (6) Candesartan for Prevention of Cardiovascular Events After Cypher or Taxus Coronary Stenting (4C) Trial. ClinicalTrials.gov (ID:NCT00139386). (7) Prevention of Diabetes and Hypertension (PHIDIAS). ClinicalTrials.gov (ID:NCT00456963).	
9	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy **Recently Published Research:** (1) Cost-effectiveness analysis of ARB monotherapy in patients with HTN (from Netherlands). Modeled cost-effectiveness of 4 ARBs and found olmesartan to be most cost effective option. Am J Cardiovasc Drugs, 2010; 10(1):49-54 (2) Cost-utility analysis of eprosartan vs. enalapril in primary prevention of CVD in Europe. Found eprosartan to be cost effective compared to ACEI (~25,000Euro/Qualy) and CCB (~9300Euro/Qualy) Value Health, 2009; 12(6):857-71 **Active Clinical Trials:** (1) Clinical trial of copayment reduction/elimination for post MI therapy **(**Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).)	
10	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence **Recently Published Research:** (1) Analysis of TRANSCEND (telmisartan vs. placebo in 5927 adults) on outcome of dialysis or doubling of serum creatinine. No difference between two groups, however only 17 patients required dialysis. Ann Intern Med, 2009; 151(1):1-10, W1-2 (2) Cross sectional study of 1119 pts with DM2 evaluating PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria. Report significantly higher risk for developing proteinuria in Pro/Pro homozygotes, with this group benefiting more from early ACEI. Diabetes, 2009; 58(12):2920-9 (3) RCT of 81 patients with diabetes, hypertension, and albuminuria on ACEI. Pts randomized to losartan add on or spironolactone for 48wks. Found that addition of spironlactone to ACE was better than adding ARB to ACE for proteinuria reduction. J Am Soc Nephrol, 2009; 20(12):2641-50 (4) RCT of 26 pts with diabetic nephropathy comparing aliskirin, irbesartan or both. Aliskirin and irbesartan produced similar reductions in proteinuria. The combination of the two agents reduced proteinuria more than monotherapy. Diabetes Care, 2009; 32(10):1873-9 **Active Clinical Trials:** (1) Triple Blockade of the Renin Angiotensin Aldosterone System in Diabetic (Type	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	1&2) Proteinuric Patients. ClinicalTrials.gov (ID:NCT00961207). (2) Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov (ID:NCT00427271). (3) Effectiveness Study on Fosinopril and/or Losartan in Patients With Chronic Kidney Disease Stage 3 (FLIP). ClinicalTrials.gov (ID:NCT00565396). (4) Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov (ID:NCT00630708). (5) NEPHRON-D: Diabetes iN Nephropathy Study. ClinicalTrials.gov (ID:NCT00555217). (6) Rationale and Design for Shiga Microalbuminuria Reduction Trial. ClinicalTrials.gov (ID:NCT00202618). (7) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. Includes evaluation of renal outcomes as secondary endpoint. ClinicalTrials.gov (ID:NCT00129233). (8) A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov (ID:NCT01075698). (9) Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID). ClinicalTrials.gov (ID:NCT00494715). (10) Preventing Microalbuminuria in Type 2 Diabetes (VARIETY). ClinicalTrials.gov (ID:NCT00503152). (11) Effect of Enalapril and Losartan Association Therapy on Proteinuria and Inflammatory Biomarkers in Diabetic Nephropathy: a Clinical Trial on Type 2 Diabetes Mellitus. ClinicalTrials.gov (ID:NCT00419835).	
11	**Research Need:** Impact of **concurrent medications** (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Subgroup analysis of EUROPA study (perindopril vs. placebo) looking at CV outcomes in patients already on calcium channel blocker. Addition of perindopril to CCB reduced total mortality by 46% compared to CCB alone. Am Heart J, 2010; 159(5):795-802 **Active Clinical Trials:** (1) Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov (ID:NCT00427271). (2) Effects of ROSIglitazone on Inflammatory Markers and Adipokines in Diabetic Patients Using an Angiotensin Receptor Blocker (TELmisartan) - The ROSITEL Study. ClinicalTrials.gov (ID:NCT00486187).	
12	**Research Need:** Impact of **genetic differences** (such as ACE or Angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Cross sectional study of 1119 pts with DM2 evaluating PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria. Report significantly higher risk for developing proteinuria in Pro/Pro homozygotes, with this group benefiting more from early ACEI. Diabetes, 2009; 58(12):2920-9	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	(2) Sub analysis of RCT (n=217 pts) of losartan vs. three other htn med. Evaluates CYP2C9 genotype and activity of rennin-angiotensin system. No impact on efficacy of losartan. J Hypertens, 2009; 27(10):2001-9 (3) Sub analysis of LIFE RCT (losartan vs. atenolol) in 3503 high risk pts. Evaluated effect of ACE gene insertion/deletion and 12 other polymorphisms on clinical outcomes and response to treatment in the LIFE study. (none influenced treatment response) Pharmacogenet Genomics, 2010; 20(2):77-85 **Active Clinical Trials:** (1) Association of Angiotensin II Type 1 R Gene Polymorphism and Diabetic Nephropathy in Type 2 Diabetes. ClinicalTrials.gov (ID:NCT01069549)	
13	**Research Need:** Impact of **class effec**t (impact of differences between specific agents within each class) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Telmisartan vs. olmesartan on metabolic parameters in 65 overweight and obese patients with hypertension. Found that Telmisartan may have greater impact than olmesartan on insulin resistence Nutr Hosp, 2010; 25(2):275-9 (2) Telmisartan vs. eprosartan on insulin sensitivity in 50 overweight hypertensive patients. Found that Telmisartan may have greater impact than eprosartan on insulin resistence Horm Metab Res, 2009; 41(12):893-8 (3) Telmisartan vs. losartan vs. candesartan on uric acid levels in 42 hypertensive patients. Found uric acid levels declined in telmisartan, candesartan, but not losartan arms. Arzneimittelforschung, 2010; 60(2):71-5 (4) Olmesartan vs. Irbesartan vs. telmisartan effects on glucose metabolism in 151 patients with hypertension and impaired fasting glucose. Found telmisartan had most favorable effects on insulin resistence. Clin Ther, 2010; 32(3):492-505 **Active Clinical Trials:** (1) Comparison of Effects of Telmisartan and Valsartan on Neointima Volume in Diabetes. ClinicalTrials.gov (ID:NCT00599885)	
14	**Research Need:** Impact of the **dose response** (impact of medication dose or dosing interval) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD **Recently Published Research:** none **Active Clinical Trials:** none	
15	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia) **Recently Published Research:** (1) Short 12wk rct evaluating safety and tolerability of an olmesartan medoxomil-based regimen in 130 patients with stage 1 hypertension. Found no difference between olmesartan and placebo in safety and tolerability. Clin Drug Investig, 2010; 30(7):473-82 **Active Clinical Trials:**	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
	(1) ACEIs and ARBs Treatment in Diabetic Patients -Drug Interactions and Adverse Drug Effects. ClinicalTrials.gov (ID:NCT00437775). (2) Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov (ID:NCT00630708). (3) Prevention of Diabetes and Hypertension (PHIDIAS). Randomize ~6000 pts to different medication and diet interventions (including ACEI and ARB arms); evaluate safety/tolerability as secondary outcomes. ClinicalTrials.gov (ID:NCT00456963).	
16	**Research Need:** The impact of ACEI/ARB in patients with stable IHD on development of **angioedema** **Recently Published Research:** (1) one case control study proposing RR of 4.5 for ACEI angioedema for patients on concurrent vildagliptin Hypertension, 2009; 54(3):516-23) **Active Clinical Trials:** none	

QUESTION: As we discussed on our September 3rd conference call, the EPC program is looking to determine how best to engage Stakeholders to help prioritize future research needs in comparative effectiveness reviews. Please provide in the space below any specific suggestions that you might have for how to make this process successful:

Appendix C. Summary of Ongoing Studies and Recently Published Studies, Systematic Reviews, and Meta-Analyses

RESEARCH AREA, RECENTLY PUBLISHED AND ONGOING STUDIES
Research Need: Strategies to enhance greater **evidence-based use** of ACEIs/ARBs **Recently Published Research:** None **Active Clinical Trials:** Choudhry: Clinical trial of copayment reduction/elimination for post MI therapy (Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov.[1]
Research Need: The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function) **Recently Published Research:** (1) Haywood 2009: Comparison of atrial fibrillation incidence in ALLHAT (lisinopril vs. chlorthalidone vs. amlodipine). No difference in incidence between different classes of medication.[2] (2) McMurray 2010: Effect of valsartan vs. placebo in 9306 patients with impaired fasting glucose on the incidence of diabetes and cardiovascular events. 14% risk reduction for incident diabetes; no effect on CV outcomes.[3] (3) Pela 2009: Small trial of 26 patients on perindopril vs. placebo on outcome of LV structure and function measured by Doppler tissue echocardiography. Found slightly improved LV systolic/diastolic performance on perindopril.[4] (4) Rizos 2010: Olmesartan vs. irbesartan vs. telmisartan effects on glucose metabolism in 151 patients with hypertension and impaired fasting glucose. Found less insulin resistance in telmisartan group compared to other two.[5] (5) Schneider 2010: Meta-analysis of 23 trials evaluating ACEI or ARB for prevention of atrial fibrillation. Overall found odds ratio for atrial fibrillation reduced 33%, but significant heterogeneity between trials.[6] (6) Verdecchia 2009: Evaluation of ramipril, telmisartan, both, or placebo on development of LVH or regression of LVH in patients with this at baseline (subanalysis from ONTARGET/TRANSCEND). Less incident LVH and greater LVH regression in telmisartan group compared to placebo. No benefit of dual therapy compared to either alone.[7] **Active Clinical Trials:** (1) Davis: Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Small mechanistic study looking at glucose metabolism. ClinicalTrials.gov.[8] (2) Matsubara: Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). Evaluates new diagnosis of atrial fibrillation and DM as secondary outcomes. ClinicalTrials.gov.[9] (3) Matsubara: Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). New diagnosis of diabetes is secondary outcome. ClinicalTrials.gov.[10] (4) Murohara: Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov.[11] (5) Zanchetti: Prevention of Diabetes and Hypertension (PHIDIAS). Randomize ~6000 patients to different medication and diet interventions (including ACEI and ARB arms) to prevent development of hypertension or diabetes. ClinicalTrials.gov.[12]
Research Need: Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Bohm 2010: Subgroup analysis of ONTARGET/TRANSCEND (ramipril, telmisartan, or both) looking at outcomes in patients with or without ED. Found ED predicted CV events, but no interaction between treatment effect and ED.[13] (2) Borghi 2009: Subgroup analysis of Survival of MI Long Term Evaluation study (zofenopril vs. placebo in 1400 patients) comparing RR with ACEI for patients with high baseline and low baseline cholesterol. Possible increased benefit of zofenopril in patients with higher baseline cholesterol.[14]

RESEARCH AREA, RECENTLY PUBLISHED AND ONGOING STUDIES
(3) McMurray 2010: In patients with impaired glucose tolerance trial of valsartan vs. placebo for new onset DM or cardiovascular outcomes (n = 9300 patients). No difference in CV events.[3] (4) Czernichow 2010: Subgroup analysis of PROGRESS (perindopril vs. placebo) examining interaction between treatment effect and BMI. Found comparable risk reduction across entire range of BMIs.[15] **Active Clinical Trials:** (1) Kingwell: Angiotensin Converting Enzyme (ACE) Inhibition and Peripheral Arterial Disease. Ramipril vs. placebo in ~264 patients with peripheral arterial disease. ClinicalTrials.gov.[16]
Research Need: The impact of ACEI/ARB in patients with stable IHD on patient **quality of life** **Recently Published Research:** None **Active Clinical Trials:** None
Research Need: Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Arima 2010: Subgroup analysis of PROGRESS study (perindopril vs. placebo in ~ 6100 patients) comparing effects between Asian and Western participants. Found possible greater RRR in Asian participants compared to Western.[17] **Active Clinical Trials:** None
Research Need: The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD **Recently Published Research:** None **Active Clinical Trials:** (1) Choudhry: Clinical trial of copayment reduction/elimination for post MI therapy (Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov.[1]
Research Need: The benefit of ACEI/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Persson 2009: Renal effects of aliskiren compared with and in combination with irbesartan in 26 patients with type 2 diabetes, hypertension, and albuminuria. Found similar albuminuria reduction with aliskiren and irbesartan.[18] (2) Schwander 2009: Cost-utility analysis of ARB compared to ACEI in primary prevention and nitrendipine (CCB) in secondary prevention in Europe—the HEALTH model. Found eprosartan to be cost-effective compared to ACEI (~25,000Euro/Qualy) and CCB (~9300Euro/Qualy).[19] **Active Clinical Trials:** (1) Davis: Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Comparison of ramipril and HCTZ in approximately 48 patients. ClinicalTrials.gov.[8] (2) Fogari: Aliskiren Versus Ramipril on Antiproteinuric Effect in Hypertensive, Type 2 Diabetic Patients With Microalbuminuria. Approximately 120 total patients. ClinicalTrials.gov.[20] (3) Kashiwagi: Rationale and Design for Shiga Microalbuminuria Reduction Trial. Valsartan vs. amlodipine in approximately 160 patients. ClinicalTrials.gov.[21] (4) Kawamori: A Study on Ca Blocker Versus AII Antagonists in Hypertension With Type 2 Diabetes. Approximately 300 patients included. ClinicalTrials.gov.[22] (5) Murohara: Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. Approximately 1150 enrolled. ClinicalTrials.gov.[11]
Research Need: The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)

RESEARCH AREA, RECENTLY PUBLISHED AND ONGOING STUDIES

Recently Published Research:

(1) Arima 2010: Subgroup analysis of PROGRESS study (perindopril vs. placebo) comparing effects between Asian and Western participants. Found 20% RRR for composite of vascular events in Western patients; 38% RRR in Asian participants.[17]
(2) Bertrand 2010: Subgroup analysis of EUROPA study (perindopril vs. placebo) looking at CV outcomes in patients already on CCB. Addition of perindopril to CCB reduced total mortality by 46% compared to CCB alone.[23]
(3) Bohm 2010: Subgroup analysis of ONTARGET/TRANSCEND (ramipril, telmisartan, or both) looking at outcomes in patients with or without ED. Found similar results in patients with or without ED.[13]
(4) Borghi 2009: Subgroup analysis of Survival of MI Long Term Eval study (zofenopril vs. placebo) comparing RR with ACEI for patients with high baseline and low baseline cholesterol. In 6-week outcomes, found zofenopril provided RRR of 43% for death and CHF in high cholesterol patients; 25% RRR in low-cholesterol patients. No difference at 1 year.[14]
(5) Czernichow 2010: Subgroup analysis of PROGRESS (perindopril vs. placebo) examining interaction between treatment effect and BMI. Perindopril reduced vascular events similarly across BMI range (average RRR ~22%).[15]
(6) Deftereos 2010: Small trial (86 patients) post-PCI randomized to quinapril or placebo to evaluate impact on in-stent restenosis. Found quinapril reduced in-stent restenosis from 25.6% (placebo) to 9.3% (quinapril).[24]
(7) Hirohata 2010: Trial (n = 247patients) comparing olmesartan vs. placebo for coronary atherosclerosis progression as measured by intravascular ultrasound. Olmesartan reduced total atheroma volume at 14 months compared to placebo from 5.4% vs. 0.6%.[25]
(8) McMurray 2010: Trial of valsartan vs. placebo for new onset DM or cardiovascular outcomes (n = 9300 patients). No difference in CV events.[3]
(9) Pela 2009: Small trial of 26 patients on perindopril vs. placebo on outcome of LV structure and function measured by Doppler tissue echocardiography. Perindopril improved LV systolic/diastolic performance compared to placebo.[4]
(10) Verdecchia 2009: Secondary outcome from ONTARGET/TRANSCEND (ramipril, telmisartan, or both) on development of LVH. Less incident LVH and greater LVH regression in telmisartan group compared to placebo. No benefit of dual therapy compared to either alone.[7]

Active Clinical Trials:

(1) Egstrup: Left Ventricular Function After Acute Myocardial Infarction (AMI). Treatment With Angiotensin 2-Receptor Blockade (GLOBAL-Study). ClinicalTrials.gov.[26]
(2) Matsubara: Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). ClinicalTrials.gov.[9]
(3) Matsubara: Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). ClinicalTrials.gov.[10]
(4) Murohara: Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov.[11]
(5) Ogawa: A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov.[27]
(6) Sakamoto: Candesartan for Prevention of Cardiovascular Events After Cypher or Taxus Coronary Stenting (4C) Trial. ClinicalTrials.gov.[28]
(7) Zanchetti: Prevention of Diabetes and Hypertension (PHIDIAS). ClinicalTrials.gov.[12]

Research Need: The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy

Recently Published Research:

(1) Boersma 2010: Cost-effectiveness analysis of ARB monotherapy in patients with hypertension (from Netherlands). Modeled cost-effectiveness of 4 ARBs and found olmesartan to be most cost-effective option.[29]
(2) Schwander 2009: Cost-utility analysis of eprosartan vs. enalapril in primary prevention of CVD in Europe. Found eprosartan to be cost-effective compared to ACEI (~25,000Euro/Qualy) and CCB (~9300Euro/Qualy).[19]

Active Clinical Trials:

(1) Choudhry: Clinical trial of copayment reduction/elimination for post MI therapy (Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov.[1]

Research Need: The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence

Recently Published Research:

RESEARCH AREA, RECENTLY PUBLISHED AND ONGOING STUDIES
(1) Mann 2009: Analysis of TRANSCEND (telmisartan vs. placebo in 5927 adults) on outcome of dialysis or doubling of serum creatinine. No difference between two groups; however, only 17 patients required dialysis.[30] (2) De Cosmo 2009: Cross-sectional study of 1119 patients with DM2 evaluating PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria. Report significantly higher risk for developing proteinuria in Pro/Pro homozygotes, with this group benefiting more from early ACEI.[31] (3) Mehdi 2009: RCT of 81 patients with diabetes, hypertension, and albuminuria on ACEI. Patients randomized to losartan add-on or spironolactone for 48 weeks. Found that addition of spironlactone to ACEI was better than adding ARB to ACEI for proteinuria reduction.[32] (4) Persson 2009: RCT of 26 patients with diabetic nephropathy comparing aliskirin, irbesartan or both. Aliskirin and irbesartan produced similar reductions in proteinuria. The combination of the two agents reduced proteinuria more than monotherapy.[18] **Active Clinical Trials:** (1) Antonopoulos: Triple Blockade of the Renin Angiotensin Aldosterone System in Diabetic (Type 1&2) Proteinuric Patients. ClinicalTrials.gov.[33] (2) Camargo: Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov.[34] (3) Chen: Effectiveness Study on Fosinopril and/or Losartan in Patients With Chronic Kidney Disease Stage 3 (FLIP). ClinicalTrials.gov.[35] (4) Fried: NEPHRON-D: Diabetes iN Nephropathy Study. ClinicalTrials.gov.[36] (5) Hou: Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov.[37] (6) Kashiwagi: Rationale and Design for Shiga Microalbuminuria Reduction Trial. ClinicalTrials.gov.[21] (7) Murohara: Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. Includes evaluation of renal outcomes as secondary endpoint. ClinicalTrials.gov.[11] (8) Ogawa: A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov.[27] (9) Remuzzi: Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID). ClinicalTrials.gov.[38] (10) Ruggenenti: Preventing Microalbuminuria in Type 2 Diabetes (VARIETY). ClinicalTrials.gov.[39] (11) Zatz: Effect of Enalapril and Losartan Association Therapy on Proteinuria and Inflammatory Biomarkers in Diabetic Nephropathy: a Clinical Trial on Type 2 Diabetes Mellitus. ClinicalTrials.gov.[40]
Research Need: Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** Bertrand 2010: Subgroup analysis of EUROPA study (perindopril vs. placebo) looking at CV outcomes in patients already on CCB. Addition of perindopril to CCB reduced total mortality by 46% compared to CCB alone.[23] **Active Clinical Trials:** (1) Camargo: Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov.[34] (2) Gupta: Effects of ROSIglitazone on Inflammatory Markers and Adipokines in Diabetic Patients Using an Angiotensin Receptor Blocker (TELmisartan) - The ROSITEL Study. ClinicalTrials.gov.[41]
Research Need: Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on AC-I/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) De Cosmo 2009: Cross-sectional study of 1119 patients with type 2 DM evaluating PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria. Report significantly higher risk for developing proteinuria in Pro/Pro homozygotes, with this group benefiting more from early ACEI.[31] (2) Donner 2009: Sub analysis of RCT (n = 217 patients) of losartan vs. three other antihypertensive medications. Evaluates CYP2C9 genotype and activity of rennin-angiotensin system. No impact on efficacy of losartan.[42] (3) Nordestgaard 2010: Subanalysis of LIFE RCT (losartan vs. atenolol) in 3503 high-risk patients. Evaluated effect of ACE gene insertion/deletion and 12 other polymorphisms on clinical outcomes and response to treatment in the LIFE study. (None influenced treatment response.)[43] **Active Clinical Trials:** (1) Bhansali: Association of Angiotensin II Type 1 R Gene Polymorphism and Diabetic Nephropathy in Type 2 Diabetes. ClinicalTrials.gov.[44]
Research Need: Impact of **class effec**t (impact of differences between specific agents within each class) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD

RESEARCH AREA, RECENTLY PUBLISHED AND ONGOING STUDIES
Recently Published Research: (1) de Luis 2010: Telmisartan vs. olmesartan on metabolic parameters in 65 overweight and obese patients with hypertension. Found that telmisartan may have greater impact than olmesartan on insulin resistance.[45] (2) Fogari 2009: Telmisartan vs. eprosartan on insulin sensitivity in 50 overweight hypertensive patients. Found that telmisartan may have greater impact than eprosartan on insulin resistance.[46] (3) Hamada 2010: Telmisartan vs. losartan vs. candesartan on uric acid levels in 42 hypertensive patients. Found uric acid levels declined in telmisartan, candesartan, but not losartan arms.[47] (4) Rizos 2010: Olmesartan vs. irbesartan vs. telmisartan effects on glucose metabolism in 151 patients with hypertension and impaired fasting glucose. Found telmisartan had most favorable effects on insulin resistance.[5] **Active Clinical Trials:** (1) Lim: Comparison of Effects of Telmisartan and Valsartan on Neointima Volume in Diabetes. ClinicalTrials.gov.[48]
Research Need: Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD **Recently Published Research:** None **Active Clinical Trials:** None
Research Need: The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia) **Recently Published Research:** (1) Chrysant 2010: Short 12-week RCT evaluating safety and tolerability of an olmesartan medoxomil-based regimen in 130 patients with stage 1 hypertension. Found no difference between olmesartan and placebo in safety and tolerability.[49] **Active Clinical Trials:** (1) Golik: ACEIs and ARBs Treatment in Diabetic Patients-Drug Interactions and Adverse Drug Effects. ClinicalTrials.gov.[50] (2) Hou: Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov.[37] (3) Zanchetti: Prevention of Diabetes and Hypertension (PHIDIAS). Randomize ~6000 patients to different medication and diet interventions (including ACEI and ARB arms); evaluate safety/tolerability as secondary outcomes. ClinicalTrials.gov.[12]
Research Need: The impact of ACEI/ARB in patients with stable IHD on development of **angioedema** **Recently Published Research:** (1) Brown 2009: One case-control study proposing RR of 4.5 for ACEI angioedema for patients on concurrent vildagliptin.[51] **Active Clinical Trials:** None

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), BMI = body mass index, CCB = calcium channel blocker, CHF = congestive heart failure, CV = cardiovascular, CVA = cerebrovascular accident, CVD = cardiovascular disease, DM = diabetes mellitus, ED = erectile dysfunction, HCTZ = hydrochlorothiazide, IHD = ischemic heart disease, LV = left ventricular, LVH = left ventricular hypertrophy, MI = myocardial infarction, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, RR = relative risk, RRR = relative risk reduction

References

1. Choudhry N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).
2. Haywood LJ, Ford CE, Crow RS, et al. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). J Am Coll Cardiol 2009;54(22):2023-2031.
3. McMurray JJ, Holman RR, Haffner SM, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362(16):1477-1490.
4. Pela G, Pattoneri P, Passera M, et al. Long-term effects of perindopril on left ventricular structure and function in patients with stable coronary artery disease: a conventional and Doppler tissue echocardiographic pilot study. J Cardiovasc Med (Hagerstown) 2009;10(10):781-786.
5. Rizos CV, Milionis HJ, Kostapanos MS, et al. Effects of rosuvastatin combined with olmesartan, irbesartan, or telmisartan on indices of glucose metabolism in Greek adults with impaired fasting glucose, hypertension, and mixed hyperlipidemia: a 24-week, randomized, open-label, prospective study. Clin Ther 2010;32(3):492-505.
6. Schneider MP, Hua TA, Bohm M, et al. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. J Am Coll Cardiol 2010;55(21):2299-2307.
7. Verdecchia P, Sleight P, Mancia G, et al. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease. Circulation 2009;120(14):1380-1389.
8. Davis S. Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. ClinicalTrials.gov (ID:NCT00574834).
9. Matsubara H. Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). ClinicalTrials.gov (ID:NCT00149227).
10. Matsubara H. Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). ClinicalTrials.gov (ID:NCT00863980).
11. Murohara T. Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233).
12. Zanchetti A. Prevention of Diabetes and Hypertension (PHIDIAS). ClinicalTrials.gov (ID:NCT00456963).
13. Bohm M, Baumhakel M, Teo K, et al. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. Circulation 2010;121(12):1439-1446.
14. Borghi C, Cicero AF, Bacchelli S, et al. Serum cholesterol levels on admission and survival in patients with acute myocardial infarction treated with zofenopril: a post hoc analysis of the Survival of Myocardial Infarction Long-term Evaluation trial. Fundam Clin Pharmacol 2009;23(5):641-648.
15. Czernichow S, Ninomiya T, Huxley R, et al. Impact of blood pressure lowering on cardiovascular outcomes in normal weight, overweight, and obese individuals: the

Perindopril Protection Against Recurrent Stroke Study trial. Hypertension 2010;55(5):1193-1198.
16. Kingwell BA. Angiotensin Converting Enzyme (ACE) Inhibition and Peripheral Arterial Disease. ClinicalTrials.gov (ID:NCT00681226).
17. Arima H, Anderson C, Omae T, et al. Perindopril-based blood pressure lowering reduces major vascular events in Asian and Western participants with cerebrovascular disease: the PROGRESS trial. J Hypertens 2010;28(2):395-400.
18. Persson F, Rossing P, Reinhard H, et al. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. Diabetes Care 2009;32(10):1873-1879.
19. Schwander B, Gradl B, Zollner Y, et al. Cost-utility analysis of eprosartan compared to enalapril in primary prevention and nitrendipine in secondary prevention in Europe—the HEALTH model. Value Health 2009;12(6):857-871.
20. Fogari R. Aliskiren Versus Ramipril on Antiproteinuric Effect in Hypertensive, Type 2 Diabetic Patients With Microalbuminuria. ClinicalTrials.gov (ID:NCT01038895).
21. Kashiwagi A. Rationale and Design for Shiga Microalbuminuria Reduction Trial. ClinicalTrials.gov (ID:NCT00202618).
22. Kawamori R. A Study on Ca Blocker Versus AII Antagonists in Hypertension With Type 2 Diabetes. ClinicalTrials.gov (ID:NCT00144144).
23. Bertrand ME, Ferrari R, Remme WJ, et al. Clinical synergy of perindopril and calcium-channel blocker in the prevention of cardiac events and mortality in patients with coronary artery disease. Post hoc analysis of the EUROPA study. Am Heart J 2010;159(5):795-802.
24. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Effect of quinapril on in-stent restenosis and relation to plasma apoptosis signaling molecules. Am J Cardiol 2010;105(1):54-58.
25. Hirohata A, Yamamoto K, Miyoshi T, et al. Impact of olmesartan on progression of coronary atherosclerosis a serial volumetric intravascular ultrasound analysis from the OLIVUS (impact of OLmesarten on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. J Am Coll Cardiol 2010;55(10):976-982.
26. Egstrup K. Left Ventricular Function After Acute Myocardial Infarction (AMI). Treatment With Angiotensin 2-Receptor Blockade (GLOBAL-Study). ClinicalTrials.gov (ID:NCT00125645).
27. Ogawa H. A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov (ID:NCT01075698).
28. Sakamoto T. Candesartan for Prevention of Cardiovascular Events After Cypher or Taxus Coronary Stenting (4C) Trial. ClinicalTrials.gov (ID:NCT00139386).
29. Boersma C, Voors AA, Visser ST, et al. Cost effectiveness of angiotensin receptor blocker monotherapy in patients with hypertension in the Netherlands: a comparative analysis using clinical trial and drug utilization data. Am J Cardiovasc Drugs 2010;10(1):49-54.
30. Mann JF, Schmieder RE, Dyal L, et al. Effect of telmisartan on renal outcomes: a randomized trial. Ann Intern Med 2009;151(1):1-10, W1-W2.
31. De Cosmo S, Motterlini N, Prudente S, et al. Impact of the PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: evidence from BENEDICT. Diabetes 2009;58(12):2920-2929.

32. Mehdi UF, Adams-Huet B, Raskin P, et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol 2009;20(12):2641-2650.
33. Antonopoulos P. Triple Blockade of the Renin Angiotensin Aldosterone System in Diabetic (Type 1&2) Proteinuric Patients. ClinicalTrials.gov (ID:NCT00961207).
34. Camargo E. Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov (ID:NCT00427271).
35. Chen N. Effectiveness Study on Fosinopril and/or Losartan in Patients With Chronic Kidney Disease Stage 3 (FLIP). ClinicalTrials.gov (ID:NCT00565396).
36. Fried L. VA NEPHRON-D: Diabetes iN Nephropathy Study. ClinicalTrials.gov (ID:NCT00555217).
37. Hou F. Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov (ID:NCT00630708).
38. Remuzzi G. Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID). ClinicalTrials.gov (ID:NCT00494715).
39. Ruggenenti P. Preventing Microalbuminuria in Type 2 Diabetes (VARIETY). ClinicalTrials.gov (ID:NCT00503152).
40. Zatz R. Effect of Enalapril and Losartan Association Therapy on Proteinuria and Inflammatory Biomarkers in Diabetic Nephropathy: a Clinical Trial on Type 2 Diabetes Mellitus. ClinicalTrials.gov (ID:NCT00419835).
41. Gupta M. Effects of ROSIglitazone on Inflammatory Markers and Adipokines in Diabetic Patients Using an Angiotensin Receptor Blocker (TELmisartan)—The ROSITEL Study. ClinicalTrials.gov (ID:NCT00486187).
42. Donner KM, Hiltunen TP, Suonsyrja T, et al. CYP2C9 genotype modifies activity of the renin-angiotensin-aldosterone system in hypertensive men. J Hypertens 2009;27(10):2001-2009.
43. Nordestgaard BG, Kontula K, Benn M, et al. Effect of ACE insertion/deletion and 12 other polymorphisms on clinical outcomes and response to treatment in the LIFE study. Pharmacogenet Genomics 2010;20(2):77-85.
44. Bhansali A. Association of Angiotensin II Type 1 R Gene Polymorphism and Diabetic Nephropathy in Type 2 Diabetes. ClinicalTrials.gov (ID:NCT01069549).
45. de Luis DA, Conde R, Gonzalez-Sagrado M, et al. Effects of telmisartan vs. olmesartan on metabolic parameters, insulin resistance and adipocytokines in hypertensive obese patients. Nutr Hosp 2010;25(2):275-279.
46. Fogari R, Zoppi A, Ferrari I, et al. Comparative effects of telmisartan and eprosartan on insulin sensitivity in the treatment of overweight hypertensive patients. Horm Metab Res 2009;41(12):893-898.
47. Hamada T, Mizuta E, Kondo T, et al. Effects of a low-dose antihypertensive diuretic in combination with losartan, telmisartan, or candesartan on serum urate levels in hypertensive patients. Arzneimittelforschung 2010;60(2):71-75.
48. Lim D. Comparison of Effects of Telmisartan and Valsartan on Neointima Volume in Diabetes. ClinicalTrials.gov (ID:NCT00599885).
49. Chrysant SG. Safety and tolerability of an olmesartan medoxomil-based regimen in patients with stage 1 hypertension: a randomized, double-blind, placebo-controlled study. Clin Drug Investig 2010;30(7):473-482.

50. Golik A. ACEIs and ARBs Treatment in Diabetic Patients -Drug Interactions and Adverse Drug Effects. ClinicalTrials.gov (ID:NCT00437775).
51. Brown NJ, Byiers S, Carr D, et al. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension 2009;54(3):516-523.

Appendix D. Results of Prioritization Exercises

Results of Prioritization Exercise 1

Table D1. Importance of individual research areas (Prioritization Exercise 1, Likert scale)

Research area	Not at all important (1)	Somewhat unimportant (2)	Neutral (3)	Somewhat important (4)	Very important (5)	Average
Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	14.3% (1)	85.7% (6)	4.86
The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	0.0% (0)	0.0% (0)	14.3% (1)	28.6% (2)	57.1% (4)	4.43
The impact of ACEI/ARB in patients with stable IHD on **utilization and cost of therapy**	0.0% (0)	0.0% (0)	0.0% (0)	57.1% (4)	42.9% (3)	4.43
Impact of **demographic** differences (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	71.4% (5)	28.6% (2)	4.29
Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
The benefit of ACEIs/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
Strategies to enhance greater **evidence-based use** of ACEIs/ ARBs	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	14.3% (1)	0.0% (0)	0.0% (0)	14.3% (1)	71.4% (5)	4.29

Table D1. Importance of individual research areas (Prioritization Exercise 1, Likert scale) (continued)

Research area	Not at all important (1)	Somewhat unimportant (2)	Neutral (3)	Somewhat important (4)	Very important (5)	Average
The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
Impact of g**enetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	85.7% (6)	14.3% (1)	4.14
The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	28.6% (2)	28.6% (2)	42.9% (3)	4.14
The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**	0.0% (0)	0.0% (0)	28.6% (2)	28.6% (2)	42.9% (3)	4.14
Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	28.6% (2)	57.1% (4)	14.3% (1)	3.86
Impact of **class effect** (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	14.3% (1)	14.3% (1)	42.9% (3)	28.6% (2)	3.86
The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	0.0% (0)	0.0% (0)	14.3% (1)	85.7% (6)	0.0% (0)	3.86
The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**	0.0% (0)	0.0% (0)	28.6% (2)	71.4% (5)	0.0% (0)	3.71

Abbreviations in Table D1: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes

Table D2. Ranking of research priorities using average Likert scale score

Rank	Research area
1	Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD
2	The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
2	The impact of ACEI/ARB in patients with stable IHD on **utilization and cost of therapy**
3	Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD
3	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD
3	The benefit of ACEIs/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
3	Strategies to enhance greater **evidence-based use** of ACEIs/ARBs
3	The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
3	The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
4	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
4	The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**
5	Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
5	Impact of **class effect** (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
5	The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
6	The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**

Abbreviations in Table D2: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes

Table D3. Ranking of importance of research areas (Prioritization Exercise 1, top five ranking)

Research area	1	2	3	4	5	Average
The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	75.0% (3)	25.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	4.75
The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	0.0% (0)	75.0% (3)	25.0% (1)	0.0% (0)	0.0% (0)	3.75
The benefit of ACEIs/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	3.5
Strategies to enhance greater **evidence-based use** of ACEIs/ARBs	50.0% (2)	0.0% (0)	25.0% (1)	0.0% (0)	25.0% (1)	3.5
Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	3
The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	25.0% (1)	25.0% (1)	0.0% (0)	25.0% (1)	25.0% (1)	3
The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**	0.0% (0)	0.0% (0)	100.0% (1)	0.0% (0)	0.0% (0)	3
Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	75.0% (3)	25.0% (1)	0.0% (0)	2.75
Impact of **class effect** (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	25.0% (1)	25.0% (1)	0.0% (0)	50.0% (2)	2.25
Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (1)	0.0% (0)	2
The impact of ACEI/ARB in patients with stable IHD on **utilization and cost of therapy**	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (1)	0.0% (0)	2
Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	1.5

Table D3. Ranking of importance of research areas (Prioritization Exercise 1, top five ranking) (continued)

Research area	1	2	3	4	5	Average
The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	1
Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0

Abbreviations in Table D3: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes

Table D4. Ranking of research priorities using top five ranking score

Rank	Research area
1	The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
2	The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
3	The benefit of ACEI/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
3	Strategies to enhance greater **evidence-based use** of ACEIs/ARBs
4	Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
4	The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD
6	Impact of **class effect** (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
7	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD
7	The impact of ACEI/ARB in patients with stable IHD on **utilization and cost of therapy**
8	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD
9	The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
10	Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
10	The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**
10	The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)

Abbreviations in Table D4: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes

Results of Prioritization Exercise 2

Table D5. Research area ranking and summary statistics after Prioritization Exercise 2

	E: Evidence-based use	J: New diagnoses	A: Comorbidities	K: Quality of life	B: Demographic differences	F: Adherence	I: Alternative medication	L: Cardiovascular outcomes	M: Utilization and cost	N: Renal insufficiency	C: Concurrent medications	D: Genetic differences	H: Class effect	G: Dose response	O: Nonangioedema adverse effects	P: Angioedema
Stakeholder 1	16	2	4	7	12	9	6	5	13	3	10	11	1	8	14	15
Stakeholder 2	1	8	12	5	4	7	2	15	6	10	11	3	16	9	14	13
Stakeholder 3	4	5	9	3	7	2	6	1	10	14	8	11	12	13	16	15
Stakeholder 4	16	2	3	6	7	13	11	1	15	5	4	8	12	14	9	10
Stakeholder 5	5	3	1	13	4	6	8	2	12	11	7	15	9	10	14	16
Stakeholder 6	2	3	11	10	7	1	13	8	5	9	12	16	14	15	4	6
Stakeholder 7	1	15	5	4	6	2	8	13	3	14	9	11	7	10	12	16
Stakeholder 8	1	9	5	6	8	15	7	16	3	2	11	4	13	12	10	14
SUMMARY																
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Average score	5.8	5.9	6.3	6.8	6.9	6.9	7.6	7.6	8.4	8.5	9.0	9.9	10.5	11.4	11.6	13.1
Minimum score	1	2	1	3	4	1	2	1	3	2	4	3	1	8	4	6
Maximum score	16	15	12	13	12	15	13	16	15	14	12	16	16	15	16	16
SD	6.50	4.55	3.96	3.28	2.53	5.22	3.34	6.32	4.72	4.69	2.62	4.67	4.75	2.50	3.85	3.48
Variance	42.21	20.70	15.64	10.79	6.41	27.27	11.13	39.98	22.27	22.00	6.86	21.84	22.57	6.27	14.84	12.13
Median score	3	4	5	6	7	6.5	7.5	6.5	8	9.5	9.5	11	12	11	13	14.5
1st quartile	1	2.75	3.75	4.75	5.5	2	6	1.75	4.5	4.5	7.75	7	8.5	9.75	9.75	12.25
3rd quartile	7.75	8.25	9.5	7.75	7.25	10	8.75	13.5	12.25	11.75	11	12	13.25	13.25	14	15.25

Abbreviations in Table D5: SD = standard deviation

Table D6. Ranking of 16 research areas after Prioritization Exercise 2

Ranking	Research area
1	Strategies to enhance greater **evidence-based use** of ACEIs/ARBs
2	The impact of ACEI/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
3	Impact of **comorbidities** (such as hypertension, 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 effectiveness or harms in patients with stable IHD
4	The impact of ACEI/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, sex) on ACEI/ARB effectiveness or harms in patients with stable IHD
6	The impact of ACEI/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
7	The benefit of ACEIs/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACEI/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
9	The impact of ACEI/ARB in patients with stable IHD on **utilization and cost** of therapy
10	The impact of ACEI/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
11	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD
12	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD
13	Impact of **class effec**t (impact of differences between specific agents within each class) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of the **dose response** (impact of medication dose or dosing interval) of ACEIs and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACEI/ARB in patients with stable IHD on development of **nonangioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACEI/ARB in patients with stable IHD on development of **angioedema**

Abbreviations in Table D6: ACEI(s) = angiotensin-converting enzyme inhibitor(s), ARB(s) = angiotensin II receptor blocker(s)/antagonist(s), CHF = congestive heart failure, CVA = cerebrovascular accident, IHD = ischemic heart disease, LV = left ventricular, MI = myocardial infarction, PICO = population, interventions, comparators of interest, and outcomes

Prioritization Exercise 3 Results

Table D7. Research area ranking and summary statistics after Prioritization Exercise 3

	E: Evidence-based use	F: Adherence	A: Comorbidities	K: Quality of life	B: Demographic differences	J: New diagnoses	I: Alternative medication	M: Utilization and cost	L: Cardiovascular outcomes	C: Concurrent medications	N: Renal insufficiency	D: Genetic differences	G: Dose response	H: Class effect	O: Nonangioedema adverse effects	P: Angioedema
Stakeholder 1	12	6	2	3	5	1	7	13	4	11	8	14	10	9	15	16
Stakeholder 2	1	6	7	4	2	8	9	3	10	11	12	5	14	13	15	16
Stakeholder 3	1	3	6	2	8	4	7	9	5	12	10	11	14	13	16	15
Stakeholder 4	1	7	2	3	5	4	6	10	9	8	11	12	14	13	15	16
Stakeholder 5	1	4	3	6	5	2	8	10	7	9	11	12	13	14	15	16
Stakeholder 6	1	2	9	3	8	10	6	4	7	5	11	16	12	15	14	13
Stakeholder 7	1	2	4	7	5	6	9	3	10	8	11	13	12	14	15	16
Stakeholder 8	2	4	3	11	5	1	6	12	7	16	8	10	14	13	9	15
Stakeholder 9	1	5	4	2	3	14	10	9	16	8	15	11	6	12	13	7
SUMMARY																
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Original Rank	***1***	***6***	***3***	***4***	***5***	***2***	***7***	***9***	***8***	***11***	***10***	***12***	***14***	***13***	***15***	***16***
Average score	2.3	4.3	4.4	4.6	5.1	5.6	7.6	8.1	8.3	9.8	10.8	11.6	12.1	12.9	14.1	14.4
Minimum score	1	2	2	2	2	1	6	3	4	5	8	5	6	9	9	7
Maximum score	12	7	9	11	8	14	10	13	16	16	15	16	14	15	16	16
SD	3.64	1.80	2.40	2.96	1.96	4.42	1.51	3.82	3.54	3.15	2.11	3.05	2.67	1.69	2.09	2.96
Variance	13.25	3.25	5.78	8.78	3.86	19.53	2.28	14.61	12.50	9.94	4.44	9.28	7.11	2.86	4.36	8.78
Median score	1	4	4	3	5	4	7	9	7	9	11	12	13	13	15	16
1st quartile	1	3	3	3	5	2	6	4	7	8	10	11	12	13	14	15
3rd quartile	1	6	6	6	5	8	9	10	10	11	11	13	14	14	15	16

Abbreviations in Table D7: SD = standard deviation