












Summary of Recently Published Research and Active Clinical Trials



QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
1	<p>Research Need: Strategies to enhance greater evidence-based use of ACEI/ARBs</p> <p>Recently Published Research: none</p> <p>Active Clinical Trials:</p> <p>(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).)</p>	
2	<p>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)</p> <p>Recently Published Research:</p> <p>(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</p> <p>(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</p> <p>(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</p> <p>(4) 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. Clin Ther, 2010; 32(3):492-505</p> <p>(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</p> <p>(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</p> <p>Active Clinical Trials:</p> <p>(1) Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Small mechanistic study looking at glucose metabolism. ClinicalTrials.gov (ID:NCT00574834).</p> <p>(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).</p> <p>(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).</p> <p>(4) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233).</p> <p>(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</p>	




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	(ID:NCT00456963).	
3	<p>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</p> <p>Recently Published Research:</p> <ul style="list-style-type: none"> (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 <p>Active Clinical Trials:</p> <ul style="list-style-type: none"> (1) Angiotensin Converting Enzyme (ACE) Inhibition and Peripheral Arterial Disease. Ramipril vs. placebo in ~264 pts with PAD. ClinicalTrials.gov (ID:NCT00681226) 	
4	<p>Research Need: The impact of ACEI/ARB in patients with stable IHD on patient quality of life</p> <p>Recently Published Research: none</p> <p>Active Clinical Trials: none</p>	
5	<p>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)</p> <p>Recently Published Research:</p> <ul style="list-style-type: none"> (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 <p>Active Clinical Trials: none</p>	
6	<p>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</p> <p>Recently Published Research: none</p> <p>Active Clinical Trials:</p> <ul style="list-style-type: none"> (1) Clinical trial of copayment reduction/elimination for post MI therapy (Choudhry, 	

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	N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774.)	
7	<p>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</p> <p>Recently Published Research:</p> <ol style="list-style-type: none"> (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 <p>Active Clinical Trials:</p> <ol style="list-style-type: none"> (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 All 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	<p>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.)</p> <p>Recently Published Research:</p> <ol style="list-style-type: none"> (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. 	

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	<p>No difference at 1yr. Fundam Clin Pharmacol, 2009; 23(5):641-8</p> <p>(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</p> <p>(6) Small trial (86 pts) 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). Am J Cardiol, 2010; 105(1):54-8</p> <p>(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</p> <p>(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</p> <p>(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</p> <p>(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</p> <p>Active Clinical Trials:</p> <p>(1) Left Ventricular Function After Acute Myocardial Infarction (AMI). Treatment With Angiotensin 2-Receptor Blockade (GLOBAL-Study). ClinicalTrials.gov (ID:NCT00125645)</p> <p>(2) Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). ClinicalTrials.gov (ID:NCT00149227)</p> <p>(3) Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). ClinicalTrials.gov (ID:NCT00863980).</p> <p>(4) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233).</p> <p>(5) A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov (ID:NCT01075698).</p> <p>(6) Candesartan for Prevention of Cardiovascular Events After Cypher or Taxus Coronary Stenting (4C) Trial. ClinicalTrials.gov (ID:NCT00139386).</p> <p>(7) Prevention of Diabetes and Hypertension (PHIDIAS). ClinicalTrials.gov (ID:NCT00456963).</p>	
9	<p>Research Need: The impact of ACEI/ARB in patients with stable IHD on utilization and cost of therapy</p> <p>Recently Published Research:</p> <p>(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</p> <p>(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/Quality) and CCB (~9300Euro/Quality) Value Health, 2009; 12(6):857-71</p> <p>Active Clinical Trials:</p> <p>(1) Clinical trial of copayment reduction/elimination for post MI therapy (Choudhry,</p>	

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	N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).	
10	<p>Research Need: The impact of ACEI/ARB in patients with stable IHD on progression of renal insufficiency or development of dialysis dependence</p> <p>Recently Published Research:</p> <ol style="list-style-type: none"> (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 spironolactone 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 <p>Active Clinical Trials:</p> <ol style="list-style-type: none"> (1) Triple Blockade of the Renin Angiotensin Aldosterone System in Diabetic (Type 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	

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	<p>Recently Published Research:</p> <p>(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. <i>Am Heart J</i>, 2010; 159(5):795-802</p> <p>Active Clinical Trials:</p> <p>(1) Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov (ID:NCT00427271).</p> <p>(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).</p>	
12	<p>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</p> <p>Recently Published Research:</p> <p>(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. <i>Diabetes</i>, 2009; 58(12):2920-9</p> <p>(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. <i>J Hypertens</i>, 2009; 27(10):2001-9</p> <p>(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) <i>Pharmacogenet Genomics</i>, 2010; 20(2):77-85</p> <p>Active Clinical Trials:</p> <p>(1) Association of Angiotensin II Type 1 R Gene Polymorphism and Diabetic Nephropathy in Type 2 Diabetes. ClinicalTrials.gov (ID:NCT01069549)</p>	
13	<p>Research Need: 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</p> <p>Recently Published Research:</p> <p>(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 resistance <i>Nutr Hosp</i>, 2010; 25(2):275-9</p> <p>(2) Telmisartan vs. eprosartan on insulin sensitivity in 50 overweight hypertensive patients. Found that Telmisartan may have greater impact than eprosartan on insulin resistance <i>Horm Metab Res</i>, 2009; 41(12):893-8</p> <p>(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. <i>Arzneimittelforschung</i>, 2010; 60(2):71-5</p> <p>(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 resistance. <i>Clin Ther</i>, 2010; 32(3):492-505</p> <p>Active Clinical Trials:</p> <p>(1) Comparison of Effects of Telmisartan and Valsartan on Neointima Volume in</p>	

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	Diabetes. ClinicalTrials.gov (ID:NCT00599885)	
14	<p>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</p> <p>Recently Published Research: none</p> <p>Active Clinical Trials: none</p>	
15	<p>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)</p> <p>Recently Published Research:</p> <p>(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</p> <p>Active Clinical Trials:</p> <p>(1) ACEIs and ARBs Treatment in Diabetic Patients -Drug Interactions and Adverse Drug Effects. ClinicalTrials.gov (ID:NCT00437775).</p> <p>(2) Safety of Dual Blockage of Renin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov (ID:NCT00630708).</p> <p>(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).</p>	
16	<p>Research Need: The impact of ACEI/ARB in patients with stable IHD on development of angioedema</p> <p>Recently Published Research:</p> <p>(1) one case control study proposing RR of 4.5 for ACEI angioedema for patients on concurrent vildagliptin Hypertension, 2009; 54(3):516-23)</p> <p>Active Clinical Trials: none</p>	

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: