Drug Class Review

Direct Renin Inhibitors, Angiotensin Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers

Final Report
Evidence Tables

January 2010

The Agency for Healthcare Research and
Quality has not yet seen or approved this report

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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Abbreviations used in evidence tables

ACE-I, angiotensin-converting enzyme inhibitor
AE, adverse event
ANCOVA, analysis of covariance
ANOVA, analysis of variance
AIIRA, angiotensin II receptor antagonist
ARB, angiotensin receptor blocker
BID, twice daily
CCT, controlled clinical trial
CHD, coronary heart disease
CKD, chronic kidney disease
CI, confidence interval
Cr, creatinine
CVD, cardiovascular disease
d, day
dL, deciliter
DM, diabetes mellitus
DM1, type 1 diabetes
DM2, type 2 diabetes
DN, diabetic nephropathy
DRI, direct rennin inhibitor
EF, ejection fraction
eGFR, estimated glomerular filtration rate
FDA, Food and Drug Administration
F/U, follow-up
G, gram
GFR, glomerular filtration rate
GI, gastrointestinal
GP, general practitioner
HCTZ, hydrochlorothiazide
HF, heart failure
HMO, health maintenance organization
HR, hazard ratio
HT, hypertension
ITT, intention to treat
K+, potassium
L, liter
LVSD, left ventricular systolic dysfunction
LVED, left ventricular end-diastolic dysfunction
M, month
Mcg, microgram
MI, myocardial infarction
min, minute
Mmol, millimole
N, sample size
NA, not applicable
NR, not reported
NS, not significant
NSD, no significant difference
NYHA, New York Heart Association
OR, odds ratio
PPY, per person year
QD, once daily
QoL, quality of life
RAAS, renin-angiotensin-aldosterone system
RCT, randomized, controlled trial
RR, relative risk
SD, standard deviation
SE, standard error
TID, three times daily
VA, U.S. Department of Veterans Affairs
vs, compared with
WD, withdrawal
y, year

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

ACE/ARB: CHD

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Aliskiren vs placebo					
McMurray JV 2008	RCT (double-blind, parallel-group) 75 sites in 9 countries 12 weeks	Inclusion criteria: men and women ≥18 years of age; stable New York Heart Association Class II to IV heart failure for at least 1 month; past or current diagnosis of essential hypertension; stable dose of an ACE inhibitor (or ARB) and a β-blocker (unless there was a contraindication or intolerance to such therapy); and plasma brain natriuretic peptide (BNP) > 100 pg/mL Exclusion criteria: Treatment with both and ACE inhibitor and an ARB (combination of either with an aldosterone antagonist was permitted); heart failure related to obstructive valve disease or hypertrophic, restrictive, or infective cardiomyopathy, pregnancy, or lung disease; systolic blood pressure <90mm Hg; serum potassium ≥5.1 mmol/L; creatine > 2.0 mg/dL or history of dialysis or nephrotic syndrome; myocardial infarction, cerebrovascular accident or transient ischemic attack, or coronary revascularization within 6 months; cardiac resynchronization device or implantable cardioverter defibrillator, and prior malignancy or other disease likely to greatly limit life expectancy, adherence to the protocol, or absorption of the drug.	12-week randomized, double-blind, parallel-group phase in which patients received either placebo or aliskiren 150mg once daily in an equal ratio	Run in: 2-week single-blind with placebo	Stable dose of an ACE inhibitor (or ARB) and a β-blocker

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

ACE/ARB: CHD

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Aliskiren vs placebo					
McMurray JV 2008	Patients were evaluated at 2, 4, 8 and 12 weeks after randomization Blood chemistry was checked at each of these time points	**Placebo/Aliskiren** Mean age: 68/67 years Gender (% male): 76/80 Ethnicity (% white): 99/96	**Placebo/Aliskiren (at baseline)** LVEF (%): 31.1±5.5/30.6±5.5 BMI: 27.3±4.8/27.8±4.8 Systolic blood pressure, mm Hg Seated: 128±16.4/130±18.3 Standing: 126±15.6/129±19.1 Diastolic blood pressure, mm Hg Seated: 76.4±8.4/78.1±10.4 Standing: 75.9±9.2/78.8±11.3 Heart rate, bpm Seated: 70±11.3/70±12.1 Standing: 72±12.0/72±31.1 Heart failure history **Duration (years):** 4.9±5.4/4.1±3.9 **Etiology (%):** Ischemic: 54/55 Hypertensive: 17/16 Idiopathic: 20/23 Other: 9/6 LVEF (%) **≤40%:** 77/80 **>40%:** 23/20 New York Heart Association Class: I: 0.7/0 II: 60/63 III: 40/36 IV: 0/1 Medical History (%): Myocardial Infarction: 49/46 Angina Pectoris: 21/21 Diabetes mellitus: 30/31 Atrial fibrillation: 32/32	776/641/302 (156 aliskiren, 146 placebo)	Aliskiren: 13/1/142 Placebo: 10/1/135

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

ACE/ARB: CHD

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Aliskiren vs placebo		
McMurray JV 2008	**Placebo/Aliskirin** Prespecified safety assessment (%): Renal dysfunction: 1.4/1.9 Symptomatic hypotension: 1.4/3.2 Hyperkalemia: 4.8/6.4 Any of the above: 7.5/10.9 Biochemical abnormalities: Urea, >14.3 mmol/L: 10.4/8.3 Creatine, >177 µmol/L: 5.6/7.1 Creatine, >265 µmol/L: 2.1/0 Potassium, <3.5 mmol/L: 4.9/1.3 Potassium, >5.5 mmol/L: 8.3/8.3 Potassium, ≥ 6.0 mmol/L: 4.2/1.9 Echocardiographic measurements (baseline/end of study/change) **End-diastolic volume index, mL/m^2:** Aliskiren: 124±24/123±24/-2.7±6.7 Placebo: 123±30/121±28/3.4±12.9 P-value: 0.56 **End-systolic volume index, mL/m^2:** Aliskiren: 87.2±22/84.9±22/-4.0±8.1 Placebo: 85.4±25/82.4±24/4.3±10.7 P-value: 0.67 **LVEF, %:** Aliskiren: 30.6±5.5/31.5±5.5/1.7±3.1 Placebo: 31.1±5.5/32.5±5.6/1.6±2.9 P-value: 0.96 Neurohumoral measurements, mean (baseline/end of study) **NT-proBNP, pg/mL** Aliskiren: 2158±2269/1915±2373 Placebo: 2123±3858/2885±6393 Ratio (Aliskiren/Placebo) (95% CI): 0.75 (0.61, 0.94) P-value: 0.0106 **BNP, pg/mL** Aliskiren: 301±269/240±307 Placebo: 273±246/261±272 Ratio (Aliskiren/Placebo) (95% CI): 0.75 (0.59, 0.95) P-value: 0.0160 **Aldosterone, pmol/L** Aliskiren: 334±364/285±281 Placebo: 307±316/276±273 Ratio (Aliskiren/Placebo) (95% CI): 0.99 (0.93, 1.18) P-value: 0.9064 **Urinary aldosterone, nmol/d** Aliskiren: 38±43/29±33 Placebo: 37±41/31±33 Ratio (Aliskiren/Placebo) (95% CI): 0.79 (0.66, 0.96) P-value: 0.0150 **Plasma renin concentration, ng/L** Aliskiren: 69±112/155±177 Placebo: 79±120/74±116 Ratio (Aliskiren/Placebo) (95% CI): 2.60 (1.97, 3.44) P-value: <0.0001	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

ACE/ARB: CHD

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Aliskiren vs placebo		
McMurray JV 2008	NR	Patients were evaluated at 2, 4, 8 and 12 weeks after randomization Blood chemistry was checked at each of these time points

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

ACE/ARB: CHD

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Aliskiren vs placebo			
McMurray JV 2008	**Placebo/Aliskiren (%)** Nasopharyngitis: 2.7/3.8 Asthenia: 1.4/3.2 Diarrhea: 1.4/3.2 Hyperuricemia: 1.4/3.2 Hypotension: 0.7/3.2 Nausea: 0/3.2 Cardiac failure: 4.1/2.6 Dyspnea: 3.4/1.9 Dizziness: 3.4/1.3 Death: 1.4/0.6	Aliskirin: 7 Placebo: 4	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Candesartan vs enalapril					
McElvie RS 1999 Tsuyuki RT, 1997 Canada, Switzerland, US, Italy RESOLVD: Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study Fair	RCT 60 out-patient clinics 43 weeks	NYHA classification II, III, or IV, 6-min walk distance <500m; EF <0.40. Exclusion criteria: acute illness, renal impairment, contraindications to the study medications.	Total N=768 Stage 1: Enalapril 10 mg bid + placebo (n=109) Enalapril 10 mg bid + candesartan 4 or 8 mg qd (n= 332) Candesartan: randomized to 4, 8, or 16 mg qd (n=327) "medications were blindly titrated upward over 4-6 weeks" Stage II: randomization to metoprolol or placebo in addition to stage I treatments; start with 1-w run-in 12.5 mg qd, then randomized to metoprolol or placebo to target dose of 200 mg qd	Run-in: 3, 1-w phases: Enalapril 2.5 mg bid + placebo Enalapril 2.5 mg bid + candesartan 2 mg qd Enalapril 2.5 mg bid + placebo (stated in both publications) Washout: none	Use of nonstudy ACE-I or ARBs not permitted; other medications were not restricted, except other beta-blockers in Stage II
Irbesartan vs ramipril					
Yip GWK 2008 Hong Kong Fair	RCT Hospital and F/U clinic F/U 52 weeks	Inclusion criteria: >18y, history of HF within 2m; NYHA class II to IV; LVEF >45%, therapy with diuretics with stable dose >14d. Exclusion criteria: Mi in prior 3m; unstable angina within 1m; significant valvular heart disease, uncontrolled HT, serious cardiac arrhythmias, concurrent therapy with calcium channel blockers, beta-blockers, inotropic agents (except digitalis), other ACI-I or ARBs.	Diuretic: either furosemide or thiazide (n= 50) Irbesartan: 18.75 mg qd titrated to 75 mg qd + diuretic (n=56) Ramipril: 2.5 titrated to 10 mg qd + diuretic (n=45)	NR NR	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Candesartan vs enalapril					
McElvie RS 1999 Tsuyuki RT, 1997 Canada, Switzerland, US, Italy RESOLVD: Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study Fair	Outcomes assessments at 17/18 weeks and 43 weeks	Age: C 62.8(11.0); C+E 63.5(10.5); E 62.2(11.6) Sex (% female): C 20, C+E 15; E 10 Race: NR	NYHA class II/III/IV (number): C 62/36/2; C+E: 66/33/1; E 56/40/4 EF: C .27; C+E 0.28, E 0.27	1 withdrawn for protocol violation; no others reported	NR/NR/NR ; it appears that all but 1 patient were analyzed, but not explicitly stated
Irbesartan vs ramipril					
Yip GWK 2008 Hong Kong Fair	"all outcomes were reviewed blind to treatment allocation" 12, 24, 52 weeks	Data for diuretic only group Age: 73 (8.4) Sex: 56% female Race: NR	Hypertension: 80% Diabetes: 20% NYHA class II: 70%	NR/NR/150	12/0/NR Diuretic: 3 deaths Irbesartan: 1 death, 1 withdrawal due to a fib (Table 1 states 3 total withdrawals/deaths from this group) ramipril: 4 withdrawals due to cough, 1 withdrawal due to uncontrolled BP, 1 refused to continue; 0 deaths

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Candesartan vs enalapril		
McElvie RS 1999 Tsuyuki RT, 1997 Canada, Switzerland, US, Italy RESOLVD: Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study Fair	6-min walk test (meters) at 43w: C 390 (6); C+E 385 (6); E 387 (11): NSD between groups NYHA classification: NSD among 3 groups at 18 or 43w NSD among groups for death, any CHF hospitalization (P-value across group 0.09), any hospitalization, renal dysfunction Deaths at up to 43w: C 16 mg 4.6%, C 16 mg + E 11.4%; E 20 mg 3.7% (P-value across groups 0.15)	Quality of life (Minnesota Living with Heart Failure): NSD between groups
Irbesartan vs ramipril		
Yip GWK 2008 Hong Kong Fair	6-min walk test: increased slightly in all groups; NSD within or between groups (between-group P=0.8) Cardiovascular deaths (number): diuretic 1, irbesartan 1, ramipril 0 Other deaths (number): diuretic 0 (cancer), irbesartan 0, ramipril 0	QoL measured with Minnesota Heart Failure Symptom Questionnaire: improved all 3 groups by 12w (P<0.01); NSD between groups (P-value NR) Readmission for HF: diuretic 12.2%, irbesartan 11.1%, ramipril 11.4% (P-values NR)

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Candesartan vs enalapril		
McElvie RS 1999 Tsuyuki RT, 1997 Canada, Switzerland, US, Italy RESOLVD: Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study Fair	NR	
Irbesartan vs ramipril		
Yip GWK 2008 Hong Kong Fair	NR	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Candesartan vs enalapril			
McElvie RS 1999 Tsuyuki RT, 1997 Canada, Switzerland, US, Italy RESOLVD: Randomized Evaluation of Strategies for LV Dysfunction, Pilot Study Fair	Symptomatic hypotension: NSD between groups: C 16 mg 0.9%; C+E: 1.8%; E 20 mg 0.93%	NR/NR/NR	During trial (mean F/U time NR), concern that mortality and CHF hospitalization higher for C, so trial stopped 6 weeks early (there were no pre-determined stopping rules as was a pilot study) Pilot study: not powered for mortality or morbidity
Irbesartan vs ramipril			
Yip GWK 2008 Hong Kong Fair	NR	12/0/NR Diuretic: 3 deaths Irbesartan: 1 death, 1 withdrawal due to a fib (Table 1 states 3 total withdrawals/deaths from this group) Ramipril: 4 withdrawals due to cough, 1 withdrawal due to uncontrolled BP, 1 refused to continue; 0 deaths	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Losartan vs captopril					
Dickstein K 2002 Norway, USA, UK, Germany, Sweden, Ireland, Denmark OPTIMAAL: Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan Good	RCT, parallel group 327 centers, setting NR Mean F/U 2.7 (0.9) years	Inclusion criteria: ≥ 50y, documented acute MI and 1) HF or 2) EF <35% or 3) LVED dimension of >65mm and/or new Q-wave anterior wall AMI, new LBBB, or any reinfarction with prior pathologic Q waves in anterior wall; enrolled within 10d of onset of symptoms. Exclusion criteria: SBP <100 mm Hg, on ACE-I or ARB, unstable angina, significant stenotic valvular heart disease, or dysrhythmia, planned CABG.	Total n=5477 Losartan 12.5 mg qd, titrated to 50 mg qd, n=2744 Captopril 12.5 mg tid, titrated to 50 mg tid, n=2733	None	ASA, beta-blocker, statin, nitrates, thrombolytics, others
Pitt B, 1997 Cowley AJ, 2000 Konstam MA 2000 (ventricular function substudy) Pitt B 1995 (rationale and design) Houghton AR 1999 (exercise effects substudy) 289 centers in 46 countries ELITE (Evaluation of Losartan in the Elderly) Fair	RCT F/U: 48 weeks	Inclusion criteria: ≥ 65 years with symptomatic HF (NYHA II-IV); LVEF ≤ 40%; no history of prior ACE-I therapy. Exclusion criteria: SBP <90 mmg Hg, significant obstructive valvular disease or symptomatic arrhythmia; constrictive pericarditis; active myocarditis, cardiac surgery during study period or angioplasty in prior 72h; MI in prior 72h; other recent cardiac conditions or procedures; stroke in prior 3m; other comorbid conditions and laboratory abnormalities .	Total n=722 Captopril (C) (n=370): 6.25 mg titrated to 12.5, 25, 50 mg tid + losartan placebo; mean dosage achieved 122.7 mg qd) Losartan (L) (n=352): 12.5 mg titrated to 25, 50, qd + captopril placebo (mean dosage achieved 42.6 mg qd)	Run-in: 2 week placebo Wash-out: other drugs: NR	Other CV therapies, except open-label ACE-I

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Losartan vs captopril					
Dickstein K 2002 Norway, USA, UK, Germany, Sweden, Ireland, Denmark OPTIMAAL: Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan Good	Adjudicated endpoints by committee blinded to treatment group	Age: 67.4 (9.8) Sex: 71.2% male Race: 98.5% white	Hypertension: 38% Diabetes: 17.2% Prior MI 18.2% Any heart failure criteria: 80.6%	31738/NR/5477	438+624 discontinued treatment; 1 lost to F/U but LOCF data used; 5477 analyzed
Pitt B, 1997 Cowley AJ, 2000 Konstam MA 2000 (ventricular function substudy) Pitt B 1995 (rationale and design) Houghton AR 1999 (exercise effects substudy) 289 centers in 46 countries ELITE (Evaluation of Losartan in the Elderly) Fair	Weekly assessments during dosage titration, then q3m Adjudicated endpoints were deaths and HF admissions (study reported as double-blind; unclear if assessor blinded)	Age (y, (SD)) C: 73(6.1) L: 74 (5.8) Sex: number female C:122/370 L: 118/352 Race: NR	Heart failure due to ischemic or nonischemic heart disease (number) C: 120/370) L: 110/352 NYHA classification II, III, IV C: 237/126/7 L: 231/116/5 Diabetes (number) C: 89/370 L: 94/352	NR/NR/722	C: 64/NR L: 111/NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Losartan vs captopril		
Dickstein K 2002 Norway, USA, UK, Germany, Sweden, Ireland, Denmark OPTIMAAL: Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan Good	All-cause mortality (%): L 18%, C 16%, RR 1.13 (95% CI, 0.99 to 1.28), P=0.07; did not satisfy the non-inferiority criterion Sudden death or resuscitated arrest: RR 1.19 (95% CI, 0.99 to 1.43), P=0.072 Fatal or nonfatal reinfarction: RR 1.03 (95% CI, 0.89 to 1.18), P=0.72 Cardiovascular deaths: RR 1.17 (95% CI, 1.10 to 1.34), P=0.032 All-cause hospital admission: RR 1.03 (95% CI, 0.97 to 1.10), P=0.36	Days in hospital for initial admission: L 13.6 (23.9); C 13.1 (21.6) (no statistics)
Pitt B, 1997 Cowley AJ, 2000 Konstam MA 2000 (ventricular function substudy) Pitt B 1995 (rationale and design) Houghton AR 1999 (exercise effects substudy) 289 centers in 46 countries ELITE (Evaluation of Losartan in the Elderly) Fair	Renal dysfunction (primary composite endpoint): increase serum Cr by ≥ 0.3 mg/dL from baseline, confirmed with second test 5-14d later: C: 10.5% L: 10.5% Risk reduction 2% (95% CI, -51 to 36%), P=0.63 Death and/or HF admissions (N=711) C: 13.2% L: 9.4% Risk reduction 32% (95% CI, -4 to 55%), P=0.075; primarily due to a decrease in all-cause mortality; lower total mortality in L due to decrease in sudden cardiac deaths NYHA class: 80% of L and 81% of C were class I or II at the end of the study, compared with 66% of L and 64% of C at baseline	Hospital admissions (Pitt 1997) Total: C 29.7%, L 22.2%, P=0.014 For HF: C 5.7%, L 5.7%, P=0.89 Cowley AJ, 2000 n=278 (of 300 eligible); 203 completed Both C and L improved in all domains of the Sickness Impact Profile (C=L); one-sided test for difference favoring C, P=0.311; favoring L, P=0.689 Both C and L improved in the Minnesota Living with Heart Failure Questionnaire: improved with both drugs; one-sided test for a treatment difference favoring L, P=0.586; favoring C, P=0.414 Dasbach 1999 Overall rate of hospitalization per patient: C 0.40; L 0.37 Number of hospital days per patient: C 3.81, L 3.81 Number of ER visits per patient: C 0.07, L 0.07 Nonstudy medications used: NSD

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Losartan vs captopril		
Dickstein K 2002 Norway, USA, UK, Germany, Sweden, Ireland, Denmark OPTIMAAL: Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan Good	Beta-blocker use at randomization: NSD with treatment L or C (P=0.88) NSD for other subgroups examined: age stratum, sex, diabetes, Killip class, infarct location, prior MI, heart failure, thrombolytic use	Prespecified AEs
Pitt B, 1997 Cowley AJ, 2000 Konstam MA 2000 (ventricular function substudy) Pitt B 1995 (rationale and design) Houghton AR 1999 (exercise effects substudy) 289 centers in 46 countries ELITE (Evaluation of Losartan in the Elderly) Fair	Pitt 1997: mortality difference was generally consistent across different subgroups (age, EF, cause of HF, NYHA functional status) More deaths in women: C 8/122; L 9/118 Konstam MA 2000 (ventricular function substudy) (n=33): patients had radionuclide ventriculogram at baseline and were randomized to C or L: Deaths: C 1/16; L 0/13 (these data are a subset of the main study deaths) Houghton AR 1999 (exercise effects substudy): duration of substudy: 24w, n=18, unclear how selected; L 10, C 8 (only 4/8 completed study due to withdrawals due to AEs (3) and death (1)): NSD within or between groups in 100-m corridor walk test or in pedometer scores	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Losartan vs captopril			
Dickstein K 2002 Norway, USA, UK, Germany, Sweden, Ireland, Denmark OPTIMAAL: Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan Good	Serious AEs: C>L, P=0.10 (graphical data) Serious AEs, drug-related: C>L, P=0.002 (graphical data) Hypotension: 2 episodes with C Cough: L 9.3%, C 18.7%, P<0.0001; Cough causing discontinuation: L 1.0%, C 4.1%, P<0.001 Angioedema: L 0.4%, C 0.8%, P=0.034; Angioedema causing discontinuation: L 0.1%, C 0.5%, P=0.019 Hypotension: L 13.3%, C 16.3%, P=0.002 CHF: L 14.6%, C 14.0%, P=0.537 Skin rash causing discontinuation: L 0.1%, C 0.7%, P=0.0008 Dizziness: NSD between groups, P=0.36 Taste disturbance: L 0.0%, C 0.6%, P<0.0001	Discontinuation of study drug for any reason: L 17%, C 23%, RR 0.77 (95% CI, 0.62 to 0.79), P<0.0001 Discontinuation due to AEs: L 7%, C 14%, RR 0.50 (95% CI, 0.42 to 0.59), P<0.001	
Pitt B, 1997 Cowley AJ, 2000 Konstam MA 2000 (ventricular function substudy) Pitt B 1995 (rationale and design) Houghton AR 1999 (exercise effects substudy) 289 centers in 46 countries ELITE (Evaluation of Losartan in the Elderly) Fair	Patients with discontinuation due to various AEs: Cough: C 3.8%, L 0% (P≤ 0.002) Worsening HF: C 9/370; L 3/352 (P-value NR) Hyperkalemia: C 6/370; L 2/352 (P-value NR) Other AEs: Persisting increase in K+ of ≥ 0.5 mmol/L C; 22.7%, L 18.8%, P=0.069 Hypotension-related symptoms: 24% overall, P>0.05 Deaths (per protocol): L: 3.7% C: 8.5%, P=0.013	Total (including deaths) C: 30.0% L: 18.5%, P <0.0001 Due to AEs (excluding death) C: 20.8% L: 12.2%, P≤ 0.002	HQOL study was administered to the US cohort only; since there was a higher withdrawal rate in the C group due to AEs or death, so a composite statistical approach was used to account for non-ignorable discontinuation differences

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Pitt B, 2000 Konstam MA, 2005 Pitt B 1999 (rationale, design, baseline characteristics) US, UK, Norway, Germany ELITE II (Evaluation of Losartan in the Elderly) Fair	RCT NR F/U: median for each group: 1.5 years	Inclusion criteria: ≥ 60 years; symptomatic HF (NYHA class II-IV); LVEF of ≤40%; ACE-I naive or ≤7d of ACE-I or ARB in prior 3m Exclusion criteria: SBP <90 mmg Hg, DBP>95; significant obstructive valvular disease; active pericarditis or myocarditis, various recent cardiac procedures or MI; stroke in prior 6w; significant renal artery stenosis; hematuria, serum CR > 220 umol/L Note: inclusion and exclusion criteria differ somewhat from ELITE	Total n=3152 Captopril (C) (n=1574): 6.25 mg titrated to 12.5, 25, 50 mg tid + losartan placebo Losartan (L) (n=1578): 12.5 mg titrated to 25, 50, qd + captopril placebo	Run -in: 1-28d of single-blind placebo to enable stabilization and assessment of patients and to ensure adherence Washout- NR	Other CV therapies, except open-label ACE-I
Losartan vs enalapril					
Dickstein K 1995 Norway, Sweden, Finland Fair	RCT Multicenter, setting NR 8 weeks	Inclusion criteria: NYHA class III or IV who had been stabilized on ACE-I, no other details. Exclusion criteria: NR	Total n= 166 Losartan 25 mg qd (n=52) Losartan 50 mg qd (n=56) Enalapril 20 mg qd (n=58)	Run-in: minimum of 3 weeks of placebo tablets, while continuing to receive ACE-I	diuretics, digitalis, kept as stable as possible through double-blind period

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Pitt B, 2000 Konstam MA, 2005 Pitt B 1999 (rationale, design, baseline characteristics) US, UK, Norway, Germany ELITE II (Evaluation of Losartan in the Elderly) Fair	Weekly assessments during dosage titration, then q4m	Age C: 71.5 (6.9) L: 71.4 (6.7) Sex (% female) C: 31 L: 30 Race/ethnicity (%) White: C 82, L 82 Black: C 2, L 2 Asian: C 5, L 5	NYHA class II, III, IV (%) C: 52, 43, 5 L: 52, 43, 5 History of ischemia: C 79%, L 79% Diabetes: C 42%, L 24%	NR/NR/3152	Withdrawn/Loss to F/U: C 221/1; L 125/1 Analyzed: C 1103; L 1173
Losartan vs enalapril					
Dickstein K 1995 Norway, Sweden, Finland Fair	Clinical assessments at weeks 1,2,3,4,6 and 8	Age: 64 (10) 22% female Ethnicity: NR	NYHA Class III 87%, Class IV 13% Mean LVEF: 23% (6)	NR/1NR/166	10/NR/156

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Pitt B, 2000 Konstam MA, 2005 Pitt B 1999 (rationale, design, baseline characteristics) US, UK, Norway, Germany ELITE II (Evaluation of Losartan in the Elderly) Fair	All-cause mortality (%): L 17.7; C 15.9 HR 1.13 (95% CI, 0.95 to 1.35) P=0.16 Sudden death or resuscitated arrest, %: C 7.3, L 9.0, HR 1.25 (95% CI, 0.98 to 1.60), P=0.08 Konstam 2005 NSD between L and C in crude events rates or time-to event for: 1) composite of all-cause mortality and all-cause hospitalization (HR 1.07 (95% CI, 0.97 to 1.19), P=0.59; and 2) composite of all-cause mortality and hospitalization secondary to HF (HR 1.04, (95% CI, 0.91 to 1.19), P=0.59)	Hospital admissions Total: C 40.5%, L 41.8%, NR 1.04 (95% CI, 0.94 to 1.16), P=0.45 For HF: C 18.6%, L 17.1%, HR 0.92 (95% CI, 0.78 to 1.08), P=0.32 Konstam 2005 Number of patients with hospitalization for any cause: C 41%, L 42%, HR 1.04 (95% CI, 0.94 to 1.16), P=0.45 Number of patients with 1 or more admissions for HF: C 19%, L 17%, HR 0.92 (95% CI, 0.78 to 1.08), P=0.32 Repeat analyses per patient-year alive for both outcomes: NSD between groups Study drug discontinuation for worsening of HF: C 3.8%, L 3.7%, HR 0.95 (95% CI, 0.66 to 1.36), P=0.77 HF class improved significantly in both groups (P<0.01) HRQL (Euroqual 5D), n=1540 (had available data out of 1882 eligible); 1-y change from baseline: no significant change in either C or L; due to large effect on QoL score of nonsurvivors; in survivor subgroup both groups improved with NSD between groups
Losartan vs enalapril		
Dickstein K 1995 Norway, Sweden, Finland Fair	Exercise capacity (6-min walk test): mean change (%) at 8w: Losartan 25 mg: 4.5; Losartan 50 mg: 3.0; enalapril: 0.0; P>0.05 within and between groups Dyspnea-fatigue Index profile (8w): improved with losartan 25 mg (P<0.05) and enalapril (P<0.001); NSD between groups Incidence of worsening symptoms (exertional dyspnea, edema, orthopnea, worsening NYHA class): NSD among treatment groups; functional class improved in 30% overall, evenly distributed across groups Pulmonary rales, increase (%): losartan 25 mg: 7.6; losartan 50 mg 16.0, enalapril 3.4 (P<0.05 between losartan 50 and enalapril)	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Pitt B, 2000 Konstam MA, 2005 Pitt B 1999 (rationale, design, baseline characteristics) US, UK, Norway, Germany ELITE II (Evaluation of Losartan in the Elderly) Fair	All-cause mortality: did not differ by age group (< or > 70y); sex, NYHA class, EF, use of beta-blockers Konstam 2005: NSD between C and L for 1) all-cause mortality and/or all-cause hospitalization; or 2) all-cause mortality and/or all-cause hospitalization due to HF for baseline NYHA HF class, EF, sex, age, history of ischemia; A fib, prior MI; among patients on prior beta-blocker therapy, more events occurred with L than C for both of these composite outcomes (P=0.024 and P=0.015) (this was NS for primary outcome off all-cause mortality); event rates were higher for both C and L in patients not on beta-blockers	NR
Losartan vs enalapril		
Dickstein K 1995 Norway, Sweden, Finland Fair	Subgroup analyses based on age, sex, EF and NYHA class: NSD between groups	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Pitt B, 2000 Konstam MA, 2005 Pitt B 1999 (rationale, design, baseline characteristics) US, UK, Norway, Germany ELITE II (Evaluation of Losartan in the Elderly) Fair	Worsening HF: C 25%, L 25% NSD heart rate, BP between groups (data NR)	Total (excluding deaths) C: 221/1574 (14.0%) L: 125/1578 (7.9%); P-value NR Due to any AEs (excluding death) (data from graph) C: 20.8% L: 12.2%; P<0.001 Due to drug-related AEs (excluding death) (data from graph) C: 8% L: 3%; P<0.001 Due to cough (data from graph) C: 3, L <1; P<0.001	
Losartan vs enalapril			
Dickstein K 1995 Norway, Sweden, Finland Fair	Most common AEs: dyspnea, dizziness, hypotension, cough (E 6.9%, L25 3.8%, L 50 7.1%), edema, URI; NSD between groups Laboratory changes: NSD between groups for serum sodium, uric acid BUN, Cr, K+: increase with enalapril, decrease in losartan (both groups), P<0.05; none considered clinically significant	Total withdrawals: 10/166 Withdrawal due to AEs (number patients): losartan 25 1, losartan 50 2, enalapril 5 (NSD among groups) Deaths: losartan 25: 0; losartan 50 2; enalapril 2 Any AE: losartan 25: 36, losartan 50: 38; enalapril: 30 (NSD among groups)	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Guazzi M 1999 Italy Fair	RCT, cross-over (at 8-w intervals) Single center, University clinic Each treatment for 8 weeks	Stable CHF, NYHA class II or III, had cardiac enlargement, EF <40%; not using ACE-I or ARB; no COX inhibitor in last 3 months. Exclusion criteria: MI or CABG in last 6m; significant valvular heart disease, angina, exercise limitation due to PAD, others.	Total n=20 Randomized to receive the following sequence, or in reverse order: Placebo+placebo Enalapril 20 + placebo Losartan 50 mg + placebo Enalapril + losartan Each treatment lasted 8 weeks	2 week placebo run-in: clinical stability confirmed Wash-out: NR	All were maintained on furosemide and digitalis; no beta-blockers
Guazzi M 1997 Italy Poor	RCT, cross-over, 3w of treatment for each treatment Single center, University clinic Each treatment for 8 weeks	Inclusion criteria: chronic, stable CHF referred to clinic; male; NYHA classification II or III due to ischemic heart disease or idiopathic cardiomyopathy; stable for prior 6m; EF <40% able to complete maximum cardiopulmonary bicycle exercise test. Exclusion criteria: therapy with ACE or ARB in last 6m or on COX inhibitor in last 3m; exercise limitation due to PAD, others. Controls: 6 normal volunteers and 2 mild primary hypertensive patients not on therapy.	Total n=16 Randomized to receive the following sequence, or in reverse order: Placebo Enalapril 10 mg bid Losartan 50 mg qd Enalapril + ASA 325 mg qd Losartan + ASA Each treatment prior lasted 3w, with 3-week wash-out	3-week wash-out between treatments	Furosamide, nitrates

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Guazzi M 1999 Italy Fair	Outpatient visits q2w	Age 58 (8) Sex: 20% female Race: NR	Ischemic cardiomyopathy 6/20, idiopathic dilated cardiomyopathy 14/20 Mean LVEF 30 %(5)	NR/NR/20	2 withdrew of 20
Guazzi M 1997 Italy Poor	On bicycle ergometer patient exercised to a symptom-limited endpoint o dyspnea and/or fatigue	Age: 61 (6) Sex: 100% men Race: NR	Mean ejection fraction: 32% (5)	NR/NR/16 (with 6 healthy controls and 2 with hypertension	NR/NR/NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Guazzi M 1999 Italy Fair	NR	Minnesota Living with Heart Failure questionnaire: small improvement while on E+P and L+P compared with P (P>0.05); no further improvement with E+L; NSD between groups (graphical data only)
Guazzi M 1997 Italy Poor	Exercise tolerance: NSD between any 2 groups (range 516 seconds (placebo) to 602 seconds (losartan + ASA)	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Guazzi M 1999 Italy Fair	NR	NR
Guazzi M 1997 Italy Poor	NR	Not assessed

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Guazzi M 1999 Italy Fair	1 patient withdrew due to hypotension on E=P; 1 withdrew due to cough on E	Total withdrawals: 2/20 Withdrawals due to AEs: 2 (hypotension, cough)	"order of drug administration was uninfluential on the overall results, and the data of each corresponding treatment step were pooled together independently of the sequence"
Guazzi M 1997 Italy Poor	NR	NR	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Lang RM 1997 US Fair-poor	RCT, parallel group Multicenter 12 weeks Losartan Pilot Exercise Study	Inclusion criteria: on stable dose of ACI-I and diuretic for 6-12w minimum; symptomatic HF (NYHA II to IV), LVEF ≤ 45% Exclusion criteria: NR	Total n=116 Losartan 12.5 to 25 mg qd (n=38) Losartan 12.5 to 50 mg qd (n=40) Enalapril 2.5 to 10 mg bid (n=38)	Baseline exercise period, duration NR Placebo-run-in, with ACE-I, duration NR Wash-out period NR	Digoxin, non-ACE-I vasodilators
Vescovo G 1998 Italy Poor	RCT, parallel group Clinic 6 months	Men with CHF diagnosed with clinical criteria; symptoms for at least 2m; no prior treatment with ACE-I or ARB. Exclusion criteria: diabetes, PVD, neuromuscular disease, heart valve disease, lung disease.	Total n=16 (with an additional 8 healthy controls) Losartan: start 25 mg qd, titrated up to 50 mg qd after 1w Enalapril: started at 5 mg bid, titrated up to 10 mg bid after 1w	None	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Lang RM 1997 US Fair-poor	Assessments at weeks 1,2,4,6,9,11,12	Age: 58 (13) Sex: 78% male Race: 71% white	NYHA class II 47%, class III 51% Mean LVEF: 25% (7)	NR/NR/116	NR/NR/NR
Vescovo G 1998 Italy Poor	Maximal, symptom-limited cardiopulmonary exercise testing with a modified Naughton protocol	Age: L 56.7(2.7); E 59.7(5.5) Gender: 100% male Race: NR	Dilated cardiomyopathy: 9/16 Ischemic heart disease: 416 Hypertensive heart disease: 3/16 NYHA classification: I 2/16; IV 4/16	NR/NR/16 (plus 8 healthy controls)	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Lang RM 1997 US Fair-poor	6-min walk test (meters) at 12w: NSD between groups (change 2.3% (L25) to 0% (E20)) Treadmill test (s): increase L25 6.6% (p=0.028), L 50 6.7% (P=006), E 20 9.4% (P=0.03); NSD between any group and another Dyspnea-fatigue index: improved with L25 only (P=0.03) Signs and symptoms of HF: NSD between groups for these symptoms at F/U; NSD in worsening of HF; NSD in change in NYHA class (no change in 76 to 79% in each group)	NR
Vescovo G 1998 Italy Poor	Exercise duration: increase in both groups, P=0.03 for both L and E; between-group P-value NR	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Lang RM 1997 US Fair-poor	NSD in walk distance and exercise duration outcomes for age, sex, race, LVEF, and functional class	NR
Vescovo G 1998 Italy Poor	NR	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Lang RM 1997 US Fair-poor	Any AE (%): L25 65.8, L50 67.5; E20 60.5% Deaths: L25: 1 (sudden death); L 50 5 (sudden death, worsening HF, V arrhythmia, septicemia, unknown cause); E20: 0 "most common adverse clinical experiences … were dyspnea, worsening HF, dizziness, … URTI" One or more laboratory AE: L25: 16%; L50 25%; E20 11% NSD between groups at 12w in BUN, K+, Na+, uric acid Change serum Cr (mg/dL) at 12w: L25 0.02 (SD 0.14); L50 0.02 (SD 0.28); E20 0.08 (SD 0.15) (L50 vs E 20, P<0.05; E 20 vs baseline E20, P<0.05)	Total withdrawals: NR Withdrawals due to AEs: 1 patient from each of the 3 groups	
Vescovo G 1998 Italy Poor	NR	NR	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Telmisartan vs enalapril					
Dunselman PHJM 2001 The Netherlands REPLACE (the replacement of angiotensin converting enzyme inhibition) Fair	RCT, parallel-group Setting: NR 12 weeks	Inclusion criteria: ambulatory patients >=21y, in sinus rhythm, chronic moderate symptomatic HF (NYHA class II to III); LVEF <40%; in stable condition on a diuretic plus enalapril 10 mg bid for 20d prior to randomization. Exclusion criteria: any life-threatening diseases, clinically significant stenotic valvular disease, aortic or mitral regurgitation, hypertrophic or restrictive cardiomyopathy, history of MI, unstable angina, syncopy, surgery in prior 6m; others.	Enalapril 10 mg bid (continued from screening phase) (n=77) Telmisartan 10 mg qd (n=75) Telmisartan 20 mg qd (n=72) Telmisartan 40 mg qd (n=77) Telmisartan 80 mg qd (n=77)	Run-in: "screening phase": patients must be stable on at least enalapril 10 mg bid and a diuretic Wash-out	Diuretic, nitrates, beta-blockers, others

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Telmisartan vs enalapril					
Dunselman PHJM 2001 The Netherlands REPLACE (the replacement of angiotensin converting enzyme inhibition) Fair	Exercise capacity assessed using bicycle exercise testing protocol at 4 and 12 weeks	Total group Age: 64 (10) % male: 89 Race: NR	NYHA class II: 64% NYHA class III: 64% EF: 26.4% (7.2)	NR/NR/NR 378 took at least the first does of study treatment	11/NR/367

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Telmisartan vs enalapril		
Dunselman PHJM 2001 The Netherlands REPLACE (the replacement of angiotensin converting enzyme inhibition) Fair	Exercise duration: increase in all groups, from 1.4sec for enalapril 20 mg qd to 8.6 sec with telmisartan 10mg qd; NSD between baseline and F/U for any group; NSD between any telmisartan group and enalapril NYHA classification: NSD for any group Death: 2 on telmisartan 20 mg (v fib, sudden death); 1 on telmisartan 40mg (sudden death); 1 on telmisartan 80 mg (sudden death); 2 on enalapril 20mg (sudden death, MI)	Quality of life (Minnesota Living with Heart Failure): NSD between groups, NSD within any group (n=365)

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Telmisartan vs enalapril		
Dunselman PHJM 2001 The Netherlands REPLACE (the replacement of angiotensin converting enzyme inhibition) Fair	NR	Data on serious AEs regularly reviewed by monitoring committee; serious defined as fatal, life-threatening, disabling, or requiring or prolonging hospitalization

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Telmisartan vs enalapril			
Dunselman PHJM 2001 The Netherlands REPLACE (the replacement of angiotensin converting enzyme inhibition) Fair	Any AE: 54% overall; similar across treatment groups Cough: telmisartan any dose 9/301; enalapril 4/71 (N=0.3) Standard laboratory tests: NSD between groups; "few clinically relevant laboratory test abnormalities during study treatment"	Total withdrawals: 11 (exclusion), 3 for AEs, 6 deaths (total 20/378) Reasons for exclusion: failure to follow exercise protocol, no background diuretic, baseline K+ outside normal range Withdrawal due to AEs: telmisartan: 3 patients (2 worsening HF, 1 ataxia, dizziness, dyspesia); 0 with enalapril	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Telmisartan vs ramipril					
The ONTARGET Investigators 2008 40 countries ONTARGET: The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial Good	RCT, parallel group, noninferiority study of ARB compared with ACE; superiority of combination to ramipril International, out-patient, 733 centers F/U median 56 months	Inclusion criteria: ≥ 55y; coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. Exclusion criteria: major renal artery stenosis, uncontrolled hypertension, symptomatic CHF.	Total: 25620 Ramipril 5 mg qd, increased to 10 mg qd (n=8576) Telmisartan 80mg qd (n=8542) Ramipril + telmisartan (n=8502)	3-week, single-blind run-in where received ramipril 2.5 mg qd for 3d; then telmisartan 40mg qd and ramipril 2.5 mg qd for 7d; then ramipril l5mg and telmisartan 40 mg for 11-18d	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Telmisartan vs ramipril					
The ONTARGET Investigators 2008 40 countries ONTARGET: The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial Good	Visits at 6 weeks, then q6m	Age: R 66.4(7.2); T 66.4 (7.1); T+R 66.5(7.3) Sex: 27% women Race: Asian 13.7%; European 73%; Native/aboriginal 8.7%	CAD: 74% MI: 49% CVD: 85% Hypertension: 69% Diabetes: 38%	NR/29019 (began run-in)/25620	Withdrawn, total: 43/25,620 (not followed to primary end-point or end of study) Loss to F/U: NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Telmisartan vs ramipril		
The ONTARGET Investigators 2008 40 countries ONTARGET: The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial Good	Composite, primary outcome (death from CVD causes, MI, stroke, hospitalization for HF) R 16.5%; T 16.7%; R+T 16.3%; RR T vs R 1.01 (95% CI, 0.94 to 1.09); upper CI lower than the predefined noninferiority boundary of 1.13 (P=0.004), indicating that T is not inferior to R; lower boundary of the CI indicates that T was not superior to ramipril; RR R+T vs R 0.99 (95% CI, 0.92 to 1.07) Death from CVD causes, MI or stroke (secondary outcome): R 14.1%; T 13.9%; R+T; RR 0.99, 95% CI, 0.91 to 1.07; P=0.0001 for noninferiority; results consistent for all components of the primary outcome; RR T+R vs R, 0.99 (95% CI, 0.92 to 1.07) Total deaths: RR T vs R: 0.98 (95% CI, 0.90 to 1.07); RR R=T vs R, 1.07 (95% CI, 0.98 to 1.16); NSD with respect to specific causes of death Secondary outcomes: NSD between T and T+R and R for revascularization, hospitalization for angina, worsening or new angina, new diagnosis of diabetes, any heart failure, new atrial fibrillation. Renal impairment: T vs R, RR 1.04 (95% CI, 0.96 to 1.14); T+R vs R, RR 1.33 (1.22 to 1.44) (P<0.001) Renal dialysis: NSD between groups; rate increased in T+R (vs R, P=0.10)	Renal outcomes (Mann 2008) Primary renal outcome (composite of first occurrence of any dialysis, renal transplantation, doubling of CR, or death) T 13.4%; R 13.5%;, HR 1.00 (95% CI, 0.92 to 1.09); T+R 14.5%, HR 1.09 (95% CI, 1.01 to 1.18) Doubling of Cr: T vs R, HR 1.09 (0.89 to 1.34) ; R+T vs R, HR 1.24 (1.01 to 1.51, P=0.038) Dialysis, acute: more frequent with R+T than R P=0.02); similar for R and T (P=0.221) Dialysis, chronic: similar across groups eGFR: decreased all groups, T vs R, P<0.001; R+T vs R, P<0001

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Telmisartan vs ramipril		
The ONTARGET Investigators 2008 40 countries ONTARGET: The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial Good	Primary composite outcome; NSD between T and R and between T+R and R for all subgroups examined: CVD yes/no; SBP; diabetes, age, sex (all P>0.05) Renal outcomes, Mann 2008 Primary composite outcome T vs R: similar effects in all subgroups: diabetes, no diabetes, overt diabetic nephropathy, hypertension, microalbuminuria T+R vs R: no clear benefit with overt diabetic nephropathy, HT and diabetes; but tended to be harmful in patients with low renal risk (without HT or diabetes, both P<0.05)	AEs prespecified and serious AEs were reviewed by independent data and safety monitoring board

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Telmisartan vs ramipril			
The ONTARGET Investigators 2008 40 countries ONTARGET: The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial Good	Reason for permanent discontinuation: Hypotensive symptoms: R 1.7%; T 2.7%; R+T 4.8% (T vs R, P<0.001; R+T vs R, P<0.001) Syncope: R 0.2%; T 0.2%; R+T 0.3% (T vs R P=0.49; R+T vs R, P=0.03) Cough: R 4.2%; T 1.1%; R+T 4.6% (T vs R, P<0.001; T+R vs R, P=0.19 Diarrhea: R 0.1%; T 0.2%; R+T 0.5% (T vs R, P=0.20; R+T vs R, P<0.001) Renal impairment: R 0.7%, T 0.8%, R+T 1.1% (R vs T, P=0.46; R+T vs R, P<0.001[Mann 2008 P<0.0050]) Angioedema: NSD between groups Mann 2008, renal outcomes Renal abnormalities: R 10.2%; T 10.6%; T+R, 13.5% (RR 1,33, 95% CI 1.22 to 1.44, P<0.001) Urinary albumin excretion increased in all groups at study end (P<0.05), but to a lesser extent with T+R than R (P=0.0028) Risk of developing new microalbuminuria, macroalbuminuria, or both: NSD between T and R, lower with T+R than R (P=0.003)	Study drug discontinuation: R 23.7%; T 21.0%; R+T 22.7% (both drugs), 6.7% (one drug) Discontinuation for AEs: NR; data are presented on reasons for discontinuation and all reasons were AEs (Table 2)	

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Valsartan vs captopril					
Pfeffer MA 2003 Reed SD 2005 Prisant LM 2008 Anavekar NS, 2008 Anavekar NS, 2004 (NEJM) White HD, 2005 Anderson RE, 2008 International (24 countries) VALIANT Valsartan in Acute Myocardial Infarction trial Good	RCT Hospital and F/U clinic Median F/U: 24.7 months	Men and women ≥ 18y who had acute MI 0.5 to 10d prior complicated by HF and/or evidence of LVSD (EF ≤ 0.35 on echo or contrast angiography and ≤ 0.40 on radionuclide ventriculography); SBP>100 mmg Hg; serum CR <2.5 ml/dL. Exclusion criteria: prior intolerance or contraindication to ACEI or ARB; clinically significant valvular disease; another disease known to limit life expectancy .	Initial dosing: V: Valsartan: 20 mg qd (n=4909) V+C: Valsartan 20 mg + captopril 6.25 mg qd (n=4885) C: Captopril 6.25 mg qd (n=4909) For all groups: doses increased based on patient status in 4 steps with goal of reaching 80 mg valsartan bid; or valsartan 40 mg bid + captopril 25 mg tid; or captopril 25 mg tid during initial hospitalization Step 4: 160 mg valsartan bid; valsartan 80 mg bid + 50 mg captopril tid; or captopril 50 mg tid; by 3-m visit.	Run-in: NR Wash-out: other drugs: NR	Could take ACEI or ARB up o 12h before randomization

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Valsartan vs captopril					
Pfeffer MA 2003 Reed SD 2005 Prisant LM 2008 Anavekar NS, 2008 Anavekar NS, 2004 (NEJM) White HD, 2005 Anderson RE, 2008 International (24 countries) VALIANT Valsartan in Acute Myocardial Infarction trial Good	F/U visits q2m for year 1 and q4m thereafter; outcomes assessment by a blinded committee	Age: Mean (SD) (y) V: 65.0(11.8) V+C: 64.6(11.9) C: 64.9(11.8) Race: (% white) V: 93.8 V+C: 93.2 C: 93.5 Female (%) V: 31.5 V+C: 30.5 C: 31,3	Killip class (%) Class I V: 26.5 V+C: 28.4 C: 29.1 Class IV V: 6.4 V+C: 6.4 C: 6.3 Diabetes mellitus (%) V: 23,1 V+C: 23.5 C: 22.8 Ejection fraction (%) V:35,3(10.4) V+C: 35.3(10.3) C: 35.3(10.4)	Screened: NR Eligible: NR Enrolled: 14,808 V: 4909 V+C: 4885 C: 4909	Withdrawn: Inadequate consent: 105 No study drug administered: 77 Lost to F/U: NR Analyzed: 14,808

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Valsartan vs captopril		
Pfeffer MA 2003 Reed SD 2005 Prisant LM 2008 Anavekar NS, 2008 Anavekar NS, 2004 (NEJM) White HD, 2005 Anderson RE, 2008 International (24 countries) VALIANT Valsartan in Acute Myocardial Infarction trial Good	Pfeffer 2003 HR death (97.5% CI) V vs C: 1.00 (0.90 to 1.11) V+C vs C: 0.98 (0.89 to 1.09) Subgroups (age, sex, diabetes, prior MI, HF, LVD, ACE-I use): NSD in effects of treatment on risk of death or on secondary composite CV endpoint for either V vs C or V+C vs C (P>0.05) Kaplan-Meier estimate of mortality at 1y: V: 12.5% V+C:12.3% C: 13.3% HR for death from CV cause, or MI, or HF hospitalization: (97.5% CI) V vs C: 0.95 (0.88 to 1.03) V+C vs C: 0.97 (0.89 to 1.05) Post hoc analysis of hospitalizations for MI or HF: V vs C: proportion of patients: P=0.50; number of admissions 0.51 V+C vs C: proportion of patients P=0.001; number of admissions: P=0.007 V not inferior to C for mortality by prespecified criteria	Reed 2005 Annual rates of hospitalizations by treatment group, excluding hospitalization for qualifying MI (number per patient per year) V: 0.61 (vs C, P=0.70) V+C: 0.58 (vs C, P=0.10) C: 0.60 Quality of life, Euro-QOL-5D: maintained throughout the trial; NSD among treatment groups; visual analogue scores (P=0.95) and health preference scores (P=0.13)

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Valsartan vs captopril		
Pfeffer MA 2003 Reed SD 2005 Prisant LM 2008 Anavekar NS, 2008 Anavekar NS, 2004 (NEJM) White HD, 2005 Anderson RE, 2008 International (24 countries) VALIANT Valsartan in Acute Myocardial Infarction trial Good	Prisant 2008: subset analysis including 3790 white and 340 African-American patients Baseline: African-American patients more likely (P<0.05) than whites to be younger, female, have diabetes or chronic CHF or hypertension; had lower eGFR, higher SBP and DBP, higher Killip class Treatment effects across 3 treatment groups similar for African-Americans for primary and secondary outcomes (cumulative mortality presented as a figure only) Adverse event rates Hypotension: white > African-American (P<0.0001) Dry cough: white = African-American (P=0.6) Angioedema: white 1.2%, AA 2.1% (P=0.2); most common reason for discontinuation in AAs Renal dysfunction: African Americans were more likely to develop renal dysfunction and hyperkalemia requiring valsartan discontinuation than whites (P<0.05); this difference was not significant after adjusting for baseline chronic renal insufficiency (p=0.13) Valsartan discontinuation for renal causes persisted after adjusting for baseline renal insufficiency (P<0.0001) Anavekar 2004: none of the treatments altered the association of decreased baseline eGFR and increase in CV events and deaths Diabetes vs no diabetes (Anavekar 2008) None of the 3 treatment arms altered the association between baseline eGFR and the CV composite end point (P=0.51): over all 3 treatment groups, each 10-unit decease in eGFR was associated with an increase in the HR for patients with and without diabetes (data NR) Age subgroups (White 2005) <65y (n=6988), 65-74 (n=4555), 75-84 (n=2777), >85y (n=383) Composite outcome did not differ between the 3 treatments in any age group; other outcomes NR specifically (abstract states that "outcomes did not differ...") Age subgroups (Anderson 2008) No interaction between age groups (18-45, 45-60, >65) and treatment arms, and composite CV outcome (CVD death, HF, MI, cardiac arrest, stroke)	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Valsartan vs captopril			
Pfeffer MA 2003 Reed SD 2005 Prisant LM 2008 Anavekar NS, 2008 Anavekar NS, 2004 (NEJM) White HD, 2005 Anderson RE, 2008 International (24 countries) VALIANT Valsartan in Acute Myocardial Infarction trial Good	Resulting in permanent discontinuation of treatment (%) Hypotension: V: 1.4 (vs C, P<0.05) V+C: 1.9 (vs C, P=0.05) C: 0.8 Renal causes: V: 1.1 V+C: 1.3 (vs C, P<0.05) C: 0.8 Hyperkalemia: V: 0.1 V+C: 0.2 C: 0.1 Cough V: 0.6 (vs C, P<0.05) V+C: 2.1 C: 2.5 Angioedema: V: 0.2 C+V: 0.2 C: 0.3 Taste disturbance: V: 0.2 (vs C, P<0.05) V+C: 0.3 C: 0.4 Rash V: 0.3 (vs C, P<0.05) V+C: 0.7 C:0.8	% not taking study drug at 1y V: 15.3 V+C: 19.0 C: 16.8 V vs C: P=0.07 V+C vs C: P=0.007 Total withdrawals (%) V: 29.5 V+C: 23.4 C: 21.6 Withdrawals due to AEs (%): V: 5.8 V+C: 9.0 C: 7.7	AEs in age subgroups (White 2006): angioedema did not differ between treatment groups in all age groups; in all 3 treatment groups, elderly were more likely to have study medications stopped or reduced because of renal dysfunction or have any AE lead to dose reduction; hypotension did not differ between treatment groups; coughing similar frequency in younger and older

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Study Design Setting Follow-up interval	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Valsartan vs enalapril					
Willenheimer R 2002 Sweden HEAVEN Study (Heart Failure Exercise Capacity Evaluation) Fair	RCT, parallel group, non-inferiority of valsartan to enalapril NR 12 weeks	Inclusion criteria: chronic, stable symptomatic heart failure, NYHA class II-III, LVEF ≤ 0.45, ≥ 18y, on an ACE-I for HF for at least 3m; able to perform a 6-min walk test. Exclusion criteria: significant primary valvular disease HF due to pulmonary disease, infective cardiomyopathy, recent MI, unstable CAD, Cr >200 umol/L, use of ACE-I within 3m; others.	Valsartan: start with 80 mg qd, titrate to 160 mg qd (n=70) Enalapril: start with 5 mg qd, titrate up to 10 mg bid (n=71)	2-weeks placebo run-in, continued open ACE-I No wash-out	"other medication was kept as stable as possible during the entire study"

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Valsartan vs enalapril					
Willenheimer R 2002 Sweden HEAVEN Study (Heart Failure Exercise Capacity Evaluation) Fair	Assessments at week 0, 6 and 12	Age: V 68 (NR), E 67 (NR) Sex (% female): V 51, E 44 Race: NR	NYHA classification, % II/III: V 71/29, E 70/30	NR/NR/146	23/NR/134 141/146 randomized ITT population (received 1+ doses of study medication and 1+ measure after baseline): V 67, E 67 Per protocol population: V 61, E 57 Loss to F/U NR; paper did not give

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Results	Results: Quality of life; healthcare utilization
Valsartan vs enalapril		
Willenheimer R 2002 Sweden HEAVEN Study (Heart Failure Exercise Capacity Evaluation) Fair	Change in 6-min walk test distance (ITT population, per protocol similar): least squares means treatment difference (V-E): 1.12 m (95% CI, -21.89 to 24.12). P<0.001 for noninferiority; superiority P=0.462	NSD between groups in the dyspnea-fatigue index and the Minnesota Living with HF Questionnaire

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Population subgroup analyses	Method of adverse events assessment
Valsartan vs enalapril		
Willenheimer R 2002 Sweden HEAVEN Study (Heart Failure Exercise Capacity Evaluation) Fair	Age (<65y versus ≥ 65 years), gender, pre-randomization beta-blocker use, NYHA class, and etiology of HF produced no significant difference between the two groups with regard to QoL and dyspnea-fatigue index	NR

Evidence Table 1. Data abstraction of coronary heart disease/left ventricular dysfunction/heart failure trials

Study, year Country Trial name Quality	Adverse Events	Total withdrawals; withdrawals due to adverse events	Comments
Valsartan vs enalapril			
Willenheimer R 2002 Sweden HEAVEN Study (Heart Failure Exercise Capacity Evaluation) Fair	Any AE (%): V 50, E 63 (P>0.05) Deaths: V 1.4% (1 patient due to HF), E 7.6% (5 patients, CHF, MI, sudden death (n=2), pneumonia) Worsening CHF: V 5.7%, E 1.4% Headache: V 5.7%, E 1.4% Diarrhea: V 4.3%, E 2.8% Dizziness: V 4.3%, E 8.5% Serious AEs: V 9%, E 16% (not defined, included deaths)	Total withdrawals: V 9/71; E 14/71 Withdrawals due to AEs: V 2/70; E 3/71	

Evidence Table 2. Quality assessment of coronary heart disease/left ventricular dysfunction/heart failure trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care providers masked?	Patients masked?	Was attrition reported?
Dickstein 2002	Yes	Method not described	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Dickstein 1995	Method not described	Method not described	Yes	No	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes
Dunselman 2001	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No
Guazzi 1997	Method not described	Method not described	No, hypertension and ejection fraction different between groups	Yes	Yes	Yes	Yes	Yes	No
Guazzi 1999	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Lang 1997	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No
McKelvie 1999	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes

Evidence Table 2. Quality assessment of coronary heart disease/left ventricular dysfunction/heart failure trials

Author	Were crossovers reported?	Was adherence reported?	Was contamination reported?	Method for handling carry-overs?	Were withdrawal rates differential or high?	Was loss-to-follow-up differential or high?	Was an ITT used?
Dickstein 2002	No	No	No	NA	No; Attrition 16% in one group and 22% in another group, but all	No	Yes
Dickstein 1995	No	No	No	NA	No	No	Yes; for symptom outcomes and safety
Dunselman 2001	No	No	No	NA	Unable to determine	Unable to determine	Yes; 367/378 analyzed for efficacy analyses
Guazzi 1997	No	No	No	washout	Unable to determine	Unable to determine	Unable to determine
Guazzi 1999	Yes	No	No	NR	No	No	Unable to determine
Lang 1997	No	No	No	NA	Unable to determine	Unable to determine	Unable to determine
McKelvie 1999	No	No	No	NA	No; 1% did not undergo final assessment	No	Yes

Evidence Table 2. Quality assessment of coronary heart disease/left ventricular dysfunction/heart failure trials

Author	Were there any post-randomization exclusions?	Efficacy/Quality Rating/Consensus
Dickstein 2002	No	Good
Dickstein 1995	No	Fair
Dunselman 2001	Yes; 11 exclusions for protocol violations	Fair
Guazzi 1997	Unable to determine	Poor
Guazzi 1999	No	Fair
Lang 1997	Unable to determine	Fair-poor
McKelvie 1999	Yes; 1 patient excluded for protocol violation	Fair

Evidence Table 2. Quality assessment of coronary heart disease/left ventricular dysfunction/heart failure trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care providers masked?	Patients masked?	Was attrition reported?
McMurray 2008	Yes	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Yes	Yes
ONTARGET 2008	Yes	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Pfeffer 2003	Yes	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Pitt 2000	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Pitt 1997	Method not described	Method not described	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Vescovo 1998	Method not described	Method not described	Yes	Yes	Yes	NR	NR	NR	No
Willenheimer 2002	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Yip 2008	Yes	Method not described	Yes	Yes	Yes	Yes	No	No	No

Evidence Table 2. Quality assessment of coronary heart disease/left ventricular dysfunction/heart failure trials

Author	Were crossovers reported?	Was adherence reported?	Was contamination reported?	Method for handling carry-overs?	Were withdrawal rates differential or high?	Was loss-to-follow-up differential or high?	Was an ITT used?
McMurray 2008	No	No	No	NA	No	No	No; Total attrition 9.0% and 8.5%; unclear how missing data handled
ONTARGET 2008	No	Yes	No	NA	No	No	Yes
Pfeffer 2003	Yes	Yes	Yes	NA	No	No	Yes
Pitt 2000	No	No	No	NA	No	No	Yes
Pitt 1997	No	No	No	NA	Yes; 18% in losartan group and 30% in captopril group, but all included in analysis	No	Yes
Vescovo 1998	No	No	No	NA	Unable to determine	Unable to determine	Unable to determine
Willenheimer 2002	No	No	No	NA	No	No	Yes
Yip 2008	No	No	No	NA	No	No	Unable to determine

Evidence Table 2. Quality assessment of coronary heart disease/left ventricular dysfunction/heart failure trials

Author	Were there any post-randomization exclusions?	Efficacy/Quality Rating/Consensus
McMurray 2008	8/302 excluded for protocol violation or administrative problems	Fair
ONTARGET 2008	No	Good
Pfeffer 2003	No	Good
Pitt 2000	No	Fair
Pitt 1997	No	Fair
Vescovo 1998	Unable to determine	Poor
Willenheimer 2002	Unable to determine; Withdrawals noted, but reason not stated	Fair
Yip 2008	No	Fair

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

Losartan compared with captopril

Quality Assessment						Summary of Findings				
						Results by Study			Summary effect across studies	Quality of the evidence for each outcome (GRADE)
Study Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Absolute effect		Relative effect		
						Losartan	Captopril			
All-cause mortality										
ELITE	Fair	(-1) Data inconsistent	(0) Large study, likely generalizable to like populations	(0) 3 studies, although low event rates	(0) Populations differ somewhat across studies	4.8%	8.7%	P=0.035	Results inconsistent, effect of losartan unclear, in acute MI (OPTIMAAL) losartan not noninferior to captopril	Moderate
ELITE II	Fair					15.9%	17.7%	P=0.16		
OPTIMAAL	Good					18%	16%	P=0.07; did not satisfy the non-inferiority criterion		
	Good: 1 Fair: 2 Limitations: (0)									
Cardiovascular deaths										
ELITE	Fair	(-1) Data inconsistent	(0) Large study, likely generalizable to like populations	(0) 3 studies, although low event rates	(0) Populations differ somewhat across studies	MI deaths: 1/352 (0.03%)	MI deaths: 1.1%	RR 0.76 (-0.83 to 0.97	Lower rate with losartan in earlier (ELITE) trial, but higher rates in 2 subsequent studies in somewhat different populations	Moderate
ELITE II	Fair					MI deaths: 2.0%	MI deaths: 1.8%	RR 1.11 (0.66 to 1.85)		
OPTIMAAL	Good					Cardiovascular deaths: 15.3%	Cardiovascular deaths: 13.3%	RR 1.17 (1.01 to 1.34), P=0.032		
	Good: 1 Fair: 2 Limitations: (0)									

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

Sudden death or resuscitated arrest										
ELITE	Fair	(-1) Data inconsistent	(0) Large study, likely generalizable to like populations	(0) 3 studies, although low event rates	(0) Populations differ somewhat across studies	1.4%	3.8%	RR 0.64 (0.03 to 0.86)	Lower rate with losartan in earlier ELITE trial, but higher rates in 2 subsequent studies in somewhat different populations	Moderate
ELITE II	Fair					9.0%	7.3%	P=0.08		
OPTIMAAL	Good					9.0%	7.0%	RR 1.19 (95% CI, 0.99 to 1.43), P=0.072		
	Good: 1 Fair: 2 Limitations: (0)									
Cardiovascular events										
ELITE	Fair	NA, 1 study	(0) Large study, likely generalizable to like populations	(-1) Large study, but low event rate	(0) Populations differ somewhat across studies	NR	NR	NA	NSD Fatal or nonfatal reinfarction between groups in OPTIMAAL	Moderate
ELITE II	Fair					NR	NR	NA		
OPTIMAAL	Good					Fatal or nonfatal reinfarction: 14%	Fatal or nonfatal reinfarction: 14%	RR 1.03 (95% CI, 0.89 to 1.18), P=0.72		
	Fair: 1 Limitations: (-1)									
Hospital admissions										
ELITE	Fair	(-1) Data inconsistent	(0) Large studies likely generalizable	(0) Large studies	(0) Populations differ somewhat across studies	Total: 22.2% HF: 5.7%	Total: 29.7% HF: 5.7%	Total: L < C, P=0.014 HF: L=C, P=0.89	Results inconsistent; effect unclear	Moderate
ELITE II	Fair					Total; 41.8% HF: 17.1%	Total: 40.5% HF: 18.6%	Total: P=0.45 HF: P=0.032		

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

OPTIMAAL	Good					HF: 11.2%	HF: 9.7%	HF: RR 1.16(0.98 to 1..37), P=0.072		
	Good: 1 Fair: 2 Limitations: (0)									
NYHA functional class										
ELITE	Fair	(0) Between-group analyses consistent	(0)	(0) Large sample sizes	(0) Note that OPTIMAAL population is acute MI with HF or decreased EF	Improved, P≤ 0.001	Improved, P≤ 0.001	NSD between groups	Improved in 2 HF studies; NSD between treatment groups in all 3 studies	High
ELITE II	Fair					Improved, P≤ 0.01	Improved, P≤ 0.01	NSD between groups		
OPTIMAAL	Good					NSD	NSD	NSD between groups		
	Good: 1 Fair: 2 Limitations: (0)									
Quality of life										
ELITE	Fair	(0) Consistent results in 2 studies	(0) Data likely generalizable to similar populations	(0) Large sample sizes	Populations differ somewhat across studies	↑ QoL	↑ QoL	NSD between groups	QoL improved with NSD between groups	High
ELITE II	Fair					↑ QoL	↑ QoL	NSD between groups		
OPTIMAAL	Good					NR	NR	NA		
	Good: 1 Fair: 2 Limitations: (0)									

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

Enalapril compared with losartan

Quality Assessment						Summary of Findings				
						Results by Study			Summary effect across studies	Quality of the evidence for each outcome (GRADE)
Study Design	Study quality	Inconsistency	Indirectness	Imprecision	Other considerations	Absolute effect		Relative effect		
						Losartan	Captopril			
All-cause mortality										
Dickstein 1995	Fair					NR	NR	NA		NA
Guazzi 1997	Poor					NR	NR	NA		
Guazzi 1999	Fair					NR	NR	NA		
Lang 1997	Fair-poor					NR	NR	NA		
Vescovo 1998	Poor					NR	NR	NA		
	Good: 0 Fair: 2 Fair-poor: 1 Poor: 2									
Cardiovascular deaths										
Dickstein 1995	Fair					NR	NR	NA		NA
Guazzi 1997	Poor					NR	NR	NA		
Guazzi 1999	Fair					NR	NR	NA		
Lang 1997	Fair-poor					NR	NR	NA		
Vescovo 1998	Poor					NR	NR	NA		
	Good: 0 Fair: 2 Fair-poor: 1 Poor: 2									

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

Sudden death or resuscitated arrest										
Dickstein 1995	Fair					NR	NR	NA		**NA**
Guazzi 1997	Poor					NR	NR	NA		
Guazzi 1999	Fair					NR	NR	NA		
Lang 1997	Fair-poor					NR	NR	NA		
Vescovo 1998	Poor					NR	NR	NA		
	Good: 0 Fair: 2 Fair-poor: 1 Poor: 2									
Cardiovascular events										
Dickstein 1995	Fair					NR	NR	NA		NA
Guazzi 1997	Poor					NR	NR	NA		
Guazzi 1999	Fair					NR	NR	NA		
Lang 1997	Fair-poor					NR	NR	NA		
Vescovo 1998	Poor					NR	NR	NA		
	Good: 0 Fair: 2 Fair-poor: 1 Poor: 2									
Hospital admissions										
Dickstein 1995	Fair					NR	NR	NA		NA
Guazzi 1997	Poor					NR	NR	NA		
Guazzi 1999	Fair					NR	NR	NA		

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

Lang 1997	Fair-poor					NR	NR	NA		
Vescovo 1998	Poor					NR	NR	NA		
	Good: 0 Fair: 2 Fair-poor: 1 Poor: 2									
NYHA functional class, symptoms, exercise capacity										
Dickstein 1995	Fair	(0) Data are consistent	(-1) Is outcome of interest Studies are small and potentially selected groups with limited generalizability	(-1) 3 studies with small sample sizes	(0)	NSD exercise capacity; symptoms and NYHA class improved	NSD exercise capacity; symptoms and NYHA class improved	NSD between groups	Exercise capacity and symptoms improved within both treatment groups; NSD between groups	Low
Guazzi 1997	Poor					NR	NR	NSD exercise tolerance between groups		
Guazzi 1999	Fair					NR	NR	NA		
Lang 1997	Fair-poor					↑ exercise tolerance 50mg group (P=0.06); ↑ walk test (P-value NR)	↑ exercise tolerance (P=0.03); ↑ walk test (P-value NR)	NSD between groups in exercise tolerance, signs and symptoms of HF		
Vescovo 1998	Poor					↑ exercise tolerance, P=0.03	↑ exercise tolerance, P=0.03	NR		
	Good: 0 Fair: 2 Fair-poor: 1 Poor: 2									
Quality of life										
Dickstein 1995	Fair	NA	(-1) Is outcome of	(-1) Study is	(0)	NR	NR	NA	NSD between groups	Low

Evidence Table 3. Evidence profile of coronary heart disease/left ventricular dysfunction/heart failure

Dickstein 1995	Fair	NA	(-1) Is outcome of interest Study is very small and potentially selected population	(-1) Study is small (n=20)	(0)	NR	NR	NA	NSD between groups	Low
Guazzi 1997	Poor					NR	NR	NA		
Guazzi 1999	Fair					NSD	NSD	NSD between groups		
Lang 1997	Fair-poor					NR	NR	NA		
Vescovo 1998	Poor					NR	NR	NA		
	Fair: 1 Limitations: (-1)									

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration	Run-in/Washout Period
Andersen 2005 CALM II	Parallel design Double-blind Single Center:	Inclusion: Type 1 and 2 diabetics with seated office SBP between 120 and 160 mm Hg during treatment with lisinopril 20 mg once daily for at least 1 month; male or female, ≥ 18 years of age Exclusion: Age < 18 and > 75 years; nondiabetic cause of secondary hypertension or malignant hypertension; cardiovascular events within 6 months before randomization; impaired renal function with a serum creatinine ≥ 130 μmol/l or plasma potassium outside normal range; pregnancy or breast feeding	Up-titration of lisinopril, total daily dose of 40 mg Dual therapy with lisinopril 20 mg plus candesartan 16 mg x 12 months	Run-in NR Washout NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (Data are mean ± SD and geometric mean (range), unless otherwise indicated)	Number screened/ eligible/ enrolled
Andersen 2005 CALM II	Other antihypertensive drugs, like diuretics, calcium channel blockers, or beta blockers were allowed, as long as the dosage of these drugs was not changed during the study period	Serum creatinine, urinary albumin excretion, albumin-to-creatinine ratio (UACR), creatinine clearance	Lisinopril/dual blockade Age, years, mean (SD): 56±9/54±9 75% male Ethnicity NR	Lisinopril/dual blockade: BMI, kg/m^2: 30±5/29±5 Urine albumin, mg/l: 53 (7-675)/56 (8-914) UACR, mg/mmol: 2.0 (1-134)/2.1 (1-160) Duration of diabetes, years: 11 (1-43)/12 (1-46) Duration of hypertension, years: 6.3 (1-25)/8.8 (1-30) HbA_{1c}: 8.2±1.3/8.4±1.3 Concomitant antihypertensive treatment, N (%): None: 21 (57%)/13 (34%) Thiazide: 8 (22%)/20 (53%), *P*<0.05 Calcium channel blocker: 8 (22%)/9 (24%) Beta blocker: 5 (13%)/6 (16%)	NR/NR/75

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse events assessment
Andersen 2005 CALM II	9 (12%)/0/60 (80%)	Lisinopril vs dual blockade: Urinary albumin excretion rate, mg/mmol, mean reduction at final follow-up: -0.16 vs -0.42; *P*=0.38 UACR, mg/ml: *P*=0.38, data shown in graphical form only Serum creatinine, mg/dL: 1.00±0.19 vs 0.97±0.17, *P*=0.66 Creatinine clearance, ml/min: 114±32 vs 119±30, *P*=0.65	NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Andersen 2005 CALM II	Any adverse event: NR	Lisinopril vs dual blockade	
	Increases in potassium: 1 (2.7%) vs 2 (5.3%), *P*=NR	Total withdrawals: 5 (13.5%) vs 4 (10.5%), *P*=NR	
	Serious drug-related events: None	Withdrawals due to adverse events: 2 (5.4%) vs 3 (7.9%); *P*=NR	
	Fatigue and dizziness: 1 (2.7%) vs 1 (2.6%), *P*=NR	Withdrawals due to increased potassium: 1 (2.7%) vs 2 (5.3%), *P*=NR	

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration	Run-in/Washout Period
Fogari R, 2008 Italy	Double-blind, randomized, parallel-group, study Single center	Inclusion: Outpatients of either sex, with mild essential hypertension (140 systolic blood pressure (SBP) < 160 mm Hg and/or 90 < diastolic blood pressure (DBP) < 100 mm Hg), in sinus rhythm but with at least two electrocardiogram (ECG)-documented episodes of symptomatic AF in the previous 6 months, and without any antiarrhythmic treatment. Previous AF episodes could be self-terminating or terminated after pharmacological and/or electrical cardioversion; cardioversion, however, had to be performed between a maximum of 6 months and a minimum of 8 weeks before enrollment and no patient underwent cardioversion in the last 8 weeks. Exclusion: In treatment with AT1R blockers, ACE-Is, or antiarrhythmic agents, cardioversion within the last 8 weeks, secondary hypertension, myocardial infarction or stroke in the preceding 6 months, congestive heart failure, coronary heart disease, valvular disease, diabetes mellitus, a left atrium size >45 mm, need to continue the use of digitalis, cardiac surgery during the pervious 6 months, significant thyroid, pulmonary, renal, or hepatic disease, pregnancy or fertile female, known hypersensitivity or contraindications to the study medications.	Amlodipine 5 mg once daily (o.d.) or ramipril 5 mg o.d. or valsartan 160 mg o.d. one year	2-week antihypertensive placebo period

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (Data are mean ± SD and geometric mean (range), unless otherwise indicated)	Number screened/ eligible/ enrolled
Fogari R, 2008 Italy	NR	Clinic blood pressure (BP) and a 24-h electrocardiogram (ECG) were evaluated monthly. Patients were asked to report any episode of symptomatic AF and to perform an ECG as early as possible.	Amlodipine / Ramipril / Valsartan Age (years) 65 ± 7 / 64 ± 7 / 66 ± 8 0.64 Male 44.7% / 46.0% / 46.7% Ethnicity NR	Weight (kg) 73 ± 9 / 74 ± 10 / 73 ± 10 Smoking (%) 14 / 15 / 16 SBP (mm Hg) 154 ± 8 / 152 ± 7 / 153 ± 7 0.55 DBP (mm Hg) 95 ± 3 / 95 ± 2 / 95 ± 3 HR (beats/min) 74 ± 11 / 75 ± 10 / 76 ± 11 Echocardiogram E DLV dimension (mm) 51.1 ± 0.8 / 50.6 ± 0.6 / 49.9 ± 0.7 Ejection fraction (%) 60.4 ± 8.2 / 62.1 ± 8.4 / 61.2 ± 9.1 LA inferosuperior dimension (mm) 40.4 ± 2.2 / 40.1 ± 1.9 / 40.6 ± 2.4 Septal thickness (mm) 10.8 ± 0.26 / 10.9 ± 0.31 / 10.7 ± 0.27 Patients with LVH (%) 17 (13.8) / 14 (11.3) / 16 (13.1) Previous AF episodes (N) 2.2 ± 0.9 / 2.4 ± 1.1 / 2.3 ± 1.0	450/ 428/ 369

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse events assessment
Fogari R, 2008 Italy	80/0/369	Amlodipine / Ramipril / Valsartan Recurrence of AF at 12 weeks 17/11/5** at 1 year 46/26*/16** *** Days to recurrence n(SD) 61 ± 55/126 ± 79*/160 ± 94* *P < 0.05 vs. amlodipine; **P < 0.01 vs. amlodipine; ***P < 0.05 vs. ramipril.	NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Fogari R, 2008 Italy	Only those that caused withdrawals	Amlodipine / Ramipril / Valsartan 80 withdrawals (26 (21.1%) / 31 (25%) / 23 (18.9%)), 12 due to AEs (6 (4.9%) / 5 (4.0%) / 1 (1%))	

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration	Run-in/Washout Period
Menne J, 2008 Hungary, Germany The Valeria trial	RCT (active-controlled, double-blind, parallel-group) Multicenter (24 primary and hospital centers in Hungary and Germany)	Inclusion: Men and women 18-75 years of age; essential hypertension (defined as mean sitting diastolic blood pressure ≥85 mm Hg and <110 mm Hg) and microalbuminuria (defined as UACR in women ≥3.5 mg/mmol/l and ≤35.0 mg/mmol and in men ≥2.5 mg/mmol/l and ≤ 25.0 mg/mmol). To fulfill the criteria of microalbuminuria , 2 of 3 first morning void urines needed to be positive during the 3 week screening phase Exclusion: Primary kidney disease; renal impairment defined as creatine clearance less than 30 ml/min; serum potassium values > 5.5 mmol/l; heart failure; significant arrhythmias or bradycardia; relevant valvular disease; type I diabetes; uncontrolled type II diabetes mellitus with HbA1c > 80%; history of myocardial infarction, percutaneous transluminal coronary angioplasty, bypass surgery, or stroke within the last 12 months prior to study inclusion; unstable angina pectoris; renal transplantation; severe hepatic disease or hepatic failure; any malignant concomitant diseases or history of malignant diseases within the last 5 years; systematic inflammatory diseases; pregnancy or breast feeding; psychiatric disease; history of drug or alcohol use or both	Lisinopril 40mg Valsartan 320 mg Combination of Valsartan/Lisinopril 320/20 mg Screening (3 weeks), active-treatment (30 weeks) Following the washout period, all patients received single-blind placebo for 1 week, then were randomized to study group. During the first 6 weeks of treatment the medication dose was titrated in three steps to the maximum tolerated dose The dose ranges were 10-40 mg Lisinopril, 80-320 mg Valsartan, and the combination of 80/10 - 320/20 mg Valsartan/Lisinopril. Most patients were treated to the maximum dose	Washout/placebo- run-in phase of 3 weeks

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (Data are mean ± SD and geometric mean (range), unless otherwise indicated)	Number screened/ eligible/ enrolled
Menne J, 2008 Hungary, Germany The Valeria trial	In the case of inadequate BP control 9 weeks after randomization, the addition of either hydrochloride (12.5/25 mg) or amlodipine (5/10 mg) or both as concomitant antihypertensive medication was allowed in order to achieve the target BP of <130/80 mmHg. Other antihypertensive medications were not allowed	Outcomes were assessed by regular monitoring and recording of adverse advents, physical examinations, and laboratory assessments. A complete physical examination was performed at visits 1 and 12, and vital signs were taken at each visit. Fasting blood samples were taken at visits 1, 4-9, and 12	Lisinopril/Valsartan/Combination Lisinopril and Valsartan Age ± SD 59.7±9.5/57.0±11.4/59.2±11.4 % male: .2/66.7/77.5 Ethnicity NR	Lisinopril/Valsartan/Combination Lisinopril and Valsartan BMI (kg/m^2): 32.9±5.9/31.3±7.1/31.5±5.7 Creatinine clearance (mg/ml): 105.4±36.3/118.8±48.3/120.7±58.4 UACR (mg/mmol): 9.6/9.1/9.5 Concomitant diseases (%) Cardiac disorders: 25.5/11.6/18.6 Type II diabetes: 74.5/74.4/76.7 Hyperlipidemia/dyslipidemia: 51.1/41.9/34.9 Prior antihypertensive medication (%) ACE inhibitors: 59.6/51.1/53.5 AT II receptor blocker: 23.4/11.7/9.4 Calcium antagonists: 19.1/16.3/23.3 Beta blockers: 38.1/27.9/32.5 Diuretics: 19.3/16.3/11.7	331/NR/133 (47 to Lisinopril, 43 to Valsartan, 43 to Valsartan/Lisinopril)

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse events assessment
Menne J, 2008 Hungary, Germany The Valeria trial	Lisinopril/Valsartan/Combination Lisinopril and Valsartan Number withdrawn: NR/2/3 Lost to FU: NR/NR/NR Analyzed: 47/42/40	Lisinopril/Valsartan/Combination Lisinopril and Valsartan Geometric mean UACR at baseline (mg/mmol): 9.6/9.1/9.5 Geometric mean UACR after 30 weeks of treatment (mg/mmol): 5.7/4.5/3.6 Reduction in UACR: Valsartan/Lisinopril vs Lisinopril: adjusted ratio: 60%, CI: 38-94%, p=0.029 Valsartan/Lisinopril vs valsartan: adjusted ratio: 80%, CI: 50-126%, p=0.332 Valsartan vs Lisinopril: adjusted ratio: 76%, CI: 48-118%, p=0.213 After 30 weeks of antihypertensive treatment, microalbuminuria had normalized in 38% of patients on Valsartan/Lisinopril, 31% of Valsartan, and 17% on Lisinopril, and the difference between the Valsartan/Lisinopril and Lisinopril groups was statistically significant (p=0.034) There were 6.4% of patients on Lisinopril, 7.1% on Valsartan, and 2.5% on Valsartan/Lisinopril still with macroalbuminuria at the end of the study period; the differences were not statistically significant	The type and severity of adverse events was recorded at each visit

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Menne J, 2008 Hungary, Germany The Valeria trial	Lisinopril/Valsartan/Combination Lisinopril and Valsartan Total: 29/27/31 Mild: 11/10/16 Moderate: 13/15/13 Severe: 5/2/2 Serious: 5/1/4 AE leading to permanent discontinuation: 4/3/3 AE possibly related to study drug: 6/8/11 Hypotension: 1/4/5 Vertigo: 2/1/1 Dizziness: 1/1/1 Hyperkalemia:1/1/1 Cough:2/0/1 Headache: 1/1/0	Lisinopril/Valsartan/Combination Lisinopril and Valsartan Total withdrawals: NR/2/3 Withdrawals due to AEs: 4/3/3	

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration	Run-in/Washout Period
Rake 2001 United States	Double-blind, randomized, parallel-group, study Multicenter (18)	Inclusion: Male and female patients, of at least 18 years of age, with mild to moderate hypertension and a history of ACE inhibitor induced cough Exclusion : NR	Eprosartan, enalapril and placebo 6 weeks	4-5 week placebo run in, 3-4 weeks enalapril then 2 to 4 weeks placebo washout then 6 week RCT

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (Data are mean ± SD and geometric mean (range), unless otherwise indicated)	Number screened/ eligible/ enrolled
Rake 2001 United States	NR	PGWB and self reported dry unproductive cough	Placebo / Enalapril / Eprosartan Age 57/58/55 % male 48/50/59 Ethnicity NR	Placebo / Enalapril / Eprosartan Smoking history? Yes 5 (12%) / 3 (7%) / 4 (9%) No 37 (88%) / 41 (93%) / 42 (91%) Smokers cough? Yes 1 (2%) / 0 (0%) / 0 (0%) No 41 (98%) / 44 (100%) / 46 (100%)	231/NR/136

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse events assessment
Rake 2001 United States	27 withdrawals/4 LTF/132	Mean change from baseline in PGWB Anxiety −0.49 vs. 0.33 vs. −0.14 Depression −0.39 vs. 0.02 vs. −0.18 Positive wellbeing 0.10 vs. 0.40 vs. 0.12 Self-control −0.05 vs.−0.02 vs. 0.00 General Health 0.63 vs.−0.38 vs. −0.13 Vitality 0.36 vs. 0.60 vs. 0.14 PGWB total 0.20 vs. 0.94 vs. −0.29 all P = NS Definite dry cough 2 vs. 5 vs. 1 Probable dry cough 0 vs. 4 vs. 1 Possible dry cough 0 vs. 0 vs. 0 All coughs 2 vs. 9 vs. 2 P = 0.02	NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Rake 2001 United States	NR	(Placebo / Enalapril / Eprosartan) 27 (20.5%) withdrawals (24% / 22% / 15 %) 7 due to AEs (4.4% / 8.9% /2.2%)	

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration	Run-in/Washout Period
Scaglione 2005 Italy	Randomized double-blind, three-arm double-dummy trial Single center	Inclusion: Stage 1 and 2 essential hypertension, urinary albumin excretion (UAE) 0.02 g/24 h (20 mg/24 h) with maintained renal function (serum creatinine concentration <1.30 mg% in women and <1.40 mg% in men) Exclusion: Presence of any form of secondary hypertension, stage III essential hypertension, any irreversible and organ damage due to arterial hypertension, left ventricular hypertrophy, cardiovascular disease, diabetes, dyslipidemia, hepatic disease, malignant disease. In all hypertensives, M- and B-mode echocardiography was performed to assess left ventricular hypertrophy (LVH). Accordingly, all the patients with indexed left ventricular mass (LVM/height) ≥ 50 g/m2.7 for men and ≥ 47 g/m2.7 for women were considered to have LVH	Losartan (50 mg/day), ramipril (5 mg/day) and combined (losartan 50 mg/day plus ramipril 5 mg/day) 24 weeks	4-week run-in with placebo Washout NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (Data are mean ± SD and geometric mean (range), unless otherwise indicated)	Number screened/ eligible/ enrolled
Scaglione 2005 Italy	NR	UAE, by immunonephelometric assay; circulating TGFb1 by a solid-phase specific sandwich enzyme-linked immunosorbent assay (ELISA); and blood urea nitrogen (BUN), creatinine and creatinine clearance and potassium, by routine laboratory methods, were determined after placebo treatment and 24 weeks follow-up.	Losartan/Ramipril/Combined Age 56/54/58 % male 47/47/47 Ethnicity NR	MBP(mmHg) 116(8) vs. 118 (9) vs. 116 (10) UAE (g/24 h) 0.35 (0.24) vs. 0.44 (0.31) vs. 0.46 (0.32) BUN(mg/dl) 42(9) vs. 37 (9) vs. 42 (11) Creatinine (mg/dl) 1.05(0.2) vs. 1.02 (0.1) vs. 1.02(0.2) Creatinine Clearance 70(14) vs. 73(17) vs. 70(17) Serum potassium 4.7(0.5) vs. 4.5(0.6) vs. 4.6 (0.6) TGFb1 (ng/ml) 6.3(4.3) vs. 5.6 (3.1) vs. 7.2(3.6)	NR (authors say many) /NR/51

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse events assessment
Scaglione 2005 Italy	0/0/51	UAE (g/24 h) 0.21(0.11) vs. .33 (0.17) vs. 0.22(0.21) BUN(mg/dl) 42(8) vs. 38(6) vs. 43(10) Creatinine (mg/dl) 1.09(0.2) vs. 1.03 (0.2) vs. 1.06(0.2) Creatinine Clearance 69(17) vs. 75 (16) vs. 67(15) Serum potassium 4.7(0.7) vs. 4.7 (0.8) vs. 4.8 (0.7) TGFb1 (ng/ml) 2.9(2) vs. 3.2(2.4) vs. 1.2(0.4)	NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Scaglione 2005 Italy	NR	0/0	

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration	Run-in/Washout Period
Tanser, 2000 Multinational	Randomized, double-blind comparison Multicenter	Inclusion : Male and female outpatients aged 20 to 80 years with primary hypertension and a history of ACE-inhibitor–induced cough Exclusion: Obstructive pulmonary disease, smoking, and concomitant medication including NSAIDs, aspirin, codeine, and other antitussive agents; secondary or malignant hypertension, sitting diastolic blood pressure (DBP) >105 mm Hg or systolic blood pressure (SBP) >180 mm Hg, severe cardiovascular, liver, renal, or allergic disease, renal artery stenosis or transplantation, past or present drug abuse, childbearing potential, or hypersensitivity to study drugs.	Candesartan cilexetil, enalapril, or placebo 8 weeks	1 to 4-week enalapril (10 mg) challenge period, and those who experienced dry cough according to the symptom assessment (SA) questionnaire on two consecutive visits continued to a 1- to 4-week placebo dechallenge period.
Zhu 2009 China	Double blind RCT Single center	Inclusion: Patients with high blood pressure Exclusion: Infectious and inflammatory diseases, the presence of any form of secondary hypertension, heart failure with left ventricular hypertrophy, diabetes, metabolic disease, hepatic disease, renal disease and malignancy.	Benazepril vs. Valsartan vs. Combined	Run-in NR Washout 1 week

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (Data are mean ± SD and geometric mean (range), unless otherwise indicated)	Number screened/ eligible/ enrolled
Tanser, 2000 Multinational	NR	Symptom assessment questionnaire, frequency of dry cough by a visual analog scale, and the possible impact on quality of life by the minor symptom evaluation (MSE) profile.	Age, mean (SD) 61 (8) / 60 (11) / 60 (11) %male NR Ethnicity Caucasian 22 /49 / 54 Mongoloid 0 / 1 / 1 Other 4 / 12 / 11	BMI, kg/m2, mean (SD) 29 (5) / 28 (5) / 29 (5)	NR/NR/301 and 156 randomized
Zhu 2009 China	NR	Serum TGF-β1, plasma angiotensin (Ang) II and urinary albumin were quantified by immunoassays at baseline and 12 weeks	Benazepril vs. Valsartan vs. Combined Age (sd) 55(11) / 57 (10) / 56 (10) % male 57 / 59 / 56 Ethnicity NR	BMI (kg/m2) 28.6 ± 3.5 / 28.4 ± 3.4 / 27.8 ± 4.1 BUN (mg/dl) 16.0 ± 5.1 / 15.7 ± 4.8 / 16.2 ± 5.3 Creatinine (mg/dl) 1.04 ± 0.12 / 1.05 ± 0.11 / 1.05 ± 0.12 ACR (mg/g) 332 ± 66 / 324 ± 57 / 330 ± 57 TGF β1 (ng/ml) 65.3 ± 9.6 / 64.8 ± 8.7 / 66.9 ± 9.5 Ang II (pg/ml) 75.3 ± 14.8 / 74.2 ± 13.7 / 74.8 ± 15.1	NR/NR/90

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse events assessment
Tanser, 2000 Multinational	NR/2/154	Cough Placebo 26.9% candesartan cilexetil 35.5% (P .>.20 vs. placebo) enalapril 68.2% (P < .001 vs. candesartan cilexetil). MSE contentment, candesartan cilexetil vs. placebo (mean difference 7.6 mm, 95% CI 0.7 to 14.4 mm, P = .03) Sleep Candesartan cilexetil vs. enalapril (mean difference 5.5 mm, 95% CI 20.6 to 111.5 mm, P = .08).	Patient or investigator reported
Zhu 2009 China	8 withdrawn and LTF 82 analyzed	BUN (mg/dl) 15.7 ± 5.3 vs. 16.0 ± 5.0 vs.16.0 ± 4.5 Creatinine (mg/dl) 1.06 ± 0.15 vs. 1.04 ± 0.14 vs. 1.08 ± 0.15 ACR (mg/g) 215 ± 54∗ vs. 211 ± 52∗ vs. 158 ± 45∗∗, † TGF β1 (ng/ml) 44.5 ± 6.1∗ vs. 47.2 ± 7.0∗ vs. 35.7 ± 4.9∗∗, † Ang II (pg/ml) 56.8 ± 11.7∗ vs. 92.8 ± 16.7∗ vs. 76.4 ± 19.5 ∗P < 0.05; ∗∗P < 0.01 versus baseline; †P < 0.05 versus benazepril or valsartan group post-treatment	NR

Evidence Table 4. Data abstraction of hypertension trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Tanser, 2000 Multinational	NR except as a general statement of most common adverse events with placebo were dry mouth, flush, headache, and aggravated hypertension; with candesartan cilexetil, respiratory infection and dizziness; and with enalapril, headache and back pain and Cough placebo 11% CC 16% Enalapril 31%	NR for withdrawals 11(7%) due to AEs Placebo 3 (11.5%) candesartan cilexetil 5 (8.1%) enalapril 3 (4.5%) excluding cough	
Zhu 2009 China	NR except for 2 patients that withdrew due to cough	8 (9%) withdrawals 2 (3.6%) due to AEs	

Evidence Table 5. Quality assessment of hypertension trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessor masked?	Care provider masked?	Patient masked?
Andersen 2005	Method not described	Method not described	No; more patients in dual blockade group on thiazide diuretics (53% vs 22%, P<0.05)	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Avanza 2000	No	No	Not reported; Only provided baseline characteristics for 76% who completed the trial.	Yes	NR	No	No
De Rosa 2002	Method not described	Method not described	NR; only reported for 42 (84%) who completed trial	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Derosa 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Elliott 1999	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Fogari 2002	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Fogari 2008	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Karlberg 1999	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 5. Quality assessment of hypertension trials

Author	Was attrition reported?	Were crossovers reported?	Was adherence reported?	Was contamination reported?	What methods were used to handle carry-over effects?	Was withdrawal rate differential or high?	Was loss-to-follow-up differential or high?
Andersen 2005	Yes	No	Yes	No	none	No	No
Avanza 2000	Yes	No	Yes	No	washout	Yes; withdrawal rate of 24% overall.	No
De Rosa 2002	Yes	No	No	No	washout	No	No
Derosa 2003	No	No	No	No	washout	Unable to determine	Unable to determine
Elliott 1999	Yes	No	No	No	NR	No	Unable to determine
Fogari 2002	Yes	No	No	No	washout	No	No
Fogari 2008	Yes	No	No	No	washout	Yes; 80/364 (22%)	No
Karlberg 1999	Yes	No	Yes	No	washout	No	No

Evidence Table 5. Quality assessment of hypertension trials

Author	Was an ITT analysis used?	Were there any post-randomization exclusions?	Overall quality rating
Andersen 2005	No; Excluded 15/75 (20%)	No	Poor
Avanza 2000	No; excluded noncompleters (24%)	No	Poor
De Rosa 2002	Unable to determine	No	Fair
Derosa 2003	Unable to determine	Unable to determine	Fair
Elliott 1999	No; Excluded 10/529 (2%) from PGWB	Unable to determine	Fair
Fogari 2002	No; Excluded 3/85 (3.5%)	No	Fair
Fogari 2008	No; Excluded 80/364 (22%)	Unable to determine	Fair
Karlberg 1999	No; Excluded 6 (2.2%)	No	Fair

Evidence Table 5. Quality assessment of hypertension trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessor masked?	Care provider masked?	Patient masked?
Kavgaci 2002	Method not described	Method not described	No; fosinopril group 10 years older, but NSD because of small sample size	Yes	NR	No	No
Malacco 2004	Yes	Yes		Yes	Yes	Yes	Yes
Malmqvist 2000	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Menne 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rake 2001	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Roca-Cusachs 1997	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Rosei 2005	Method not described	Method not described	No; ACR higher for candesartan (112.4 vs 40.4)	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Ruilope 2001	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Scaglione 2005	Method not described	Method not described	Yes	Yes	Yes	Yes	Yes

Evidence Table 5. Quality assessment of hypertension trials

Author	Was attrition reported?	Were crossovers reported?	Was adherence reported?	Was contamination reported?	What methods were used to handle carry-over effects?	Was withdrawal rate differential or high?	Was loss-to-follow-up differential or high?
Kavgaci 2002	Yes	No	No	No	washout	No	No
Malacco 2004	Yes	No	No	No	washout	No	No
Malmqvist 2000	Yes	No	Yes	No	washout	No	No
Menne 2008	Yes	No	Yes	No	washout	No	No
Rake 2001	Yes	No	No	No	washout	Yes; 28/136 (20%)	No
Roca-Cusachs 1997	Yes	No	No	No	washout	No	No
Rosei 2005	Yes	No	Yes	Yes	washout	No	Unable to determine
Ruilope 2001	Yes	No	No	No	washout	No	Unable to determine
Scaglione 2005	Yes	No	No	No	NR	No	No

Evidence Table 5. Quality assessment of hypertension trials

Author	Was an ITT analysis used?	Were there any post-randomization exclusions?	Overall quality rating
Kavgaci 2002	Unable to determine	No	Fair
Malacco 2004	No; Excluded 28/1213 (2.3%)	No	Good
Malmqvist 2000	No; Excluded 26/429 (6%)	No	Fair
Menne 2008	No; Excluded 4/133 (3%)	No	Fair
Rake 2001	No; 5/131 (4%)	No	Fair
Roca-Cusachs 1997	No; Excluded 3/396 (< 1%)	No	Fair
Rosei 2005	No; Excluded 33/129 (25%)	Unable to determine	Poor
Ruilope 2001	No; Excluded 3/334 (< 1%)	Unable to determine	Fair
Scaglione 2005	Yes	No	Good

Evidence Table 5. Quality assessment of hypertension trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessor masked?	Care provider masked?	Patient masked?
Schram 2005	Method not described	Method not described	Yes	Yes	Yes	Yes	Yes
Shand 2000	Method not described	Method not described	NR; only reported comparison of age and Ccr	Yes	NR	No	No
Tanser 2000	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Tikkanen 1995	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	NR
Uchiyama-Tanaka 2005	Method not described	Method not described	NR; Only reported for 43/57 (75%)	Yes	NR	No	No
Williams 2006	Method not described	Method not described	Yes	Yes	Yes	No	No
Zhu 2008	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 5. Quality assessment of hypertension trials

Author	Was attrition reported?	Were crossovers reported?	Was adherence reported?	Was contamination reported?	What methods were used to handle carry-over effects?	Was withdrawal rate differential or high?	Was loss-to-follow-up differential or high?
Schram 2005	Yes	No	No	No	washout	No	No
Shand 2000	Yes	No	No	No	washout	No	No
Tanser 2000	No	No	No	No	NR	Unable to determine	Unable to determine
Tikkanen 1995	Yes	No	No	No	washout	No	Unable to determine
Uchiyama-Tanaka 2005	No	No	No	No	NR	Unable to determine	Unable to determine
Williams 2006	Yes	No	No	No	washout	No	No
Zhu 2008	Yes	No	No	No	washout	No	No

Evidence Table 5. Quality assessment of hypertension trials

Author	Was an ITT analysis used?	Were there any post-randomization exclusions?	Overall quality rating
Schram 2005	No; Excluded 10/70 (14%)	No	Fair
Shand 2000	No; Excluded 2/29 (7%)	No	Fair
Tanser 2000	No; Excluded 2/156 (1%)	Unable to determine	Fair
Tikkanen 1995	No; Excluded 8/407 (2%)	Unable to determine	Fair
Uchiyama-Tanaka 2005	Unable to determine	Unable to determine	Poor
Williams 2006	Yes	No	Fair
Zhu 2008	No; Excluded 8/90 (9%)	No	Fair

Evidence Table 6. Evidence profile of hypertension trials: Losartan compared with enalapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Creatinine								
Shand 2000 n = 29	RCT	Fair	Inconsistent	Direct	Imprecise	None	No significant change in either group	Low
Tikkanen 1995 n = 407	RCT	Fair					Small, but significant increase for enalapril, but not losartan	
Avanza 2000 n = 61	RCT	Poor					No significant change in either group	
Overall withdrawals								
Tikkanen 1995 n = 407	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Low
Avanza 2000 n = 61	RCT	Poor					NSD between groups	
Myocardial infarction								
Avanza 2000 n = 61	RCT	Poor	N/A	Direct	Imprecise	None	1 (4%) event in the enalapril group, none in losartan group	NA
Quality of life								
De Rosa 2002 n = 50	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	NA
Creatinine clearance								
Shand 2000 n = 29	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	NA
GFR								
De Rosa 2002 n = 50	RCT	Fair	N/A	Direct	Imprecise	None	GFR increased significantly for losartan but not enalapril	NA
Withdrawals due to adverse events								
De Rosa 2002 n = 50	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Moderate
Tikkanen 1995 n = 407	RCT	Fair					NSD between groups	
Avanza 2000 n = 61	RCT	Poor					NSD between groups	

Evidence Table 6. Evidence profile of hypertension trials: Losartan compared with enalapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Cough								
De Rosa 2002 n = 50	RCT	Fair	Inconsistent	Direct	Imprecise	None	Bother due to cough: Nonsignificantly lower incidence for losartan	Low
Tikkanen 1995 n = 407	RCT	Fair					Cough: Significantly lower incidence for losartan	
Shand 2000 n = 29	RCT	Fair					Withdrawal due to cough: Nonsignificantly lower for losartan	
Overall adverse events								
Tikkanen 1995 n = 407	RCT	Fair	N/A	Direct	Imprecise	None	Significantly lower incidence with losartan	NA

Evidence Table 7. Evidence profile of hypertension trials: Candesartan compared with enalapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Quality of Life								
Tanser 2000 n = 156	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Moderate
Malmqvist 2000 n = 129	RCT	Fair					NSD between groups	
Albumin								
Rosei 2005 n = 429	RCT	Poor	N/A	Direct	Imprecise	None	Significantly greater reduction for candesartan	Very low
Overall withdrawals								
Rosei 2005 n = 429	RCT	Poor	N/A	Direct	Imprecise	None	NSD between groups	Very low
Overall adverse events								
Rosei 2005 n = 429	RCT	Poor	Consistent	Direct	Imprecise	None	NSD between groups	Low
Malmqvist 2000 n = 129	RCT	Fair					NSD between groups	
Cough								
Tanser 2000 n = 156	RCT	Fair	Consistent	Direct	Imprecise	None	Significantly greater incidence with enalapril	Moderate
Malmqvist 2000 n = 129	RCT	Fair					Significantly greater incidence with enalapril	
Withdrawals due to adverse events								
Tanser 2000 n = 156	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	Very low

Evidence Table 8. Evidence profile of hypertension trials: Eprosartan compared with enalapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Mortality								
Elliott 1999 n = 529	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Low
Ruilope 2001 n = 334	RCT	Fair					NSD between groups	
Quality of Life								
Elliott 1999 n = 529	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Moderate
Rake 2001 n = 136	RCT	Fair					NSD between groups	
Overall withdrawals								
Elliott 1999 n = 529	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	High
Rake 2001 n = 136	RCT	Fair					NSD between groups	
Ruilope 2001 n = 334	RCT	Fair					NSD between groups	
Cough								
Elliott 1999 n = 529	RCT	Fair	Consistent	Direct	Imprecise	None	"Gained a definite or possible cough at monotherapy endpoint" and "coughing as an on-therapy AE": NSD between groups	High
Rake 2001 n = 136	RCT	Fair					All coughs: NSD between groups	
Ruilope 2001 n = 334	RCT	Fair					Cough: NSD between groups	
Overall adverse events								
Elliott 1999 n = 529	RCT	Fair	Inconsistent	Direct	Imprecise	None	NSD between groups	Low
Ruilope 2001 n = 334	RCT	Fair					Significantly lower incidence for eprosartan	
Withdrawals due to adverse events								
Elliott 1999 n = 529	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Moderate
Rake 2001 n = 136	RCT	Fair					NSD between groups	
Serious adverse events								
Elliott 1999 n = 529	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	Very Low

Evidence Table 9. Evidence profile of hypertension trials: Valsartan compared with lisinopril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Mortality								
Menne 2008 n=133	RCT	Fair	Consistent	Direct	Imprecise	None	1 death (2%) occurred in the lisinopril group	Moderate
Malacco 2004 n=1213	RCT	Good					No deaths occurred in either group	
Overall withdrawals								
Menne 2008 n=133	RCT	Fair	Consistent	Direct	Precise	None	NSD between groups	High
Malacco 2004 n=1213	RCT	Good					NSD between groups	
Cough								
Menne 2008 n=133	RCT	Fair	Inconsistent	Direct	Precise	None	NSD between groups	Low
Malacco 2004 n=1213	RCT	Good					Significantly higher incidence in lisinopril group	
Overall adverse events								
Menne 2008 n=133	RCT	Fair	Inconsistent	Direct	Precise	None	NSD between groups	Low
Malacco 2004 n=1213	RCT	Good					Significantly higher incidence in lisinopril group	
Withdrawals due to adverse events								
Menne 2008 n=133	RCT	Fair	Inconsistent	Direct	Imprecise	None	NSD between groups	Low
Malacco 2004 n=1213	RCT	Good					Significantly higher incidence in lisinopril group	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Agarwal 2001 US no trial name Fair	Study design: cross-over, randomized, controlled trial. Setting: NR Duration: not explicitly stated: 10 weeks based on treatment groups and wash-out period.	Inclusion criteria: Age 18-80 Proteinuria ≥ 1 gm/day Hypertension (mean arterial pressure >97 mmHg) Serum potassium ≤ 5.5 mEq/L Current use of Lisinopril 40 mg/day for > 3 mo Exclusion criteria: Previous use of ARB Estimated creatinine clearance < 30 ml/min	Types of CKD: 4 glomerulonephritis 12 Diabetic nephropathy Proteinuria ≥ 1 gm/day required. Baseline proteinuria ranged from 3-4 gm/d	Stage of CKD not specifically addressed. Estimated CrCl required to be >30 ml/min; baseline CrCl NR. Baseline GFR ranged from 60-70 ml/min GFR obtained via iothalamate clearance

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Agarwal 2001 US no trial name Fair	Participants randomized to two groups: P: Placebo x4 weeks first then crossover to Losartan 50mg/d x4 weeks. L: Losartan 50mg/d x4 weeks first then crossover to Placebo x4 weeks.	2 week wash-out between initial arm and cross-over arm	Patients were maintained on baseline dose of Lisinopril 40mg/d as well as other anti-hypertensive therapy. Other anti-hypertensive's used included: calcium channel blockers β-blockers α-blockers Loop diuretics Thiazide diuretics	Primary hypothesis stated to be that Losartan would decrease proteinuria by at least 25% when added to ACE-I compared to placebo added to ACE-I. Assessment done 4 times (before and after each treatment period, and included: GFR via iothalamate 24 hr urine collection of protein Serum laboratory values

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Agarwal 2001 US no trial name Fair	Mean age: 53 +/- 9 Gender (male/female): 14/16 Ethnicity: 6 white 10 black	Mean baseline creatinine overall: 2.0 +/- 0.8 mg/dL Baseline proteinuria per group: P: 3.6 +/- 0.71 gm/d L: 3.56 +/- 0.75 gm/d Baseline GFR per group: P: 69 +/- 10 ml/min L: 63 +/- 9 ml/min Baseline seated blood pressure: 156 (SD 18,88) +/- 12 mmHg	Number screened: NR Number eligible: NR Number enrolled: 17	Number withdrawn: 1 Lost to follow up: not reported (one withdrawal was due to inability to keep scheduled appointments - unclear if "lost" to follow up). Analyzed: 16

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Agarwal 2001 US no trial name Fair	Change in proteinuria (baseline to post treatment): P: 3.6 +/- 0.71 gm/d to 3.08 +/- 0.55 gm/d L: 3.56 +/- 0.75 gm/d to 3.42 +/- 0.87 gm/d Placebo corrected change: +1% 95% CI -20% to +28% p = 0.82, no significant difference noted between groups. Change in creatinine (baseline to post treatment): P: 2 +/- 0.2 mg/dL to 2.1 +/- 0.21 mg/dL L: 2.1 +/- 0.22 to 2.1 +/- 0.23 mg/dL Placebo corrected change -0.11 95% CI -0.31 to +0.10 p = 0.30, no significant difference noted between groups. Change in GFR (baseline to post treatment): P: 69 +/- 10 ml/min to 64 +/- 9 ml/min L: 63 +/- 9 ml/min to 68 +/- 11 ml/min Placebo corrected change +14% 95% CI 3% to 26% p = 0.017; GFR found to increase significantly in L vs. P No statistically significant change in systolic or diastolic ambulatory blood pressures between groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Agarwal 2001 US no trial name Fair	NR	NR	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Agarwal 2001 US no trial name Fair	Withdrawal: 1 *due to patients inability to keep scheduled appointments for assessment testing Withdrawals due to adverse effects: none reported		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Bakris 2000 US VAL-K Fair	Study design: multicenter, randomized, double-crossover Setting: NR Duration: not explicitly stated; 12 weeks based on treatment groups and wash-out periods.	Inclusion criteria: Age 18-75 Serum potassium between 4.3-5.5 mEq/L History of Hypertension CrCl 30-80 ml/min Exclusion criteria: Unstable renal function/active renal disease Use of diuretics for edema Use of 3+ drugs for HYPERTENSION control Recent drug or alcohol abuse Allergy to ACE-I/ARB or allergy to iodine History of HIV Liver disease (AST or ALT >3 times upper limit of normal or total bilirubin or alkaline phosphatase >2.5 upper limit of normal) Average BP >200/115 (sitting) Unstable angina or acute MI treatment within 3 mo History of stroke within 3 mo, transient ischemic attack within 6 mo History of ventricular arrhythmia requiring therapy HF (NYHA Class II, III, or IV) Use of NSAIDS (>20 days per mo; ASA okay) Pregnancy, lactation, or women of childbearing potential History of GI malabsorption or GI surgery	Types of CKD: NR Proteinuric: NR	Stage of CKD not specifically addressed. Participants required to have calculated CrCl between 30-80 ml/min, confirmed with 24 hr urine collection at time of enrollment. GFR at baseline noted to be: 62 +/- 4 ml/min/1.73m2 pre-Lisinopril 66 +/- 5 ml/min/1.73m2 pre-Valsartan GFR measured via iohexal clearance.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Bakris 2000 US VAL-K Fair	Crossover study with 4 phases. After initial run-in, participants were randomized (1:1 fashion) to either: [L] Lisinopril 10mg/d [V] Valsartan 80 mg/d Each treatment period lasted 4 weeks, followed by washout and then cross-over for 4 weeks into the alternate group.	2 week run-in pre-randomization 2 week wash-out between cross-over arms No anti-hypertensive therapy during run-in or wash-out	No additional meds noted If diastolic blood pressure >115 mmHg during initial wash-out, participant was excluded If blood pressure could not be reduced to <180 mmHg systolic or <100 mmHg diastolic while on randomized drug of interest, then that participant was excluded.	Primary analysis was to compare the average percentage change from baseline in serum potassium levels between ACE-I and ARB. Secondary analysis was to compare the average differences from baseline in levels of plasma renin, angiotensin II, and urinary values of potassium, aldosterone, and sodium. At the end of run-in and washout and at the end of each 4 week treatment period, the following were measured: -GFR via iohexol clearance -24 hr urine collection for sodium, potassium, and aldosterone -serum labs including potassium and creatinine

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bakris 2000 US VAL-K Fair	Mean age: 56 +/- 2 years Gender (male/female) 21/14 Ethnicity 19 of 35 African American 16 of 35 Caucasian	Baseline pre-treatment GFR: L: 62 +/- 4 ml/min/1.73m2 V: 66 +/- 5 ml/min/1.73m2 Baseline pre-treatment systolic blood pressure: L: 150 +/-4 mmHg V: 149 +/- 3 mmHg	Number screened: 84 Number eligible: 37 Number enrolled: 37	Number withdrawn: 2 Lost to follow-up: NR (unclear if any of the withdrawals were due to loss of follow up). Analyzed: 35

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Bakris 2000 US VAL-K Fair	No significant change in GFR noted with therapy in either group L: post GFR 65 +/- 5 (p = 0.37) V: post GFR 64 +/- 5 (p = 0.53) 95% CI NR Similar decline in blood pressure between groups. No information given on statistical differences in blood pressure control between groups.	N/A

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Bakris 2000 US VAL-K Fair	Participants were sub-divided into groups based on eGFR > or < 60 ml/min/1.73m2, but no outcomes of interest were examined for these subgroups.	NR	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Bakris 2000 US VAL-K Fair	Withdrawals: 2 (reason for withdrawal not stated)	The primary purpose of this study was to examine changes in potassium, aldosterone, and angiotensin II levels in patients with CKD on ACE-I vs. ARB. No significant difference was found in potassium levels between those treated with ACE-I vs. ARB ($p > 0.05$). Whether or not these patients had proteinuria was not stated.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Campbell 2003 Italy no trial name Fair	Study design: prospective, randomized, cross-over study Setting: outpatient nephrology clinic Duration:32 weeks	Inclusion criteria: Age 18 and older CrCl between 20-70 ml/min Proteinuria of > 1 gm/d Hypertension (diastolic blood pressure 90-115 mmHg or less in patients on anti-hypertensive therapy) Exclusion criteria: Contraindication to withdrawal of chronic ACE-I or ARB therapy Treatment with steroids, NSAIDS, immunosuppressive or cytotoxic agents in 6 mo prior. History of renovascular disease Obstructive uropathy Unstable angina Acute myocardial infarction or cerebral vascular accident in 6 mo prior NYHA class III-IV serum potassium >6 Clinically significant hepatic disease (AST or ALT >3 times normal, bilirubin >1.5 times normal) White blood cell count <3000/mm3 Clinical suspicion of renal vein thrombosis Known hypersensitivity to ACE-I or ARB Cancer Collagen vascular disease Treatment with other investigational drugs Pregnancy / lactation / ineffective contraception	Types of CKD: IgA nephropathy Chronic glomerulonephritis Other Unknown (no biopsy) Biopsy proven? Not required Degree of proteinuria: >1 gm/d required. At baseline, mean proteinuria was 3.3 gm/d. Baseline proteinuria determined by mean value of protein in two 24-hr urine collections 2 weeks apart.	Stage of CKD: not specifically addressed CrCl 20-70 ml/min required. CrCl average at baseline was 69 ml/min CrCl measured on 24 hr urine as the mean of 3 urine collections. GFR measured via inulin and para-aminohippuric acid.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Campbell 2003 Italy no trial name Fair	After completing run-in, participants were randomized to one of six treatment sequences. These sequences allowed each participant to cross-over into each of the following treatment groups: (V80) Valsartan 80mg/d (B10) Benazepril 10mg/d (V40+B5) Valsartan 40mg/d + Benazepril 5 mg/d After 2 weeks doses were increased as follows: (V160) Valsartan 160 mg/d (B20) Benazepril (V80+B10) *If hyperkalemia or symptomatic hypotension resulted after dose increase, then doses were reduced to initial lower levels.* Each treatment period lasted 8 weeks. 23 of 24 received higher (second) dose of each medication. 1 of 24 received only lower dose of each medication as that participant's diastolic blood pressure was <90 mmHg on lower doses of medication.	8 week run-in prior to randomization. No ACE-I, ARB, or potassium sparing diuretics were allowed during that time. No wash-out period described.	Diastolic blood pressure goal was <90. Additional medications were allowed during run-in and during treatment groups if needed to achieve that goal. Additional meds included: Clonidine Loop diuretics Thiazide diuretics	Primary end point not described. Primary aim stated as: to test the hypothesis that, among proteinuric patients with chronic nephropathies, combined therapy with half doses of ACE-I and ARB may achieve greater reduction of proteinuria than treatment with full doses of each drug. Second aim was noted to be to assess to which extent the antiproteinuric effect of each treatment was due to an effect on glomerular barrier size selectivity or on a specific intrarenal hemodynamic effect. At the end of run-in and at the end of each treatment period, the following measurements were completed: -blood pressure -three 24 hr collections of urine for CrCl, protein, and urine sodium. -blood chemistries -GFR via inulin and para-aminohippuric acid clearance studies

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Campbell 2003 Italy no trial name Fair	Mean age: 48.9 +/- 13.2 years Gender (male/female): 23/1 Ethnicity: NR	Urinary protein excretion at baseline: 3.28 +/- 2.6 gm/d CrCl at baseline: 69.14 +/- 19.86 ml/min Serum creatinine at baseline: 1.67 +/- 0.46 mg/dL GFR at baseline: 46.5 +/- 12.8 ml/min/1.73m2	Number screened: NR Number eligible: NR Number enrolled: 24	Number withdrawn: zero Lost to follow-up: zero Analyzed: 24

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Campbell 2003 Italy no trial name Fair	Protein reduction from baseline to end of treatment (percent reduction): V: 3.28 +/- 2.6 gm/d to 2.04 +/- 2.36 gm/d (-41.5%) B: 3.28 +/- 2.6 gm/d to 1.76 +/- 1.88 gm/d (-45.9%) V+B: 3.28 +/- 2.6 gm/d to 1.39 +/- 1.54 gm/d (-56%); greater reduction (compared to V, p<0.002 and compared to B, p = 0.02) Reduction in proteinuria was numerically superior in B vs V, but that difference was not statistically significant Maximal protein reduction was achieved in the following patterns (mean baseline proteinuria levels in parentheses) V: in 4 participants (2 +/- 1.1 gm/d) B: in 7 participants (2.4 +/- 2.4 gm/d) V+B: in 13 participants (4.4 +/- 2.7 gm/d) *Those who achieved greatest protein reduction in V+B also had significantly higher baseline proteinuria values, p<0.01 vs B and p < 0.05 vs V, 95% CI NR). CrCl at baseline and after treatment: V: 69.14 +/- 19.86 ml/min to 67.88 +/- 17.21 ml/min B: 69.14 +/- 19.86 ml/min to 66.22 +/- 15.33 ml/min V+B: 69.14 +/- 19.86 ml/min to 67.65 +/- 18.49 ml/min GFR at baseline and after treatment: V: 46.5 +/- 12.8 ml/min/1.73m2 to 47.9 +/- 14.6 ml/min/1.73m2 B: 46.5 +/- 12.8 ml/min/1.73m2 to 47.7 +/- 14.6 ml/min/1.73m2 V+B: 46.5 +/- 12.8 ml/min/1.73m2 to 48.1 +/- 17.1 ml/min/1.73m2 Change in GFR in V+B vs V showed p = 0.04, V+B vs B showed p = 0.048, 95% CI NR. Systolic and Diastolic blood pressures at baseline (groups were not statistically different): V: 129+/-12 and 79+/-8 mmHg B: 126+/-9 and 80+/-8 mmHg V+B: 124+/-12 and 78+/-9 mmHg	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Campbell 2003 Italy no trial name Fair	NR	Serum and urine lab studies as noted. Otherwise NR.	Hyperkalemia of >0.5 mEq/L above baseline (necessitating change in therapy): zero among all groups.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Campbell 2003 Italy no trial name Fair	Total withdrawals: zero Total withdrawals due to adverse events: zero		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Chrysostomou 2006 Australia no trial name Fair	Study design: randomized, double-blind, placebo-controlled study. Setting: Participants recruited from nephrology dept of Royal Melbourne Hospital. Duration: 3 months	Inclusion criteria: Age 18-75 24-hr urine protein excretion >1.5 gm/d on 2 occasions 3 months apart Creatinine <2.2 mg/dL with <20% variability n preceding 3 months Treatment with ACE-I for at least 6 mo prior to enrollment. Exclusion criteria: Diastolic blood pressure >115 mmHg Systolic blood pressure >220 mmHg Serum potassium level >5 mmol/L Serum bicarbonate ≤ 20 mmol/L Acute myocardial infarction or stroke in 6 mo prior Treatment with steroids, NSAIDS, or immunosuppressant agents. Evidence or suspicion of renovascular disease, obstructive uropathy, collagen disease, cancer, drug or alcohol abuse, pregnancy, breastfeeding, or ineffective contraception.	Types of CKD: Diabetic nephropathy Glomerulonephritis Interstitial nephritis Other Biopsy proven: NR Degree of proteinuria: >1.5 gm/d required. Baseline characteristics indicate proteinuria ranged from 1.2-9.9 gm/d.	Level of CKD: not specifically addressed Creatinine <2.2 mg/dL required. CrCl at month zero ranged from 57-81 ml/min. For purposes of inclusion, CKD was defined primarily by presence of proteinuria. CrCl was followed during the study, via 24-hr urine collections and Cockroft Gault calculations.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Chrysostomou 2006 Australia no trial name Fair	Simple randomization followed by 4-12 week run-in. After run-in patients entered "compliance" phase during which they were on Ramipril 5mg/d in addition to losartan-placebo and spironolactone-placebo. Minimum time for compliance phase was 4 weeks. After compliance, patients were randomized to blinded treatment phase: (R) Ramipril 5 mg/d + Irbesartan placebo + Spironolactone placebo (n= 10) (R + I) Ramipril 5mg/d + Irbesartan 150 mg/d + Spironolactone placebo (n= 10) (R + S) Ramipril 5 mg/d + Irbesartan placebo + Spironolactone 25mg/d (RIS): Ramipril 5 mg/d + Irbesartan 150 mg/d + Spironolactone 25mg/d Patients remained randomized and double-blinded for 3 months on these regimens. Doses were changed only for hyperkalemia (potassium >6 mmol/L). After 3 mo patient codes were opened, but patients remained on allocation until 6 mo and were given the option to begin spironolactone. Treatment was continued for 12 months.	4-12 week run-in after randomization. Patients were treated with Ramipril alone 10mg/d during run-in. Diastolic blood pressure goal was < 90 mmHg.	Target diastolic blood pressure was <90 mmHg. Additional non-ACE-I, non-ARB, and non-dihydropyridine CCBs could be utilized to achieve that goal. Additional BP meds used included: -diuretics -central α agonists -dihydropyridine calcium channel blockers - β-blockers - α-blockers	Primary end point: between group difference in percentage reduction in 24 hour urinary protein excretion after 3 months of therapy. Secondary end points: -between group difference in urinary protein excretion at 6 months -percentage reduction of 24 hour urine protein excretion at 3 and 6 mo separately for each group -changes in blood pressure and CrCl Post hoc analysis: -reduction in protein excretion at 6 and 12 months among those who received spironolactone. Serum labs and vital signs were measured: -at the beginning and end of compliance phase, and every 4 weeks during initial 12 weeks of treatment phase -then every 3-6 months *serum potassium was additionally measured one week after treatment phase was started.* 24-hr urine studies for protein and creatinine were measured: -at the beginning of compliance phase -at end of compliance phase -at the end of 12-week treatment phase -at 6 mo and at 12 mo

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Chrysostomou 2006 Australia no trial name Fair	Mean age: R: 59.2 R + I: 56.3 Gender (male/female): R: 7/3 R + I: 8/2 Ethnicity: NR	Mean 24 hr urinary protein excretion: R: 2.6 gm/d R + I: 2.5 gm/d Mean CrCl at month zero: R: 81.6 ml/min (range 46.9-122) R + I: 67.4 mil/min (range 41.7-94.3) Mean Systolic blood pressure at month zero: R: 133 +/- 19.5 (range 110-1160) mmHg R+I: 132 +/- 11.4 (range 120-150) mmHg	Number screened: NR Number eligible: NR Number enrolled: 41	Withdrawn: 1 Lost to follow-up: NR Analyzed: 41

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Chrysostomou 2006 Australia no trial name Fair	Percent change in proteinuria at 3 mo: R: -1.4, 95% CI -16.7, 13.9 R+I: -15.7, 95% CI -35.2, 3.8 Inter group comparison ANOVA p = 1 Percent change in proteinuria at 6 mo: R: 0.8, 95% CI -38.5, 40.1 R+I: -11.1, 95% CI -35.9, 13.7 Inter group comparison ANOVA p = 1 Mean creatinine clearance at 3 mo: R: 84.5 ml/min R+I: 67.4 ml/min p = 0.45 Mean creatinine clearance at 6 mo: R: 82.4 ml/min R+I: 65.2 ml/min p = 0.26 No statistically significant differences in systolic blood pressures between groups at any time point. At 6 months there was a difference in that diastolic blood pressure was higher in R compared to other groups (p = 0.046).	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Chrysostomou 2006 Australia no trial name Fair	Analysis among diabetic nephropathy vs. non-diabetic nephropathy as CKD etiology; no evidence of interaction between treatment effects was found based on cause of nephropathy. Diabetic vs. non-diabetic likelihood ratio test: 3 mo χ^2 (3) = 1.65, p = 0.649 6 mo χ^2 (3) = 4.50, p = .0213	NR	Feeling unwell / light-headed: R: 1 R+I: zero R+S: zero RIS: zero Potassium >6 mmol/L: R: zero R+I: zero R+S: 1 (at 2 mo) RIS: 2 (one at 3 mo and one at 6 mo)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Chrysostomou 2006 Australia no trial name Fair	Total withdrawal: 1 (due to feeling unwell / light-headed); no hypotension documented Withdrawals due to adverse events: 1 (as above) Withdrawals due to reason other than adverse events: zero	This study also compared use of spironolactone in reduction in proteinuria. Those participants treated with ACE-I + spironolactone or ACE-I + ARB + spironolactone showed significant reduction in proteinuria compared to ACE-I alone. There was no difference in reduction of proteinuria between ACE-I + spironolactone or ACE-I + ARB + spironolactone.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Esnault 2005 France no trial name Fair	Study design: single-center, prospective, randomized, open label, crossover study. Setting: outpatient clinic Duration: 25 weeks	Inclusion criteria: Age 18-80 Glomerulonephritis that has not required and is not resistant to immunosuppressive treatments Proteinuria at >1 gm/d after 6 mo therapy with Ramipril and other anti-hypertensive's*. No changes in proteinuria by >50% for 2 mo prior to enrollment Exclusion criteria: Creatinine >2.8 mg/dL Increase in serum creatinine by >20% after introduction of Ramipril History of intolerance to or contraindication to ACE-I or ARB Office systolic blood pressure of <110 mmHg *Other antihypertenives included: calcium channel blockers, central acting drugs, diuretics, β-blockers, and α-blockers	Types of CKD: Diabetic nephropathy IgA nephropathy Focal segmental glomerulosclerosis Minimal change disease Amyloidosis Mesangioproliferative glomerulonephritis Biopsy proven: NR Degree of proteinuria: >1 gm/d required for enrollment. Mean baseline level of proteinuria was 3.7 gm/d.	Level of CKD: not specifically addressed. Creatinine <2.8 required. No GFR or CrCl measurements noted

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Esnault 2005 France no trial name Fair	After run-in, participants were randomized to: (V) Valsartan 160 mg/d (R) Ramipril 10 mg/d (V+R) Valsartan 80mg/d and Ramipril 5 mg/d 3 treatment sequences were used to ensure every treatment was represented equally during each treatment period as part of the cross-over design. Patients remained on each treatment for 4 weeks; between each cross-over arm there was a 4 week wash-out period. All participants were to receive each therapy option for 4 weeks as part of cross-over design. Participants entered 4th treatment period for 4 weeks: V+R + Furosemide (40mg/d if not on any previously, or 40mg/d additionally to previous furosemide dose)	Patients were required to have been on Ramipril 5mg/d for 6 mo prior to enrollment. 1 week run-in; medications during run-in NR 4 week washout between each treatment arm during which time patients were on Ramipril 5mg/d (with diuretic if needed)	Other anti-hypertensives were allowed, and included: calcium channel blockers, central acting drugs, diuretics, β-blockers, and α-blockers	Primary end point: mean urinary protein/creatinine ratio in two consecutive 24 hour collections of urine at the end of each treatment period. Secondary end points: -mean 24 hr proteinuria -home systolic and diastolic blood pressure -serum creatinine levels The following measurements were made at the end of run-in, at the end of each 4 week treatment period, and at the end of each wash-out period: -two 24-hr urine samples for protein, creatinine, electrolytes, and albumin -serum lab tests (including creatinine) review of home vital signs At the end of each active treatment period, participants underwent physical exam and vital sign measurements.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Esnault 2005 France no trial name Fair	Mean age: 49.3 +/- 20.4 yrs Gender (male/female): 12:6 Ethnicity: NR Race: 100% Caucasian	Mean proteinuria: 3.71 +/- 2.1 gm/d Mean creatinine: 1.7 +/- 0.7 mg/dL Mean systolic blood pressure: 149.06 +/- 29.1 mmHg Mean number of additional anti-hypertensive drugs: 2.6 (range 1-6)	Number screened: NR Number eligible: NR Number enrolled: 18	Number withdrawn: 2 Lost to follow-up: zero Analyzed: 18 (intention to treat)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Esnault 2005 France no trial name Fair	Mean urinary protein/creatinine ratio after treatment: R: 2.98 +/- 2.02 gm/g V: 3.2 +/- 2.32 gm/g V+R: 3.01 +/- 2.68 gm/g For inter-group comparison, no significant difference was found, p = 0.39 with serum creatinine and systolic blood pressure as fixed effects, and p = 0.48 without (95% CI NR). Mean 24 hr urinary protein excretion after treatment: R: 3.60 +/- 2.9 gm/d V: 3.02 +/- 1.51 gm/d V+R: 3.01 +/- 2.07 gm/d For inter-group comparison, p = 0.63 with serum creatinine and systolic blood pressure as fixed effects, and p = 0.70 without (95% CI NR). No significant difference noted between these treatment groups and the baseline ramipril dose of 5mg/d (p = 0.8 for baseline vs R, p = 0.47 for baseline vs V, and p = 0.78 for V+R). 95% CI NR. Serum creatinine levels after treatment: R: 1.9 mg/dL V: 1.8 mg/dL V+R: 1.8 mg/dL Reported as no significant difference;p value and 95% CI NR No significant difference between groups for systolic or diastolic blood pressure.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Esnault 2005 France no trial name Fair	Subgroup analysis was done comparing individuals with and without diabetes. Protein/creatinine ratio was higher at baseline in diabetics vs. non-diabetics (p = 0.033). In both diabetic and non-diabetic, there was no significant difference in reduction in protein/creatinine ratio in any treatment groups vs. baseline (Ramipril 5mg/d). There was a trend for V+R to lead to a greater reduction in proteinuria among diabetics vs. non-diabetics (p = 0.08, 95% CI NR).	At each physical exam (after each active treatment period), participants were asked questions regarding symptomatic hypotension and side effects.	No significant difference in number of symptomatic hypotension events was observed between treatment groups.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Esnault 2005 France no trial name Fair	Total withdrawals: 2 Withdrawals due to adverse events: 1 (laryngeal edema; noted in the context of increased ACE dose - specific group during event not reported) Withdrawals due to reason other than adverse events: 1 (pregnancy)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Ferrari 2002 Switzerland no trial name Fair	Study design: prospective, randomized, open-blinded endpoint cross-over. Setting: outpatient nephrology clinics Duration: 32 weeks	Inclusion criteria: Biopsy proven glomerulonephritis Increased office blood pressure >140/90 mmHg, MAP >107 mmHg, or history of anti-hypertensive treatment. Stable proteinuria of >1.5 gm/d CrCl >30 ml/min Exclusion criteria: Pregnant/nursing women Diabetes Use of immunosuppressive therapy Refractory edema BP >200/110 when off anti-hypertensives for 2 weeks prior to initiation of study	Types of CKD: Focal segmental glomerulosclerosis Membranoproliferative glomerulonephritis IgA nephropathy Biopsy proven: yes Degree of proteinuria: >1.5 gm/d required. Baseline values NR.	Stage of CKD: not specifically addressed CrCl >30 ml/min required. CrCl measured via 24 hr urine assessment. Baseline CrCl 77 +/- 27 ml/min.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Ferrari 2002 Switzerland no trial name Fair	After run-in, participants were randomized to one of three groups: (F) Fosinopril 20mg/d (I) Irbesartan 150 mg/d (F+I) Fosinopril 20mg/d + Irbesartan 150mg/d Each treatment period lasted 6 weeks.	6 week run-in (control) period. 4 week wash-out between each treatment arm.	Diuretics allowed if participants required diuretics at time of enrollment to control edema. 4 patients received diuretic therapy (3 furosemide, 1 metolazone).	Primary end points not specifically stated. Goal stated to be to test whether or the antiproteinuric effect of a combination of ACE-I and ARB is superior to monotherapy with either agent. Reported outcomes included: -blood pressure -urinary protein excretion -CrCl -serum labs including electrolytes and creatinine Blood pressure and 24 hr urine studies were completed: -at baseline -at week 3 and week 6 of each study period -at the end of each wash-out period Serum lab values (blood chemistry, complete blood count with reticulocyte count) and ambulatory blood pressures were additionally assessed: -at the end of each treatment period.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ferrari 2002 Switzerland no trial name Fair	Mean age: 48 +/- 4 years Gender: 7 men, 4 women Ethnicity: NR	Mean serum creatinine at baseline: 1.5 +/- 0.7 mg/dL Mean CrCl at baseline: 77 +/- 27 ml/min Mean systolic and diastolic blood pressures at baseline: 144+/-12 mmHg systolic 91+/-9 mmHg diastolic	Number screened: NR Number eligible: NR Number enrolled: 11	Withdrawn: 1 Lost to follow-up: NR Analyzed: 10

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Ferrari 2002 Switzerland no trial name Fair	Mean reduction in proteinuria baseline to endpoint: F: 7.9 +/- 7.2 to 5.3 +/- 5.2 gm/d (-33%) I: 7.9 +/- 7.2 to 5.0 +/- 4.9 gm/d (-37%) F+I: 7.9 +/- 7.2 to 3.3 +/- 3.7 gm/d (-58%) Combination therapy reduced proteinuria more than either drug alone (p = 0.039, 95% CI NR). When values were corrected for concomitant changes in CrCl, the reduction in proteinuria in F+I remained significantly more than in F or I alone (p < 0.05, 95% CI NR). Changes in blood pressure did not correlate significantly with changes in proteinuria. (Pearson correlation matrix 0.149, p = 0.43). No statistically significant differences in blood pressure control between treatment periods. Mean CrCl, creatinine, and potassium remained the same throughout the study.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Ferrari 2002 Switzerland no trial name Fair	NR	NR	Transient dizziness: F: zero I: zero F+I: 2 Cough: F: zero I: zero F+I: zero Reversible increase in serum creatinine: F: 2 I: zero F+I: zero Serum potassium >5 mmol/L: F: 2 I: 1 F+I: 2 *none required changes in therapy, no potassium values of ≥ 5.5 mmol/L.*

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Ferrari 2002 Switzerland no trial name Fair	Total withdrawals: 1 Withdrawals due to adverse events: zero Withdrawals due to reasons other than adverse events: 1 *for development of nephrotic syndrome during baseline period.*		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Hannedouche 2001 France no trial name Fair	Study design: multi-center, parallel group, double-dummy active-control trial Setting: NR Duration: 12 weeks	Inclusion criteria: Age 18-70 Diastolic supine blood pressure 95-114 mmHg Stable renal disease (meaning change in serum creatinine ≤ 20% in 3 mo prior) CrCl 30-80 ml/min Exclusion criteria: History of renal transplantation Renal artery stenosis (bilateral or unilateral if solitary kidney) Secondary hypertension Nephrotic syndrome Recent history HF, myocardial infarction, cardiac surgery, or coronary angioplasty Diabetes requiring insulin therapy	Types of CKD: NR Biopsy proven: NR Baseline proteinuria ranged from 1.6-1.8 +/- 2.4 gm/d. (Some patients may not have been proteinuric per this data.)	Stage of CKD was not specifically addressed. CrCl 30-80 ml/min required. Baseline serum creatinine ranged from 1.8-1.9 +/- 0.8 mg/dL. Baseline CrCl ranged from 50-51 +/- 15 ml/min.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Hannedouche 2001 France no trial name Fair	Participants were initially randomized to: Telmisartan 40mg/d (T40) (n = 45) Enalapril 10mg/d (E10) (n = 26) *randomization 2:1 in favor of Telmisartan.* At 4 weeks: T40 with supine trough diastolic blood pressure <90 mmHg = no change T40 with supine trough diastolic blood pressure 90-114 mmHg changed to 80 mg/d (T80) E10 with supine trough diastolic blood pressure <90 mmHg = no change E10 with supine trough diastolic blood pressure 90-114 mmHg chnaged to 20 mg/d (E20) At 8 weeks: T40 with supine trough diastolic blood pressure <90 mmHg = no change T40 with supine trough diastolic blood pressure 90-114 mmHg changed to 80 mg/d (T80) E10 with supine trough diastolic blood pressure <90 mmHg = no change E10 with supine trough diastolic blood pressure 90-114 mmHg chnaged to 20 mg/d (E20) T80 with supine trough diastolic blood pressure 90-114 mmHg, once daily furosemide 40 mg/d started (T80+F) E20 with supine trough diastolic blood pressure 90-114 mmHg, once daily furosemid 40 mg/d started (E20+F)	14 day single-blind placebo run-in; patients received double-dummy Telmisartan and Enalapril placebo.	NR 29% of Telmisartan-treated patients and 43% of Enalapril treated patients met requirements for addition of furosemide.	Primary safety endpoint was percent change from baseline in CrCl (calculated); >20% change considered significant. Primary efficacy endpoints were changes in mean diastolic and systolic blood pressures after treatment. Secondary safety endpoints included changes in baseline EKG and orthostatic changes in vitals signs. Secondary efficacy endpoints included change in systolic and diastolic blood pressure. Evaluations at 2 weeks prior to randomization, and then as follows: Week zero (time of initial randomization) Week 2 Week 4 Week 8 Week 12 *Evaluations included serum laboratory values, 24 hour urine collection for protein and creatinine, and blood pressure measurements.* Medication counts were done at each visit to evaluation compliance.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Hannedouche 2001 France no trial name Fair	Mean age: Telmisartan: 53.6 +/- 12.1 Enalapril: 53.1 +/- 11.0 Gender (% male/female): Telmisartan: 69/31 Enalapril: 81/19 Ethnicity: NR	Mean creatinine: Telmisartan (T): 1.9 +/- 0.8 mg/dL Enalapril (E): 1.8 +/- 0.5 mg/dL Mean proteinuria: T: 1.6 +/- 2.4 gm/d E: 1.8 +/- 2.4 gm/d Mean CrCl: T: 50.1 +/- 15.3 ml/min E: 51 +/- 13 ml/min Mean supine systolic blood pressure trough: T: 164.2 +/- 15.5 mmHg E: 166.8 +/- 22.8 mmHg Mean supine diastolic blood pressure trough: T: 102 +/- 5.6 mmHg E: 102.3 +/- 6.4 mmHg	Screened: 95 Eligible: NR Enrolled: 71	Withdrawn: 10 Lost to follow-up: 2 reported Completed protocol: 57 **2 participants not accounted for in withdrawals; additional info NR.** Analyzed: for safety outcome: 66 for efficacy outcome: 68

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Hannedouche 2001 France no trial name Fair	Mean change in proteinuria: T: -0.44 +/- 1.1 gm/d (decrease by 26.5%) E: -1.0 +/- 1.6 mg/d (decrease by 57.2%) Difference in decrease in proteinuria between groups was not statistically significant, p = 0.14). Mean change in serum creatinine: T: 0.2 +/- 0.3 mg/dL E: 0.1 +/- 0.2 mg/dL Median percent decrease in CrCl: T: 4.6% E: 2.8% No participants reached primary safety endpoint (meaning no change in CrCL >20%). Change in CrCl between T and E reported as not significant. There was no statistically significant change in blood pressure between groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Hannedouche 2001 France no trial name Fair	NR	Adverse events spontaneously reported by participant or observed by investigator were recorded at each visit.	Hypotension (n; %): T: 1; 2.2 E: 0; 0 Asthenia (n; %): T: 0; 0 E: 1; 3.8 Pain: (n; %): T: 1; 2.2 E: 0; 0 Dizziness (n; %): T: 1; 2.2 E: 0; 0 Abdominal pain; diarrhea/nausea/anorexia: T: 0; 0 E: 4; 15.2 Cough (n; %): : T: 0; 0 E: 1; 3.8 Uremia (n; %): T: 0; 0 E: 1; 3.8 Dysuria (n; %): T: 1; 2.2 E: 0; 0

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Hannedouche 2001 France no trial name Fair	6 withdrawals due to adverse events: -1 for UTI -1 for acute renal failure in setting relapsed renal neoplasm -1 for acute renal failure (did not improve after withdrawal) -3 for GI disturbance/ nausea/ headache/ hypotension/ vertigo	There is a typo on page 250 in table 1; plasma creatinine for Telmisartan is listed as 1169.2 micromole/L; actually 169.2 micromole/L.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Hou 2007 China ROAD (Reno protection of Optimal Antiproteinuric Doses) Good	Study design: prospective, randomized, open blinded end-point study Setting: Nanfang Hospital renal division Duration: 3 years	Inclusion criteria: Age 18-70 No ACE-I or ARB for at least 6 weeks prior to screening Serum creatinine 1.5-5 mg/dL CrCl 20-70 ml/min Less than 30% variation in CrCl in the 3 mo prior to screening History of non-diabetic renal disease (based on history, blood tests, and biopsy) Proteinuria > 1 gm/d for at least 3 mo prior to screening in the absence of urinary tract infection or overt HF (NYHA class III or IV). Exclusion criteria: immediate need for dialysis current treatment with corticosteroids, NSAIDS, or immunosuppressive drugs. Hyper or Hypokalemia (serum potassium ≥ 5.6 mmol/L or ≤ 3.5 mmol/L renovascular disease myocardial infarction or cerebrovascular accident in the year preceding screening connective tissue disease obstructive uropathy	Types of CKD: Glomerular Hypertension Polycystic kidney disease Interstitial Unknown Biopsy proven? Unclear > 1 gm/d proteinuria required. Baseline proteinuria ranged from 1.4-2 gm/d Proteinuria was measured via 24 hr urine collection.	Stage of CKD: not specifically addressed. CrCl 20-70 ml/min required. Baseline CrCl ranged from 33-35 ml/min Baseline eGFR ranged from 30.38-33.6 ml/min/1.73m2

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Hou 2007 China ROAD (Reno protection of Optimal Antiproteinuric Doses) Good	Participants were block randomized into 4 groups: (B10) Benazepril 10mg/d (n = 90) (Bmax) Benazepril started at 10mg/d, then up-titrated (n = 90) (L50) Losartan 50mg/d (n = 90) (Lmax) Losartan started at 50mg/d, then up-titrated (n = 90) After the run-in, participants in Bmax and Lmax followed the following up-titration schedule (B10 and L50 remained on starting doses): Bmax: monthly up-titration by 10mg to 20mg/d, 30mg/d, and then 40 mg/d. Lmax: monthly up titration by 50 mg to 100 mg/d, 150 mg/d, and then 200 mg/d. Urinary protein, serum creatinine, and serum potassium were measured every 2 weeks during up-tiration, and doses were reduced if: -urinary protein excretion did not fall by ≥ 10% compared to previous titration period (confirmed by 2 values, 4 weeks apart on same dosage) -systolic blood pressure <120 mmHg despite withdrawl of other anti-hypertensives -Serum potassium ≥ 6 mmol/L, refractory to medical treatment -creatinine >30% compared to previous value (reduced to previous dose or withdrawn) If participants were un-responsive to up-titration (meaning <10% reduction in proteinuria), they were titrated up to maximum dose. If still no response, dose was reduced to starting dose.	8 week run-in (referred to as "pre-titration phase" within the study) during which time: B10 and Bmax received Benazepril 10mg/d L50 and Lmax received Losartan 50mg/d During run-in, participants had weekly measurements of BP, serum creatinine, and serum potassium. Participants proceeded to titration phase if: -stable creatinine (<30% creatinine increase from baseline value, confirmed by 3 measurements) -Serum potassium levels <5.6 mmol/L	If blood pressure remained above 130 mmHg systolic or 80 mmHg diastolic, then additional anti-hypertensives could be added. Additional meds included: -diuretics -central α agonists -calcium channel blockers - β-blockers -combination of above (no additional ACE-I or ARB) The median number of anti-hypertensives in each group was 2.	Primary end point: time to first event for composite end point which included doubling of serum creatinine concentration, ESRD, or death. (doubling of serum creatinine was defined by a second creatinine 4 weeks later, ESRD was defined by need for long term dialysis or transplantation). Secondary end points included: Changes in urinary protein excretion rate Progression of renal disease assessed by GFR and CrCl. At baseline, after run-in, q2 q weeks in max dose groups, and q mo overall, the following tests were completed: blood pressure serum labs 24 hr urine collection for protein, CrCl, urea, chloride During run-in serum labs were done weekly

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Hou 2007 China ROAD (Reno protection of Optimal Antiproteinuric Doses) Good	Mean age: B10: 51.9 +/- 12.6 years Bmax: 49.1 +/- 14.3 years L50: 51.5 +/- 13.3 years Lmax: 51.0 +/- 13.5 years Male gender (n; %): B10: 59; 66% Bmax: 56; 62% L50: 56; 62% Lmax: 55; 61% Ethnicity: NR	Mean serum creatinine at baseline: B10: 2.7 +/- 0.9 mg/dL Bmax: 2.8 +/- 0.9 mg/dL L50: 2.8 +/- 1.1 mg/dL Lmax: 2.9 +/- 1.0 mg/dL Mean eGFR at baseline: B10: 30.6 +/- 11.3 ml/min/1.73m2 Bmax: 30.5 +/- 14 ml/min/1.73m2 L50: 31.4 +/- 14.1 ml/min/1.73m2 Lmax: 29.9 +/- 12.4 ml/min/1.73m2 Mean CrCl at baseline: B10: 33.9 +/- 14.7 ml/min/1.73m2 Bmax: 35.1 +/- 12.2 ml/min/1.73m2 L50: 34.4 +/- 15.5 ml/min/1.73m2 Lmax: 33.8 +/- 14.0 ml/min/1.73m2 Median proteinuria at baseline: B10: 1.4 gm/d Bmax: 2.1 gm/d L50: 1.6 gm/d Lmax: 2.0 gm/d	Number screened: 406 Number eligible: NR Number enrolled: 360	Number withdrawn: 50 pre-titration phase and 18 more past-titration phase. Lost to follow-up: 21 Analyzed: 360 (intention to treat)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Hou 2007 China ROAD (Reno protection of Optimal Antiproteinuric Doses) Good	Percent who reached primary end point: B10: 31.3%; Bmax: 19.9%; Significantly fewer primary end points were noted for Bmax compared to B10, p = 0.025. L50: 29.5%; Lmax: 15.5%; Significantly fewer primary end points were noted for Lmax compared to L50, p = 0.022. Overall reduction in risk of primary end point:No difference between L and B at any dose. 51% reduction in Bmax comapred B10, 95% CI 4.8; 73.3, p = 0.028 53% reduction in Lmax compared to L50, 95% CI, 5.5; 74.1, p = 0.022 Reduction in risk of primary endpoint remained statistically significant after adjustment for: -systolic blood pressure (B arm p = 0.03, L arm p = 0.031), -proteinuria (B arm p = 0.0337, L arm p = 0.039) -baseline eGFR (B arm p = 0.039, L arm p = 0.035). Percent reduction in risk of ESRD: 47% in Bmax vs B10, 95% CI 4.2,;72.1, p = 0.042 47% in Lmax vs L50, 95% CI 3.6; 76.9, p = 0.046 Reduction in decline in renal function by CrCl (and by GFR) with optimal antiproteinuric dose vs lower dose: Benazepril arm: 60%, p = 0.021 for CrCl (p = 0.02 for GFR) Losartan arm: 55%, p = 0.037 for CrCl (p = 0.03 for GFR) Optimal antiproteinuric efficacy: B20mg (61%), B30mg (16%), B40mg (4%), B>40mg (4%) L100mg (57%), L150mg (14%), L200 (11%), L>200mg (4%) There was no difference in reduction in proteinuria for Losartan versus Benazapril at any dose. Antihypertensive efficacy was similar in both arms (p > 0.05).	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Hou 2007 China ROAD (Reno protection of Optimal Antiproteinuric Doses) Good	NR	NR	Non-fatal cardiovascular events/Myocardial infarction/HF/Stroke: B10: 4/2/1/1 Bmax: 5/2/2/1 L50: 5/2/2/1 Lmax: 4/ 2/1/1 Hyperkalemia: B10: 3 Bmax: 5 L50: 3 Lmax: 5 Acute decline in renal function: B10: 2 Bmax: 3 L50: 3 Lmax: 3 Dry cough: B10: 17 Bmax: 15 L50: zero Lmax: zero Hypotension: B10: 1 Bmax: 2 L50: 1 Lmax: 1

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Hou 2007 China ROAD (Reno protection of Optimal Antiproteinuric Doses) Good	Total withdrawals: 68 Withdrawals due to adverse events: B10: 21 (17 cough, 1 elevated creatinine, 2 hyperkalemia, 1 hypotension) Bmax: 23 (cough 15, elevated creatinine 3, hyperkalemia 3, hypotension 2) L50: 6 (elevated creatinine 3, hyperkalemia 2, hypotension 1) Lmax: 6 (elevated creatinine 2, hyperkalemia 3, hypotension 1) Withdrawals for reason other than adverse events: B10: 2 (lost to follow-up) Bmax: 2 (lost to follow-up) L50: 2 (lost to follow-up) Lmax: 6 (lost to follow-up)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Kahvecioglu 2007 Turkey no trial name Poor	Study design: clinical head to head trial Setting: outpatient clinic Duration: 12 months	Inclusion criteria: Biopsy-proven non-diabetic renal disease Creatinine <2 mg/dL Stable proteinuria of >0.5gm/d (no more than 20% change in 3 mo prior) Medications only for primary renal disease (meaning steroids and/or immune suppression) Exclusion criteria: Systemic or urinary tract infections Pregnancy Hyperkalemia History of hypersensitivity to study drugs Active gastric ulcer Stage 2 or secondary hypertension Use of antihypertensive drugs Recent myocardial infarction Uncontrolled angina or serious arrhythmias Serious peripheral vascular disease Obstructive pulmonary disease Serious liver disease Diabetes Heart rate <55 beats per minute	Types of CKD: IgA nephropathy Membranous nephropathy Membranoproliferative glomerulonephritis Focal segmental glomerulosclerosis Biopsy proven: yes Degree of proteinuria: >0.5 gm/d required. Baseline characteristics indicate baseline proteinuria ranged from 1.5-2.2 gm/d Proteinuria measured by 24 hr assessment	Level of CKD: not specifically addressed Creatinine <2 mg/dL required CrCl at baseline ranged from 94-114 ml/min via Cockcroft Gault.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Kahvecioglu 2007 Turkey no trial name Poor	Participants were separated into three groups (unclear if randomized): Losartan 100mg/d (L) (n = 7) Losartan 50mg/d + Ramipril 5mg/d (L=R) (n = 7) Losartan 50mg/d + Carvedilol 25 mg/d (n = 7) Patients remained in these treatment groups for 12 months	2 week run-in during which patients received Losartan 50 mg/d. No wash-out period.	NR	End points note specifically addressed. Primary aim was stated as: to compare the effects of carvedilol with Ramipril and Losartan in patients with proteinuric glomerulonephritis. Reported outcomes included: -proteinuria -systolic and diastolic blood pressure -serum albumin -creatinine and CrCl -Serum sodium and potassium The following assessments were completed routinely: CrCl calculation Serum labs 24 hr proteinuria assessment Assessments were done at: -baseline (prior to run-in) -at time of separation into treatment groups -in follow up at 1 mo, 6mo, and 12 mo

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kahvecioglu 2007 Turkey no trial name Poor	Mean age: L: 42 +/- 11 L+R: 43 +/- 15 Gender: (female/male) L: 1/6 L+R: 1/6 Ethnicity: NR	Proteinuria before run-in: L: 1.8 +/- 1.1 gm/d L+R: 2.2 +/- 1.4 gm/d Proteinuria after run-in: L: 1.6 +/- 1.1 gm/d L+R: 2.1 +/- 1.2 gm/d Creatinine after run-in: L: 1.1 +/- 0.2 mg/dL L+R: 1.1 +/- 0.3 mg/dL CrCL after run-in: L: 96 +/- 27 ml/min L+R: 101 +/- 25 ml/min Potassium after run-in: L: 4.4 +/- 0.3 mEq/L L+R: 4.4 +/- 0.7 mEq/L Baseline systolic blood pressure: L: 137 +/- 7 mmHg L+R: 137 +/- 5 mmHg	Number screened: NR Number eligible: NR Number enrolled: 31	Number withdrawn: 10 Lost to follow-up: 6 (not specified which treatment groups) Analyzed: 21

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Kahvecioglu 2007 Turkey no trial name Poor	Comparisons were made only between baseline, 1, 6, and 12 mo assessments from within each group; inter-group comparisons were not made. Changes in proteinuria between 1st and 12th months: L: -61%; p = 0.04 L+R: -62%, p = 0.06 95% CI NR Creatinine clearance at 1st and 12th month: L: 93 +/- 21 ml/min to 94 +/- 28 ml/min L+R: 1015+/- 27 ml/min to 114 +/- 41 ml/min P values NR, 95% CI NR; reported as no statistically significant difference. No statistical comparisons for changes in blood pressure between groups were reported. They noted a statistically significant decline in systolic blood pressure for both L and L+R; they noted a statistically significant decline in diastolic blood pressure for L but not for L+R.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Kahvecioglu 2007 Turkey no trial name Poor	NR	NR	2 withdrawals were related to intolerance to anti-hypertensives (treatment groups not specified).

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Kahvecioglu 2007 Turkey no trial name Poor	Total withdrawals: 10 Withdrawals due to adverse events: 2 Withdrawals due to reason other than adverse events: 2 -both were withdrawn because they required changes in their immunosuppressive regimens (1 in Ramipril group, one in carvedilol group, zero in Losartan group). Withdrawals due to incomplete follow-up: 6		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Kim 2003 Korea No trial name Fair	Study design: randomized cross-over. Setting: Inpatient vs. outpatient unclear. Undertaken at "Inha University Hospital." Duration: 36 weeks	Inclusion criteria: Biopsy proven IgA or Diabetic nephropathy Blood pressure <130/80 on Ramipril ≥ 5 mg/d for 6 mo prior to enrollment. CrCl 25-90 ml/min/1.73 m2 Urinary protein excretion >1 gm/d Exclusion criteria: Use of steroid or cytotoxic therapy in 6 mo prior to enrollment	Types of CKD: IgA nephropathy Diabetic nephropathy Biopsy proven? Yes Proteinuria >1 gm/d required. Baseline proteinuria was 3.9 gm/d. Proteinuria was measured via 24 hr urine collection.	Stage of CKD not specifically addressed. CrCl 25-90 ml/min/1.73 m2 required. Baseline CrCl was 30.1 ml/min/1.73 m2. CrCl was established with 24 hr urine study.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Kim 2003 Korea No trial name Fair	After run-in, participants (all of whom were already on at least 5mg Ramipril) were randomized to one of the following groups: (R+C) Ramipril at prior dose + candesartan 4mg (R+P) Ramipril at prior dose + placebo Each participant was then crossed-over into the opposite group. Each study group lasted 12 weeks. The run-in period with Ramipril without ARB or placebo was considered the control group (R).	Run-in: 12 week period during which baseline medications were not changed. No washout period was reported. No analysis to remove the need for a washout was reported.	Other medications were allowed if needed for blood pressure control. Allowed medications included: Diuretic (n = 10) Diuretic + calcium channel blocker (n = 2) Diuretic + calcium channel blocker + vasodilator (n = 2) 34% of participants required additional therapy with these agents.	Primary end point not specifically stated. Main aim was reported to be to examine if the same regimen of combination therapy of ACE-I and ARB was equally effective in diabetic and non-diabetic nephropathy in the reduction of proteinuria. The following assessments were completed at the end of the 12 week run-in and after each treatment group (weeks 12, 24, 36): serum labs blood pressure 24 hour urine collection for CrCl and proteinuria

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kim 2003 Korea No trial name Fair	Mean age: 34 +/- 5 (range 24-53) Gender (female/male): 22/19 Ethnicity: NR	Mean CrCl: 60.1 +/- 4 ml/min/1.73 m2 Mean 24 hr proteinuria at baseline: 3.9 +/- 0.3 gm/d Mean dose of Ramipril: 5.7 +/- 0.4 mg/d (range5-7.5 mg/d)	Number screened: NR Eligible: NR Enrolled: 43	Number withdrawn: 2 Lost to follow up: zero Analyzed: 41

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Kim 2003 Korea No trial name Fair	Mean decrease in proteinuria: R alone (baseline): 4 +/- 0.2 gm/d R+P: 4.1 +/- 0.3 gm/d R+C: 3.5 +/- 0.2 gm/d There was a statistically significant difference between R+C and both R+P and R ($p < 0.05$ for each, 95% CI NR) Changes in creatinine clearance: R alone: 61.2 +/- 3.7 ml/min/1.73 m2 R+P: 60.3 +/- 4.1 ml/min/1.73 m2 R+C: 59.3 +/- 4.6 ml/min/1.73 m2 Differences in CrCl between groups was reported as p value NS (discrete p values and 95% CI NR). No significant change in blood pressure lowering effect between groups was noted (p was NS).	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Kim 2003 Korea No trial name Fair	Participants with IgA nephropathy were compared to those with diabetic nephropathy looking at reduction in proteinuria on these treatment regimens. Reduction in proteinuria among IgA: R: 4.2 +/- 0.3 gm/d R+P: 4.3 +/- 0.2 gm/d R+C: 3.1 +/- 0.3 gm/d There was a significant difference found between R+C and both R and R+P (p< 0.05, 95% CI NR). No change in blood pressure lowering effect was noted between groups. Reduction in proteinuria among Diabetic nephropathy: R: 4.1 +/- 0.3 gm/d R+P: 3.9 +/- 0.3 gm/d R+C: 3.8 +/- 0.2 gm/d P values for inter-group comparisons reported as NS (95% CI NR). No change in blood pressure lowering effect was noted between groups.	NR	Hyperkalemia: 1 (also had azotemia) Hypotension: 1 **not specified by study group.**

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Kim 2003 Korea No trial name Fair	Total withdrawals: 2 Withdrawals due to adverse events: 2 1 for hyperkalemia 1 for hypotension		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Laverman 2002 The Netherlands no trial name Fair	Study design: prospective, open-label, cross-over. Setting: outpatient renal clinics Duration: 78 weeks	Inclusion criteria: Age 18-70 CrCl ≥ 30 ml/min/1.73m2 Stable proteinuria at ≥ 2 gm/d Diastolic blood pressure 80-110 mmHg after 6 weeks off all anti-hypertensive medications Exclusion criteria: History of cardiovascular disorders History of diabetes Frequent NSAID use (>2 doses per week)	Types of CKD: focal segmental glomerulosclerosis membranous nephropathy IgA nephropathy Non-conclusive biopsy Biopsy proven? Alluded to, but not specifically stated Proteinuria ≥ 2 gm/d required. Baseline median proteinuria was 4.5 gm/d.	Stage of CKD not specifically addressed. CrCl ≥ 30 ml/min/1.73m2 required Baseline median CrCl was 80 ml/min/1.73m2 Method for CrCL measurement not specifically reported (via calculation vs. urine collection).

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Laverman 2002 The Netherlands no trial name Fair	All participants underwent 6 week period off all anti-hypertensive medications. If diastolic blood pressure remained between 80-110 mmHg after that period, they were randomized to either: (LIS) Lisinopril escalating doses 10mg/d, 20mg/d, 40mg/d, and 10mg/d (LOS) Losartan escalating doses 50mg/d, 100mg/d, 150mg/d, 50mg/d *Each dose treatment period was 6 weeks. After another 6 week period off medication, participants were switched to the alternate escalating dose method. After completion of second escalating dose method, all participants were placed on combination therapy of LIS+LOS at doses that had been found to be each individuals maximal proteinuria reduction dose.	6 week run-in, during which time no anti-hypertensive medication was allowed. 6 week washout between escalating dose arms during which time no anti-hypertensive medication was allowed.	None	Primary end point not specifically stated. Primary aim described as to investigate the combination of the optimal dose of ACE-I and ARB for anti-proteinuric effect, and to test whether combination of those doses results in more reduction in proteinuria than either alone. At baseline, at the end of each dose treatment period, after washout, and after combination therapy, the following evaluations were made: -two 24-hr urine collections for protein and creatinine -blood pressure measurements -calculation of day/night proteinuria ratios -serum lab tests including creatinine and electrolytes

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Laverman 2002 The Netherlands no trial name Fair	Median age: 51 (95% CI 44;55) Ratio male/female: 6/3 Ethnicity: NR Race: all Caucasian	Baseline median CrCl: 80 (95% CI 66;96) Previous medication history: 6 on Enalapril 1 on Enalapril + hydrochlorothiazide 1 on Lisinopril + hydrochlorothiazide 1 on Losartan Baseline median proteinuria: 4.5 gm/d (95% CI 3.6;6.4) Median systolic blood pressure at baseline: 137 mmHg (95% CI 130;152) Median diastolic blood pressure at baseline: 80 mmHg (95% CI 66;96)	Number screened: NR Number eligible: NR Number enrolled: 10	Number withdrawn: 1 Lost to follow-up: zero Analyzed: 9

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Laverman 2002 The Netherlands no trial name Fair	Dose of maximal antiproteinuric efficacy (proteinuria at that dose): LOS: 100mg/d (2.8 gm/d, 95% CI 1.5;4.6) LIS: 40mg/d (1.4 gm/d, 95% CI 0.5;3.2) Combined therapy dosing was based on each individuals maximal anti-proteinuric doses; doses were as follows: LOS 150 + LIS 40 in 3 participants LOS 100 + LIS 40 in 2 participants LOS 100 + LIS 20 in 2 participants LOS 50 + LIS 40 in 2 participants Reductions in proteinuria on monotherapy vs combination therapy (median; 95% CI, p vs baseline and inter-group comparisons): LOS: 2.2 gm/d (1.2;4.8) p < 0.05 vs baseline LIS: 1.4 gm/d (0.5;2.9) p < 0.05 vs baseline, p < 0.05 vs LOS LOS+LIS: 1 gm/d (0;2.6) p < 0.05 vs baseline ; p < 0.05 vs LOS or LIS Changes in CrCl (median, 95% CI, p value): LOS: 73 ml/min/1.73m2, 95% CI 59;89, p value NS compared to baseline LIS: 72 ml/min/1.73m2, 95% CI 52;92, p value NS compared to baseline LOS+LIS: 66 ml/min/1.73m2, 95% CI 51;80, p < 0.05 compared to baseline *where p values listed as NS, actual numbers NR* LOS+LIS lowered mean arterial pressures lower than LOS (p < 0.05) but not lower than LIS.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Laverman 2002 The Netherlands no trial name Fair	NR	NR	Serum potassium >5.5 mmol/L: LOS: 1 LIS: 2 LOS+LIS: 2 Dizziness: LOS: 1 LIS: 1 LOS+LIS 2 Adverse events did not lead to any withdrawals.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Laverman 2002 The Netherlands no trial name Fair	Total withdrawals: 1 Withdrawals due to adverse events: zero Withdrawals due to reasons other than adverse events: 1 (due to inability to maintain scheduled visits)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Luno 2002 Spain Fair	Study design: multi-center, prospective, open, randomized, active controlled and parallel group Setting: outpatient Duration: 24 weeks	Inclusion criteria: Age 18-80 Primary proteinuric nephropathy for >6 mo Proteinuria > 2 gm/d (by two 24-hr urine collections) GFR >50 ml/min/1.73m2 Exclusion criteria: Serum albumin <3 g/dL Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg Serum potassium > 5 mmol/L Secondary glomerular disease Diabetes, Amyloidosis, lupus Severe cardiovascular even tin 3 mo prior to randomization Severe cardiac, pulmonary, or hepatic disease HIV Neoplasia Use of corticosteroids or immune suppression therapy in 6 mo prior to entry Women who were of childbearing age but not using an effective method of birth control	Types of CKD: NR Biopsy proven? Recommended but not required Proteinuria >2 gm/d required. Baseline mean proteinuria ranged from 3.6-4 gm/d.	Stage of CKD: not specifically addressed CrCl > 50 ml/min/1.73m2 required. Baseline CrCl ranged from 84-100 ml/min/1.73m2. CrCl measured via 24 hr urine collection.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Luno 2002 Spain Fair	After 2 week run-in, participants were randomized to: [L] Lisinopril 10mg/d (n = 14) [C] Candesartan 8mg/d (n= 15) [L+C] Lisinopril 5mg/d + Candesartan 4mg/d (n = 16) If systolic blood pressure was higher than 125 mmHg or diastolic blood pressure was higher than 75 mmHg, then doses were doubled every 2 weeks to a maximum dose of: [L] Lisinopril 40mg/d [C] Candesartan 32 mg/d [L+C] Lisinopril 20mg/d + Candesartan 16 mg/d *Dose increased to achieve goal of blood pressure <125/75 mmHg.*	2 week run-in period was used. During that time only metoprolol and hydrochlorothiazide were used for blood pressure management. All previous ACE-I and ARB were held.	Additional medication was allowed to achieve blood pressure goal of <125/75 mmHg. Additional medications included: β-blockers calcium channel blockers Thiazide diuretics	Primary end point was not specifically stated. Primary objective: a reduction in proteinuria excretion with Lisinopril, candesartan, or a combination of both therapies in primary proteinuric nephropathies. Prior to run-in, at inclusion, at beginning of treatment, and at weeks 2, 4, 6, 8, 12, and 24, participants had office visits and blood pressure measurements. At baseline and at weeks 6, 12, and 24, participants had the following assessments done: -serum labs including creatinine and electrolytes -24 hr urine for protein, sodium, potassium, and creatinine.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Luno 2002 Spain Fair	Age: C: 45 +/- 18 years L: 50 +/- 16 years C+L: 42 +/- 13 Gender (men/women): C: 10/5 L: 12/2 L+C: 9/7 Ethnicity: NR	Baseline CrCl: C: 104 +/- 36 ml/min L: 84 +/- 26 ml/min C+L: 96 +/- 34 ml/min Baseline protein/creatinine ratio: C: 4 +/- 2.5 L: 3.6 +/- 2.9 C+L: 3.8 +/- 2.1 Baseline serum potassium level: C: 4.3 +/- 0.3 mmol/L L: 4.3 +/- 0.3 mmol/L C+L: 3.8 +/- 2.1 mmol/L Systolic blood pressure: C: 133 +/- 14 mmHg L: 135 +/- 20 mmHg C+L: 135 +/- 20 mmHg	Number screened: NR Eligible: NR Enrolled: 46	Number withdrawn: 1 Lost to follow-up: zero Analyzed 45 (intention to treat)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Luno 2002 Spain Fair	Urine protein/creatinine ratio (beginning to 2 mo and to 3 mo compared to baseline): (% change, 95% CI, p value) C: 3.99 +/- 0.63 to 3.14 +/- 0.67 (-28%,12,-45, p = 0.019) and 2.34 +/- 0.42 (-41%; -30,-52, p < 0.001) L: 3.6 +/- 0.7 to 3.6 +/- 0.77 (-33%; -12,-56, p = 0.008) and 2.44 +/- 0.97 (-31%; 0,-68, p = 0.019) C+L: 3.8 +/- 0.53 to 1.55 +/- 0.41 (-60%; -44,-77, p = 0.004) and 1.89 +/- 0.51)-54%; -38,-69), p < 0.001) Urine protein/creatinine ratio (beginning to after treatment at 6 mo): C: 3.99 +/- 0.63 to 2.8 +/- 0.49 (-48%, 95% CI -32 -63, p < 0.001) L: 3.6 +/- 0.7 to 1.83 +/- 0.68 (-50%, 95% CI -9;-90, p = 0.013) C+L: 3.8 +/- 0.53 to 1 +/- 0.25 (-70%, 95% CI -57; -83, p < 0.001) *p values intra-group protein reduction compared to baseline. Reduction in urinary protein excretion, between group comparisons: C+L vs C: C+L resulted in more proteinuria reduction at 2 and at 6 months (p = 0.004 at 2 months and p = 0.23 at 6 months) C+L vs L: C+L resulted in more proteinuria reducation only at 2 months (p = 0.03 at 2 mo, p at 6 mo NR). Blood pressure goal of <125/75 reportedly achieved by all groups by 4 weeks; no statistical significance of blood pressure control between groups. Changes in creatinineclearance showed no signficant difference between treatment groups at any time point.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Luno 2002 Spain Fair	Maximum dose of Candesartan (32 mg/d) was tolerated by 56%. Maximum dose of Lisinopril (40 mg/d) was tolerated in 31%. Maximum dose of combination therapy (Lisinopril 20 mg/d + candesartan 16 mg/d) was tolerated in 35%. Medium dose of Candesartan (16 mg/d) was achieved in 23%. Medium dose of Lisinopril (20mg/d) was achieved in 35%. Medium dose of combination therapy (Lisinopril 10 mg/d + candesartan Candesartan 8 mg/d) was achieved in 39%.	Lab tests done as reported. Otherwise NR.	Serum potassium >5.5 mmol/L: 8 instances Not specified by group. 2 instances > 6 mol/L. Participants in L or C+L experienced K > 5.5 mmol/L more than those on C ($p < 0.001$). No other adverse events reported.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Luno 2002 Spain Fair	Total withdrawals: 1 Withdrawals due to adverse events: zero Withdrawals due to reason other than adverse events: 1 (never took study medication, so was excluded)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Matsuda 2003 [Differing Anti-proteinuric action of candesartan and Losartan in chronic renal disease] Japan Fair	Study design: randomized controlled trial Setting: NR Duration: 96 weeks	Inclusion criteria: Hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) Proteinuria of >0.5 gm/d Serum creatinine < 3 mg/dL CrCl >30 ml/min/1.73m2 Exclusion criteria: Diabetic nephropathy Polycystic kidney disease Chronic Pyelonephritis	Types of renal disease: proliferative glomerulonephritis (n = 58) membranous nephropathy (n = 2) focal segmental glomerulosclerosis (n = 2) Biopsy proven? NR >0.5 mg/d proteinuria required for inclusion. Mean proteinuria at baseline ranged from 2.5 - 3 gm/d. Proteinuria was measured via 24 hour urine collection. assessment.	Stage of CKD not specifically addressed. CrCl >30 ml/min/1.73m@ required, Serum creatinine <3 mg/dL required. Baseline CrCl ranged from 79-97 ml/min/1.73m2 CrCl was measured via 24 hour urine collection. assessment.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Matsuda 2003 [Differing Anti-proteinuric action of candesartan and Losartan in chronic renal disease] Japan Fair	Participants were initially randomly assigned to ACE-I or ARB treatment groups. After 4 week observation period, participants divided into one of four groups: [T] Trandolapril 0.5 mg/d (n = 15) [P] Perindopril 2 mg/d (n = 15) [L] Losartan 25 mg/d (n = 15) [C] Candesartan 4 mg/d (n = 17) Doses were titrated within each group to achieve blood pressure <135/85 mmHg	4 week observation period noted prior to group assignment. No additional information reported.	14 of 62 participants were on antiplatelet therapy prior to enrollment (dipyridamole or dilazep dihydrochloride); these medications were continued.	Primary end point not specifically reported. Stated aim was to evaluate the effect of candesartan and Losartan on the development of proteinuria over 96 weeks. Blood pressure was measured at each visit. 24 hour urine for creatinine clearance and protein was completed during control period and at weeks 12, 24, 48, 72, and 96.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Matsuda 2003 [Differing Anti-proteinuric action of candesartan and Losartan in chronic renal disease] Japan Fair	Age: T: 51 +/- 4 years P: 50 +/- 5 years L: 51 +/- 3 C: 58 +/-5 Gender (male/female): T: 9/6 P: 8/7 L: 7/8 C: 9/8 Ethnicity: NR	Baseline serum creatinine: T: 0.9 +/- 0.1 mg/dL P: 0.9 +/- 0.1 mg/dL C: 1 +/- 0.1 mg/dL L: 1.1 +/- 0.2 mg/dL Baseline CrCl: T: 115 +/- 18 ml/min/1.73m2 P: 98 +/- 10 ml/min/1.73m2 C: 102 +/- 18 ml/min/1.73m2 L: 89 +/- 15 ml/min/1.73m2 Baseline urinary protein excretion: T: 2.7 +/- 0.5 gm/d P: 2.7 +/- 0.5 gm/d C: 3 +/- 0.6 gm/d L: 2.5 +/- 0.4 gm/c Baseline serum potassium: T: 4.3 +/- 0.1 mEq/L P: 4.3 +/- 0.1 mEq/L C: 4.3 +/- 0.1 L: 4 +/- 0.2 mEq/L Baseline systolic blood pressure and diastolic blood pressure (mmHg): T: 154+/-6 and 90+/-3 P: 155+/-3 and 91+/-4 C: 152+/-2 and 93+/-2 L: 150+/-4 and 93+/-3	Number screened: NR Eligible: NR Enrolled: 62	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Matsuda 2003 [Differing Anti-proteinuric action of candesartan and Losartan in chronic renal disease] Japan Fair	Percent reductions in proteinuria at 12 weeks and 96 weeks: T: 37+/-6% (p < 0.05) at 12 weeks and 53+/- 7% (no p value given) at 96 weeks. P: 42+/-6% (p<0.05) at 12 weeks and 60.7% at 96 weeks (no p value given). C: 38+/-4% at 12 weeks (no p value given) and sustained anti-proteinuric effect throughout study ((no p value given). L: 12 +/-3% (P< 0.05) at 12 weeks and 36+/-4% at 96 weeks. *Significantly less reduction in proteinuria was noted in L compared to C (p<0.05) but no comparisons of ACE to ARB were made. No significant effect on CrCl was seen throughout the study, numbers not reported. No significant differences in blood pressure were noted between treatment groups at any period, no numbers given.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Matsuda 2003 [Differing Anti-proteinuric action of candesartan and Losartan in chronic renal disease] Japan Fair	NR	Lab tests done as reported. Otherwise NR.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Matsuda 2003 [Differing Anti-proteinuric action of candesartan and Losartan in chronic renal disease] Japan Fair	NR		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Mori-takeyama 2008 Japan no trial name Fair	Study design: Prospective, parallel, open-label Setting: NR Follow-up: 36 months	Inclusion criteria: Biopsy-proven glomerulonephritis History of Candesartan dose of 4mg/d for 6 months prior to enrollment. Exclusion criteria: history of diabetes, history of renal artery stenosis, steroids or immune suppression therapy within 6 months prior, history of malignant hypertension, history of stroke, TIA, unstable angina, arrhythmia, or heart failure.	Types of CKD: Repeat biopsy was done on 52 of the 86 enrolled patients and Glomerulonephritis types were specified for those 52 as: -membranoproliferative glomerulonephritis (n=39) (mesangioproliferative Glomerulonephritis) -Minor glomerular abnormality (n= 5) -focal segmental glomerulosclerosis (n=2) (focal segmental glomerulosclerosis) -Membranous nephropathy (n=2) History of biopsy proven Glomerulonephritis was required. Proteinuria >0.3 gm/day required Mean proteinuria at baseline 1.4 gm/d	CKD stages were not specifically defined or included as inclusion/exclusion. GFR was reported in baseline characteristics and outcomes, and was measured via para-aminohippuric acid and thiosulfate clearance methods. Per the baseline characteristics table, baseline creatinine 0.8-0.9.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Mori-takeyama 2008 Japan no trial name Fair	Participants were randomly allocated to a treatment regimen based on the last digit of their ID number into group A or group B. Group A (to be referred to as "C"): candesartan alone,; candesartan dose increased from 4 mg/d to 6mg/d at study initiation. Group B (to be referred to as "C+B"): candesartan and Benazepril; dose of Benazepril of 2.5mg/d added to candesartan 4 mg/d at time of study initiation. Target BP: 125/75 In C, candesartan was increased by 8 and 12 mg every 6 months to reach target BP. In C + B, Benazepril was increased to 5 and 10 mg/d every 6 months to reach target BP.	Run in: All participants were on candesartan 4 mg/d for 6 months prior to enrollment. No wash-out following run-in	If target BP not reached at 18 months, adjuvant hypertensives could be added. (additional drugs use were not specified)	Primary endpoint not specifically stated. Aim stated to be to evaluate the antiproteinuric and renal protective effect of candesartan alone and with Benazepril in patients with chronic glomerulonephritis. The following measurements were completed every three months: -blood pressure -GFR and renal plasma flow (evaluated by para-aminohippuric acid and thiosulfate methods). -Proteinuria was quantified by pyrogallol red-molybdate method. -Complete blood count, serum electrolytes, and urea nitrogen were measured via automated analyzer. -PRA, PAC, and atrial natriuretic peptide were determined by radioimmunoassay.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Mori-takeyama 2008 Japan no trial name Fair	Mean age: C: 37.8 +/- 12 C + B: 36.9 +/- 12 % male: C: 63% C + B: 56% Ethnicity: not explicitly stated	Mean potassium: C: 4.1 +/- 0.2 C+B: 3.9 +/- 0.3 Mean serum creatinine: C: 0.8 +/- 0.3 C+B: 0.9 +/- 0.3 Mean GFR: C: 94.3 +/- 12.8 C+B: 95.6 +/- 28.6 Mean proteinuria: C: 1.4 +/- 0.6 C+B: 1.3 +/- 0.5 Mean systolic blood pressure and diastolic blood pressure: C: 132 +/- 8.6 mmHg and 84 +/- 4.9 mmHg C+B: 135.8 +/- 6.8 mmHg and 81.2 +/- 5.2 mmHg	Number screened: NR Eligible: NR Enrolled: 86	Number withdrawn: 9 Lost to follow-up: NR Analyzed: 77

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Mori-takeyama 2008 Japan no trial name Fair	Total reduction in proteinuria (baseline to post treatment): C: 1.4 +/- 0.6 gm/d to 0.7 +/- 0.3 gm/d, p < 0.01 compared to baseline C+B: 1.3 +/- 0.5 gm/d to 0.5 +/- 0.2 gm/d, p < 0.01 compared to baseline Anti-proteinuric effect of C+B was statistically greater than that of C after 18 months (p < 0.01, 95% CI NR) No significant change in GFR or renal plasma flow between groups was noted, p values and 95% CI NR. Difference in BP reduction rate was not significant between the two groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Mori-takeyama 2008 Japan no trial name Fair	n/a	NR	Only specific adverse event reported was cough, which was only reported regarding its incidence in group B (Candesartan+Benazepril, noted in 39.1%).

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Mori-takeyama 2008 Japan no trial name Fair	Total withdrawals: 9 Withdrawals due to cough: 6 (all in C+B Withdrawals classified by study group as "not due to side effects": 3 (2 in C, 1 in C+B)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Nakao 2003 Japan COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Study design: double-blind randomized trial Setting: outpatient nephrology clinic Duration: 3 years	Inclusion criteria: Age 18-70 chronic nephropathy (serum creatinine 1.5-4.5 mg/dL or eGFR 20-70 ml/min/1.73m2) Variation of creatinine or eGFR of lessl than 30% in 3 mo prior to enrollment Non-diabetic renal disease (by history, exam, urinalysis, serum labs, and biopsy if available) Proteinuria > 0.3 gm/d for at least 3 mo prior to enrollment Exclusion criteria: Evidence of urinary tract infection or stage III-IV NYHA heart failure History of allergic reaction to drugs (especially ACE-I) Immediate need for renal replacement therapy Treatment-resisstant edema Need for steroids, NSAIDS, or immunosuppressive drugs Proteinuria >10 gmd/ or serum albumin <2.8 g/dL Renovascular or malignant hypertension Myocardial infarction of cerebrovascular accident in the year prior to enrollment Severe peripheral vascular disease, HF, chronic hepatic disease, connective tissue disease, obstructive uropathy, cancer, or COPD Drug or alcohol misuse Pregnancy or breastfeeding	Types of CKD: Glomerular Hypertension Polycystic kidney interstitial Unknown Biopsy proven? Yes *Biopsies were performed after enrollment to confirm type of kidney disease.* Proteinuria >0.3 gm/d but <10gm/d required. Baseline proteinuria ranged from 2.5-2.5 gm/d	Stage of CKD not specifically addressed. eGFR of 20-70 ml/min/1.73m2 required Baseline eGFR ranged from 37.5-38.4 ml/min/1.73m2 eGFR was calculated.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Nakao 2003 Japan COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	After run-in, participants were randomized to: [L] Losartan 25mg + placebo daily (n = 89) [T] Trandolapril 1mg + placebo daily (n = 86) [L+T] Losartan 12.5gm and Trandolapril 0.5 mg daily (n = 88) Every 3-4 weeks the drug dose was increased to reach the fixed maximum dose: [L] Losartan 100 mg/d (25mg am, 25 mg, noon, 50mg evening) with placebo [T] Trandolapril 3mg/d (1.5mg bid) with placebo [L+T] Losartan 100mg/d + Trandolapril 3mg/d	Run-in: 18 week period prior to randomization. No antihypertensives were used for the first 3 weeks or last 3 weeks. After initial 3 weeks, Trandolapril was started at 0.5mg/d and increased by 1mg every 3 weeks to maximum dose of 6 mg/d to determine optimal anti-proteinuric dose. 3 urine samples for urine protein were done at the end of each 3 week period. Anti-proteinuric effect plateaud at 3mg/d; 3mg/d was then used as maximum dose of Trandolapril after randomization. Run-in identified a sub-section of participants with decreased response to ACE (change in proteinuria of -3 to -7% compared to a mean of -44% in most others. These participants were then-on referred to as "low responders."	Goal blood pressure after randomization was <130/80 mmHg. Additional blood pressure medications could be used to achieve that goal. Additional medication that was allowed included: -long acting dihydropyridine calcium channel blockers - α-blockers -centrally acting drugs	Primary endpoint: "renal survival" - combined endpoint looking at time to doubling of serum creatinine or end-stage renal disease (eGFR <7 ml/min/1.73m2) Secondary endpoint: to assess the effects of the three treatments on changes in blood pressure and daily urinary protein excretion, and to note any adverse reactions. Patient appointments were completed with a nephrologist q1 month up through 6 months and then q3 months. Each visit included the following assessments: -serum labs -urine labs -physical exam with blood pressure -24 hr urine study (done to check adherence to dietary restrictions)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Nakao 2003 Japan COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Mean age: L: 44.8 +/- 4.8 years T: 45.9 +/- 5.8 years L+T: 45.2 +/- 4.9 years Gender (male/female): L: 48/41 T: 46/40 L+T: 47/41 Ethnicity: NR	Baseline serum creatinine: L: 3 +/- 0.1 mg/dL T: 3 +/- 0.1 mg/dL L+T: 3.1 +/- 0.1 mg/dL eGFR (calculated, ml/min/1.73m2): L: 38.4 +/- 4 T: 37.9 +/- 3.7 L+T: 37.5 +/- 3.9 Urinary protein excretion (gm/d): L: 2.4 +/- 1.1 T: 2.5 +/- 1.2 L+T: 2.5 +/- 1.1 Systolic blood pressure (mmHg): L: 130 +/- 9.3 T: 129.9 +/- 10.2 L+T: 130.3 +/- 10.5 Number of "low responders" to Trandolapril: L: 11 (13%) T: 10 (12%) L+T: 11 (13%)	Number screened: 336 Number eligible: 301 Number enrolled: 263	Number withdrawn: After screening - 35 After eligible - 38 After enrolled - 7 Lost to follow-up: 7 Analyzed: 256 Stated as intention to treat; those lost to follow up could not be analyzed for primary end point.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Nakao 2003 Japan COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Primary end point, renal survival: L+T vs. T showed HR of 0.38 (95% CI 0.18-0.63, p = 0.11) for primary end point L+T vs. L showed HR 0.4, 95% CI 0.17-0.69, p = .016) for primary end point Percent in each group to reach primary end point: L: 23% (n = 20) T: 23% (n = 20) L+T: 11% (n = 10) Percent in each group to reach end stage renal disease: L: 3% (n = 3) T: 8% (n = 7) L+T: 1% (n = 1) Maximum median change in urinary protein excretion: L: -42.1% T: -44.3% L+T: -75.6% Fall in Systolic blood pressure: L: 5.1 mmHg (SD 1,6) T: 5.2 mmHg (SD 1,3) L+T: 5.3 mmHg (SD 1,4) Fall in Diastolic blood pressure: L: 2.9 mmHg (SD 0,9) T: 2.9 mmHg (SD 0,8) L+T: 3.0 mmHg (SD 0,7)	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Nakao 2003 Japan COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Participants were evaluated for primary end point via type of renal disease (glomerulonephritis vs hypertensive renal disease). -among participants with GN: L: 23% reached primary end point T: 27% reached primary end point L+T: 10% reached primary end point -among participants with hypertensive renal disease: L: 7% T: 13% L+T: 7% *Authors suggest that this indicates lesser effect on primary endpoint in hypertensive renal disease vs GN, p values NR.* Participants in L+T were analyzed by level of proteinuria for achieving primary endpoint: <1 gm/d: HR 0.69, 95% CI 0.22-2.28, p = 0.49 1-3 gm/d: HR 0.33, 95% CI 0.19-2.74, p = 0.29 >3 gm/d: HR 0.4, 95% CI 0.21-1.84, p = 0.33 "Overall effect": 0.34, 95% CI 0.19-2.68, p = 0.31 -- unclear what is compared for this overall effect statement **These values were initially reported incorrectly (p = 0.049, p = 0.029, p = 0.033) and retraction was printed in original journal at later date.** Comparison between treatment groups for antiproteinuria effect were made among participants broken down into level of baseline proteinuria. Results are reported as significantly better in L+T across all baseline protein categories. Numbers are reported for group <1 gm/d: L: -1.2% T: -1.4% L+T: -2.5% p = 0.032	Other than lab tested as noted, NR	Non-fatal cardiovascular event (Stroke/angina/myocardial infarction/hypotension/sudden death): L: 0 / 1 / 1 / 0 / 1 T: 1 / 1 / 0 / 1 / 0 L+T: 1 / 1 / 0 / 1 / 0 Hyperkalemia: L: 4 T: 8 L+T: 7 Dry cough: L: 1 T: 5 L+T: 5 Gastrointestinal symptoms/skin reaction: L: 2 / 1 T: 2 / 1 L+T: 2 / 1 Total adverse reaction: L: 11 T: 19 L+T: 18 Discontinuation/ moved away / protocol invalidation: L: 2 / 1 / 0 T: 1 / 0 / 0 L+T: 2 / 0 / 1

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Nakao 2003 Japan COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Total withdrawals: 7 Withdrawals due to adverse effects: L: 2 T: 1 L+T: 2 Withdrawals due to reason other than adverse effect: L: 1 (moved away) T: 0 L+T: 1 (protocol invalidation)	This study (the COOPERATE trial) was officially retracted by the original publishing journal, The Lancet, in October 2009. Concerns over statistical analysis prompted a formal review by the original study University Hospital in Japan. Their investigation revealed that the study was not double-blind, and that only verbal consent was obtained from patients prior to study initiation. They were unable to verify the presence or role of a statistician in the study analysis. Additionally, sample chart reviews were unable to authenticate patient data.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Nakao 2004 Japan COOPERATE sub-study (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Study design: randomized, double-blinded Setting: outpatient renal clinics Duration: 3 years	Inclusion criteria: Age 18-70 chronic nephropathy (serum creatinine 1.5-4.5 mg/dL or eGFR 20-70 ml/min/1.73m2) Variation of creatinine or eGFR of lessl than 30% in 3 mo prior to enrollment Non-diabetic renal disease (by history, exam, urinalysis, serum labs, and biopsy if available) Proteinuria > 0.3 gm/d for at least 3 mo prior to enrollment Exclusion criteria: Evidence of urinary tract infection or stage III-IV NYHA heart failure History of allergic reaction to drugs (especially ACE-I) Immediate need for renal replacement therapy Treatment-resisstant edema Need for steroids, NSAIDS, or immunosuppressive drugs Proteinuria >10 gmd/ or serum albumin <2.8 g/dL Renovascular or malignant hypertension Myocardial infarction of cerebrovascular accident in the year prior to enrollment Severe peripheral vascular disease, HF, chronic hepatic disease, connective tissue disease, obstructive uropathy, cancer, or COPD Drug or alcohol misuse Pregnancy or breastfeeding	Types of CKD: Glomerular Hypertension Polycystic kidney interstitial Unknown Biopsy proven? Yes *Biopsies were performed after enrollment to confirm type of kidney disease.* Proteinuria >0.3 gm/d but <10gm/d required. Baseline proteinuria was approximately 2.5 gm/d	Stage of CKD not specifically addressed. eGFR of 20-70 ml/min/1.73m2 required Baseline eGFR ranged from 37.5-38.4 ml/min/1.73m2 eGFR was calculated.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Nakao 2004 Japan COOPERATE sub-study (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	92 participants of the original 263 COOPERATE participants entered the ambulatory blood pressure (ABP) sub-study. After run-in, participants were randomized to: [L] Losartan 25mg + placebo daily (n = 30) [T] Trandolapril 1mg + placebo daily (n = 31) [L+T] Losartan 12.5gm and Trandolapril 0.5 mg daily (n = 31) Every 3-4 weeks the drug dose was increased to reach the fixed maximum dose: [L] Losartan 100 mg/d (25mg am, 25 mg, noon, 50mg evening) with placebo [T] Trandolapril 3mg/d (1.5mg bid) with placebo [L+T] Losartan 100mg/d + Trandolapril 3mg/d	Run-in: 18 week period prior to randomization. No antihypertensives were used for the first 3 weeks or last 3 weeks. After initial 3 weeks, Trandolapril was started at 0.5mg/d and increased by 1mg every 3 weeks to maximum dose of 6 mg/d to determine optimal anti-proteinuric dose. 3 urine samples for urine protein were done at the end of each 3 week period. Anti-proteinuric effect plateaud at 3mg/d; 3mg/d was then used as maximum dose of Trandolapril after randomization. Run-in identified a sub-section of participants with decreased response to ACE (change in proteinuria of -3 to -7% compared to a mean of -44% in most others. These participants were then-on referred to as "low responders."	Goal blood pressure after randomization was <130/80 mmHg. Additional blood pressure medications could be used to achieve that goal. Additional medication that was allowed included: -long acting dihydropyridine calcium channel blockers - α-blockers -centrally acting drugs	Primary endpoint: "renal survival" - combined endpoint looking at time to doubling of serum creatinine or end-stage renal disease (eGFR <7 ml/min/1.73m2) Secondary endpoint: to assess the effects of the three treatments on changes in blood pressure and daily urinary protein excretion, and to note any adverse reactions. Patient appointments were completed with a nephrologist q1 month up through 6 months and then q3 months. Each visit included the following assessments: -serum labs -urine labs -physical exam with blood pressure -24 hr urine study (done to check adherence to dietary restrictions) As part of sub-study, ambulatory blood pressure monitors were used for 24 hrs on the day prior to randomization, at 6mo, 1 year, 2 year's and 3 years after enrollment.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Nakao 2004 Japan COOPERATE sub-study (Combination treatment of angiotensin-II receptor blocker and angiotensin- converting-enzyme inhibitor in non-diabetic renal disease) Poor	Mean age among sub-study: L: 43.4 +/- 3.5 T: 42.9 +/- 4.8 L+T: 43.2 +/- 4.4 Gender (%male): L: 56.8% T: 55.9% L+T: 58.9% Ethnicity: NR	Baseline calculated eGFR (ml/min/1.73m2): L: 45.6 +/- 4.9 T: 46.8 +/- 4.1 L+T: 45.9 +/- 5.1 Median baseline urinary protein excretion (gm/d): L: 1.9 +/- 1.1 T: 2.0 +/- 1.2 LT: 1.9 +/- 1.1	Number screened for sub study: NR Number eligible for sub study: NR Number enrolled in sub study: 92	Number withdrawn: 7 Lost to follow-up: NR analyzed: 85

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Nakao 2004 Japan COOPERATE sub-study (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Percent reduction in daily urinary protein excretion: L: -45% (95% CI -10.2 to -54.8%) T: -44% (95% CI -11 to -50.3%) L+T: -74% (95% CI -54 to -81%) The improved anti-proteinuric effect of L+T was sustained throughout the trial (p = 0.013). Number who reached primary end point: L: 4 T: 5 L+T: 1 No difference in outpatient BP or ambulatory BP at baseline. At 6 mo, comparing three groups, no significant differences were seen (p = 0.19 outpatient blood pressure and p = 0.21 ABP). At one year, still no significant difference seen among outpatient blood pressure or ABP between groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Nakao 2004 Japan COOPERATE sub-study (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	NR	NR	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Nakao 2004 Japan COOPERATE sub-study (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease) Poor	Total withdrawals: 7 Withdrawals due to adverse effects: NR **Authors report that 3 in L, 2 in T, and 2 in L+T did not repeat ambulatory blood pressure measurements due to reasons "not related to this trial."**	This study was a sub-study of the COOPERATE trial - see comments above.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Remuzzi 1999 Italy no trial name Poor	Study design: randomized, controlled trial. Setting: outpatient nephrology clinic Duration: 2 months	Inclusion criteria: Age 20-65 Biopsy-proven IgA nephropathy Proteinuria of 0.5 - 4 mg/d Creatinine 0.9-2.4 mg/dL Exclusion criteria: Immunosuppressive or NSAID therapy in the 3 mo prior to enrollment	Types of CKD: IgA nephropathy Biopsy proven: yes Degree of proteinuria: goal range 0.5-4 gm/d. Baseline mean proteinuria ranged from 1.4-2.4 gm/d.	Level of CKD: not specifically addressed Creatinine 0.9-2.4 mg/dL required Baseline GFR ranged from 54-66 ml/min/1.73m2; GFR was determined via inulin and para-aminohippuric acid methods.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Remuzzi 1999 Italy no trial name Poor	At the end of run-in, patients were randomized to: (E) Enalapril 20mg/d (n = 11) (I) Irbesartan 100 mg/d (n = 9) Participants were followed in these groups for 28 days.	4 week single-blind placebo wash-out prior to randomization.	Use of anithypertensives were stopped prior to selection visit. Any further use of anti-hypertensive throughout (other than study meds) was NR.	Primary endpoint not explicitly stated. Reported results included: -CrCl -theoretical analysis of glomerular membrane transport -renal plasma flow -filtration fraction, fractional excretion of neutral dextrans and albumin The following assessments were completed at week 3 and week 8: -24 hr urine protein assessment -GFR measurement

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Remuzzi 1999 Italy no trial name Poor	Age: Only general range given (20-65) Gender: Female: 4 Male: 16 Ethnicity: NR	Baseline GFR: E: 66 +/- 19 ml/min/1.73m2 I: 54 +/- 15 ml/min/1.73m2 Baseline 24 hr protein values: E: 1.44 +/- 1.11 gm/d I: 2.48 +/- 2.02 gm/d Systolic blood pressure: E: 133 +/- 9 mmHg I: 147 +/- 13 mmHg	Number screened: NR Number eligible: NR Number enrolled: 20	Number withdrawn: NR Lost to follow-up: NR Analyzed: 20

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Remuzzi 1999 Italy no trial name Poor	After 28 days there was no significant decline in GFR in patients treated with either Enalapril or Irbesartan. GFR baseline vs. end of treatment: E: 66 +/- 19 to 65 +/- 25 I: 54 +/- 15 to 55 +/- 11 No inter-group comparison given, no p values or CI given. 24 hr urinary protein excretion baseline vs. end of treatment: E: 1.44 +/- 1.11 gm/d to 2.48 +/- 2.02 gm/d, 38.6% change, p < 0.05 intra-group endpoint vs. baseline I: 2.48 +/- 2.02 gm/d to 1.54 +/- 1.46 gm/d, 45.4% change, p < 0.01 intra-group endpoint vs. baseline There was no inter-group comparison between Enalapril and Irbesartan for reduction in proteinuria. Blood pressure reduction was not equal between groups. Percent change in systolic blood pressure from baseline to end of treatment: E: 6.4% I: 3% Percent change in diastolic blood pressure from baseline to end of treatment: E: 12.4% I: 9.1%	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Remuzzi 1999 Italy no trial name Poor	NR	NR	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Remuzzi 1999 Italy no trial name Poor	Total withdrawals: NR	The Enalapril group and Irbesartan group were uneven at baseline in terms of level of proteinuria and degree of hypertension. Per the results, that is why authors described a percent change in proteinuria as opposed to an inter-group comparison.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Renke 2004 Poland no trial name Fair	Study design: prospective, randomized Setting: NR Duration: 9 months	Inclusion criteria: Age 18-70 History of hypertension History of biopsy-proven Glomerulonephritis (not including IgA nephropathy). Daily proteinuria Creatinine < 2 mg/dL Exclusion criteria: Immunosuppressive therapy received in 6 mo prior Diagnosis of complete nephrotic syndrome	History of biopsy proven GLOMERULONEPHRITIS was required. Types of GLOMERULONEPHRITIS included: Mesangial GLOMERULONEPHRITIS Mesangiocapillary GLOMERULONEPHRITIS Membranous GLOMERULONEPHRITIS Focal segmental glomerulosclerosis Other Proteinuria requirement was listed as "daily" but per baseline characteristics averaged between 2-3 gm/day in each group.	CKD stages not specifically stated, but creatinine of <2 mg/dL was required. CrCl was noted in baseline characteristics for each group; >90 ml/min on average in each group. CrCl was quantified by the mean of two 24-hr urine collections.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Renke 2004 Poland no trial name Fair	Participants were randomized to one of three groups: L: 25mg Losartan daily (n=18) E: 10mg Enalapril daily (n=18) L+E: 25mg Losartan and 10mg Enalapril daily (n=16)	Run-in: 4 week period during which all ACE-I or ARB therapy was discontinued. Alternate antihypertensive therapy was used during that time to achieve BP <140/90.	Additional antihypertensives used to achieve BP <140/90. Additional meds used included β-blockers, calcium channel blockers, β-blockers with calcium channel blockers, and α-blockers. L: 8 of 18 on additional meds E: 5 of 18 on additional meds L+E: 3 of 16 on additional meds	Primary endpoint not specifically stated. Hypothesis: the combination of ACE-I and ARB will produce a more profound anti-proteinuric effect than either agent as monotherapy. Evaluations at baseline and at 3 and 9 months, which included: -two 24-hr urine studies to measure proteinuria and CrCl. Mean of two samples used to define urinary protein excretion and CrCl.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Renke 2004 Poland no trial name Fair	Mean Age: L: 40.4 +/- 11.9 E: 43.4 +/- 10.1 L+E: 37.7 +/- 12.7 Gender: (males/females) L: 7/11 E: 12/6 L+E: 11/5 Ethnicity: NR	CrCl: L: 95.5 +/- 25.3 ml/min E: 93.9 +/- 37.7 ml/min L+E: 94.8 +/- 31.8 ml/min Proteinuria: L: 2.17 +/- 1.52 gm/d E: 2.6 +/- 1.69 L+E: 3.25 +/- 1.82 Serum creatinine: L: 1.04 +/- 0.2 E: 1.25 +/- 0.3 L+E: 1.2 +/- 0.3 Mean Systolic blood pressure and Diastolic blood pressure (mmHg) : L: 137 +/- 11.6 and 88.2 +/- 7.5 E: 134 +/- 13.4 and 87.8 +/- 9.3 L+E: 140 +/- 17.2 and 90.8 +/- 11.4	Number screened: NR Number eligible: NR Number enrolled: 54	Withdrawn: 2 Lost to follow up: zero reported Analyzed: 52

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Renke 2004 Poland no trial name Fair	No significant change in CrCl in any group (p values, 95% CI NR). Percent decrease in proteinuria after 3 and 9 months respectively: L: 22.6% and 44.2%; p < 0.01 at 3 mo and at 9 mo from baseline E: 43.07% and 49.6%; p < 0.01 at 3 mo and and at 9 mo from baseline L+E: 63% and 51%; p < 0.001 at 3 mo and <0.01 at 9 mo from baseline Change in proteinuria compared between groups: Non-significant p values are NR Only statistically significant change was greater reduction in proteinuria in L+E compared to L at 3 mo (p < 0.01). No statistically significant changes in systolic blood pressure between groups. Decrease in diastolic blood pressure was more significant in Losartan at 3 mo only (p = 0.04). Decrease in diastolic blood pressure was more significant in subjects receiving combination therapy compared to Enalapril (p = 0.009)	N/A

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Renke 2004 Poland no trial name Fair	NR	NR	Not specifically reported other than with regards to withdrawals.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Renke 2004 Poland no trial name Fair	Total withdrawals: 2 Withdrawals due to adverse events: 1 *allergic reaction to study medication - to which drug not stated.* Withdrawals due to reason other than adverse events:1 *withdrawal for development of nephrotic syndrome requiring steroid therapy*	The combination therapy group started with a significantly higher burden of proteinuria compared to the single therapy groups. Mechanism for randomization was not specified.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Renke 2005 Poland No trial name Fair	Study design: randomized, open, cross-over Setting: renal outpatient clinics Duration: 20 weeks	Inclusion criteria: Age 18-60 Biopsy proven glomerulonephritis Stable proteinuria Serum creatinine <2 mg/dL History of being unable to receive maximum doses of ACE-I or ARB in the past (due to hypotension or hyperkalemia) Exclusion criteria: nephrotic syndrome Diabetes Renal artery stenosis Use of steroids or immunosuppressive agents within 6 mo prior to enrollment Pregnancy or breastfeeding History of malignant hypertension, cerebrovascular accident, transient ischemic attacks, unstable angina, arrhythmias, or decompensated HF in 6 mo prior History of hypersensitivity to ACE-I or ARB	Types of CKD: Mesangial glomerulonephritis (14) IgA nephritis (5) Mesangiocapillary glomerulonephritis (4) Membranous nephropathy (1) Biopsy proven? Yes Degree of proteinuria: only required to be stable. Baseline proteinuria mean noted to be 2.13 +/- 0.24 gm/d. Urine protein excretion was measured as the mean of two 24-hr urine collection protein values.	Stage of CKD: not specifically addressed Creatinine <2 mg/dL required. Baseline mean CrCl 85.73 +/- 7.63 ml/min. CrCl measured as mean of two 24 hour urine collections.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Renke 2005 Poland No trial name Fair	After run-in, participants were randomized to one of 6 sequences. Each sequence resulted in each participant crossing-over into each of the following groups: [L] Losartan 50mg/d [B] Benazepril 10 mg/d [L+B] Losartan 25mg/d + Benazepril 5 mg/d Each treatment period lasted 4 months.	8 week run-in: No ACE-I or ARB during run-in. First 6 weeks of run-in, blood pressure could be controlled using Doxazosin. Last 2 weeks of run-in, no anti-hypertensive medication was utilized. No washout periods. Authors explicitly planned 4 mo for each treatment group, citing evidence that treatment effect from ACE-I and ARB was known to dissipate after 2 months, so that by the end of each of their 4 mo treatment periods, no treatment effect should be present.	Doxazosin was utilized if needed to achieve BP ≤ 140/90.	Primary end point: the urine alpha 1 m level as a marker of tubular injury (assessed at the end of each of the three treatment periods). Secondary end point: plasma TGF-beta1 level and mean 24-hr blood pressure. Additional reported outcomes included changes in proteinuria and CrCl. At the end of the run-in and each treatment period, the following assessments were made: blood pressure serum labs including creatinine two 24-hr urine collections (mean of protein and CrCl utilized).

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Renke 2005 Poland No trial name Fair	Mean age: 35.46 +/- 2.36 Gender (male/female): 12/12 Ethnicity: NR	Mean creatinine: 1.18 +/- 0.08 mg/dL Mean CrCl: 85.72 +/- 7.63 ml/min Mean proteinuria: 2.13 +/- 0.24 gm/d	Number screened: NR Eligible: NR Enrolled: 30	Number withdrawn: 6 Lost to follow up: zero Analyzed: 24

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Renke 2005 Poland No trial name Fair	Changes in proteinuria: L+B reduced proteinuria more than L alone (p <0.01) L+B reduced proteinuria more than B alone (p <0.01) Specific values NR, 95% CI NR Changes in CrCl from baseline 89.69 (SEM 6.93) ml/min: L: 85.18 (6.94) ml/min B: 84.35 (6.63) ml/min L+B: 82.33 (6.9) ml/min No statistically significant differences noted from baseline or between groups. No statistically significant changes in blood pressures between groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Renke 2005 Poland No trial name Fair	NR	Lab tests done as noted. Otherwise NR.	*Results were not reported by treatment group* Hypotension: 2 Allergic reaction to Losartan: 1 Cough: 1 (on Benazepril, but unknown if B or L+B) Pregnancy: 1 Personal reasons: 1

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Renke 2005 Poland No trial name Fair	Total withdrawals: 6 Withdrawals due to adverse events: 4 Withdrawals due to reasons other than adverse events: 2 (pregnancy and personal reasons)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Ruilope 2000 Spain no trial name (from the European group for the Investigation of Valsartan in Chronic Renal Disease) Fair	Study design: multinational (France, Germany, Italy, Spain), multi-center, randomized, active-controlled, parallel group, open label. Setting: outpatient Duration: 5 weeks	Inclusion criteria: Age >18 Chronic renal disease CrCl 20-45 ml/min Mean diastolic blood pressure 80-110 mmHg *irrespective of level of proteinuria* Exclusion criteria: Secondary hypertension Malignant hypertension Serious heart or liver disease Immune disorders Malignancy Disease treated with steroids Use of NSAIDS Immune or cytotoxic therapy in prior 12 mo	Types of CKD: IgA nephropathy (5%) Other glomerulonephritis (23%) Nephrosclerosis (27%) Other (45%) Baseline proteinuria not explicitly stated, but 45-63% reportedly had ≥ 1 gm/d at baseline.	Stage of CKD was not specifically addressed. CrCl 20-45 ml/min was required. Baseline serum creatinine ranged from 2.6-2.9 mg/dL.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Ruilope 2000 Spain no trial name (from the European group for the Investigation of Valsartan in Chronic Renal Disease) Fair	Participants were initially randomized to: Valsartan 160 mg/d (V160) or Valsartan 80mg/d (V80) After 1 week, further randomization to: V160 (n = 22) V160 + Benazepril 5mg/ or 10 mg/d (B5/10) (n = 44) V80 + B5/10 (n = 42) *participants with CrCl 30-45 received 10mg/d and CrCl 20-30 received 5mg/d* 1 week later, if no change in serum creatinine by >30%, participants remained in these groups for 5 weeks.	NR	Additional non-ACE-I antihypertensives were allowed for hypertension management. Additional medications used included: furosemide nifedipine amlodipine clonidine nitrendipine atenolol	Primary end point was the number of renal events. "Renal events" was defined as acute renal failure, rapidly progressing renal failure, hospitalization due to any clinical event related to renal failure, or hospitalization due to any severe electrolyte abnormality (including hyperkalemia). Secondary end points: serum potassium and creatinine. Visit 1 was conducted upon enrollment (week 1), at time of initial randomization to V160 or V80), Visit 2 was conducted one week later (week 2), at time of additional randomization. Visit 3 was conducted 1 week later (week 3). Visit 4 was conducted in week 5. At each visit, blood and an overnight urine sample were obtained. These provided serum creatinine measurements as well as protein/creatinine ratio.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ruilope 2000 Spain no trial name (from the European group for the Investigation of Valsartan in Chronic Renal Disease) Fair	Mean age: V160: 57.3 +/- 14.8 years V160 + B5/10: 56.9 +/- 11.7 years V80 + B5/10: 57.6 +/- 12.2 years Gender (% female/male): V160: 27/73 V160 + B5/10: 34/66 V80 + B5/10: 30/70 Race: (% Caucasian/Black) V160: 96/4 V160 + B5/10: 98/2 V80 + B5/10: 100/0	Percent ≥ age 65: V160: 50 V160 + B5/10: 41 V80 + B5/10: 30 Percent with proteinuria ≥ 1 gm/d: V160: 45 V160 + B5/10: 59 V80 + B5/10: 63	Number screened: NR Number eligible: NR Number enrolled: 109	Withdrawals: 6 Lost to follow-up: NR Analyzed: 108 *1 participant not analyzed - no information reported on that participant.*

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Ruilope 2000 Spain no trial name (from the European group for the Investigation of Valsartan in Chronic Renal Disease) Fair	Change in serum creatinine by group: V160: 0.12 mg/dL (p = 0.045) V160+ B5/10: 0.10 (p = 0.03) V80 + B5/10: 0.17 (p = 0.0006) Change in proteinuria by group (p values compared to baseline within that group): V160: -0.09 +/- 1.76 gm/d (p = 0.811); 95% CI: -0.87,0.69 V160+ B5/10: -0.82 +/- 1.63 gm/d (p = 0.002); 95% CI: -1.33,0.32 V80 + B5/10: -0.36 +/- 1.26 gm/d (p = 0.071); 95% CI: -0.76,0.03 Inter-group reduction in proteinuria comparisons: V80+B5/10 vs. V160 + B5/10: p = 0.109 (95% CI -0.11 to 1.07) V80+B5/10 vs. V160: p = 0.501 (95% CI -0.95 to 0.47) V160+B5/10 vs. V160: p = 0.047 (95% CI -1.044 to -0.01) Change in systolic blood pressure was not statistically significant between groups. Change in diastolic blood pressure was statistically significantly only in V160 + B5/10 vs. V160 (p = 0.00009).	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Ruilope 2000 Spain no trial name (from the European group for the Investigation of Valsartan in Chronic Renal Disease) Fair	NR	Symptoms or signs either observed by investigator and/or reported by the patient were recorded as adverse events.	Total percent adverse events within each group: V160: 45.5% V160+ B5/10: 25% V80 + B5/10: 33.3% Event rate hyperkalemia (potassium ≥ 6 mmol/L) within each group (n; %): V160: 1; 4.5% V160+ B5/10: 5; 11.9% V80 + B5/10: 2; 4.5% Event rate dizziness within each group (n; %): V160: 1; 4.5% V160+ B5/10: 2; 4.8% V80 + B5/10: 3; 6.8% Event rate headache within each group (n; %): V160: 0; 0% V160+ B5/10: 3; 7.1% V80 + B5/10: 0; 0% Cough was reported in 2 individuals (1 in V160 and 1 in V160+B5/10)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Ruilope 2000 Spain no trial name (from the European group for the Investigation of Valsartan in Chronic Renal Disease) Fair	Withdrawals: 6 -2 for hyperkalemia (potassium ≥ 6 mmol/L) -1 for dizziness/vision changes -1 for GI symptoms -1 for malaise/headache -1 for hypotension	Primary outcome of interest in this study was number of renal events, defined as acute renal failure, rapidly progressing renal failure, hospitalization due to any clinical event related to renal failure, or hospitalization due to any severe electrolyte abnormality (including hyperkalemia). No events consistent with this primary outcome were observed.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Russo 2001 Italy no trial name Poor	Study design: randomized cross-over Setting: NR Duration: 32 weeks	Inclusion criteria: Biopsy proven IgA Nephropathy Blood pressure < 140-90 mmHg Stable proteinuria between 1-3 gm/d (non-nephrotic range) CrCl >90 ml/min/1.73 m2 No drug therapy in 12 weeks prior to enrollment Exclusion criteria: not specifically stated	Types of CKD: IgA nephropathy Biopsy proven: yes Degree of proteinuria: required 1-3 gm/d. Mean of 1.52 gm/d per baseline characteristics.	Stage of CKD; not explicitly stated Method of defining CKD: CrCl is specified, but method of obtaining that measurement NR.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Russo 2001 Italy no trial name Poor	Participants were randomized to: (E10) Enalapril 10mg/d (L50) Losartan 50mg/d Continued for 4 weeks, then dose was increased in each group: (E20) Enalapril 20mg/d (L100) Losartan 100mg/d Continued for 4 weeks (8 weeks total in these treatment groups. Then washout followed by crossover to alternate arm, again with dose increase after 4 weeks. (8 weeks total) All participants then underwent combination therapy: E+L at 10 and 50 mg/d respectively for 4 weeks, then E+L at 20 and 100 mg/d respectively fro 4 weeks (8 weeks total).	Run-in: NR Washout: 4 weeks between each 8-week treatment arm	None	Primary endpoint not specifically stated. Goal of study stated to be to evaluate whether the antiproteinuric effect of Enalapril and Losartan may be dependent on the dose of co administered drugs and influenced by the reduction in systolic blood pressure. Baseline measurements were done prior to therapy, including: serum labs office blood pressure and ambulatory blood pressure peripheral plasma renin activity measurement of urinary protein excretion (the mean of two consecutive 24 hr urine collections) These measurements were repeated at the end of each study period.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Russo 2001 Italy no trial name Poor	Mean age: 25 =/- 18 Gender (female/male): 6/4 Ethnicity: NR	Mean CrCl at baseline: 109.6 +/- 8.4 ml/min/173m2 Mean proteinuria at baseline: 1.52 +/- 0.37 gm/d Mean systolic blood pressure at baseline: 118.5+/-3.4 mmHg Mean diastolic blood pressure at baseline: 75.9+/-1.8 mmHg	Number screened: NR Number eligible: NR Number enrolled: 19	Withdrawn: 9 Lost to follow-up: 1 Analyzed: 10

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Russo 2001 Italy no trial name Poor	Reduction in proteinuria by each agent: E: reduced proteinuria from 1.56 +/- 0.3 gm/d to 0.98 +/- 0.14 gm/d (p<0.05) L: reduced proteinuria from 1.56 +/- 0.3 gm/d to 1.01 +/- 0.14 gm/d (p<0.05) E+L: reduced proteinuria from 1.56 +/- 0.3 gm/d to 0.72 +/- 0.14 gm/d (p< 0.05), with additional reduction to 0.57 +/- 0.12 gm/d (p< 0.05) when dose was doubled. No change in proteinuria reduction for E or L single drug therapy when dose was doubled. CrCl in each treatment group at low and high dose respectively: E: 108 +/- 11 ml/min/1.73m2, 108 +/- 9 ml/min/1.73m2 L: 106 +/- 8 ml/min/1.73m2, 111 +/- 9 ml/min/1.73m2 E+L: 110 +/- 9 ml/min/1.73m2, 110 +/- 12 ml/min/1.73m2 CrCl did not change significantly throughout the study. P-values and 95% CI NR. Blood pressure was statistically lower in the double dose combination group (E+L), p < 0.05.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Russo 2001 Italy no trial name Poor	NR	NR	2 withdrawals were related to cough on ACE-I (specific treatment groups not specified)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Russo 2001 Italy no trial name Poor	Total withdrawals: Total withdrawals due to adverse events: 2 (cough) Additional withdrawals not due to adverse events: -2 withdrawals for non-compliance with therapy -4 withdrew consent for reasons not related to side effects -1 moved to a different city		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Rutkowski 2004 Poland no trial name Fair	Study design: Prospective, open-label, crossover Setting: NR Follow-up: Not explicitly stated; 14 mo (based on time frame of run-in and treatment groups)	Inclusion criteria: Age 18-60 Proteinuria ≤ 3.5 gm/day Creatinine < 2 mg/dL Exclusion criteria: history of diabetes, history of renal artery stenosis, steroids or immune suppression therapy within 6 months prior, history of hypersensitivity to ACE-I/ARB, or history of any of the following within 6 months: malignant hypertension, cerebrovascular accident, transient ischemic attack, arrhythmia, decompensated HF.	History of biopsy proven GLOMERULONEPHRITIS was required. Types of GLOMERULONEPHRITIS included: Mesangial GLOMERULONEPHRITIS IgA nephropathy Mesangiocapillary GLOMERULONEPHRITIS Membranous GLOMERULONEPHRITIS Proteinuria of ≤ 3.5 gm/day was required. Per their table on baseline characteristics of participants, average proteinuria was 2.13 +/- 0.24 gm/day.	CKD stages not specifically stated. Creatinine of <2 mg/dL was required. Mean CrCl per baseline characteristics: 85.72 +/- 7.63 ml/min. CrCl obtained via 24 hr urine collections.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Rutkowski 2004 Poland no trial name Fair	Participants were randomized to therapy to one of the following groups: [L] Losartan 50mg/day [B] Benazepril 10mg/day alone [L+B] Losartan 25mg/day + Benazepril 5 mg/d Randomization allocated participants to one of 6 treatment sequences during which each participant was crossed over into each treatment group. Each treatment group lasted for 4 months.	Run-in: 8 week period during which participants were not given any ACE-I or ARB therapy. First 6 weeks of run-in patients were on Doxazosin; last 2 weeks patients were on no antihypertensive therapy. Prior to data analysis the period effect and carryover effect were tested and found to be not significant.	Addition of Doxazosin was allowed to achieve BP goal <140/90. Addition of Doxazosin was required in one subject during all treatment arms.	Primary end point: a difference in 24 hour protein measurement. Subgroup analysis was performed in participants stratified by level of baseline proteinuria (<2gm/d vs. >2gm/d). Secondary endpoints included office and ambulatory BP, serum creatinine level, K level, hemoglobin level, CrCl, and urine sodium excretion. Follow up at the end of the run-in and at the end of each treatment period included 24 hr urine collections (for both proteinuria and CrCl). Serum labs including creatinine were measured at least every 2 months.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Rutkowski 2004 Poland no trial name Fair	Mean age: 35.7 +/- 2.7 Gender: 12men, 12 women Ethnicity: NR	Mean baseline creatinine: 1.18 +/- 0.08 Number of participants treated with ACE-I/ARB prior to inclusion: 24 of 24 (19 with ACE-I and 5 with ARB). Mean CrCl: 85.72 +/- 7.63 ml/min Mean Proteinuria: 2.13 +/- 0.24 gm/d Mean SYSTOLIC BLOOD PRESSURE: 139.52 +/- 3.62 mmHg Mean DIASTOLIC BLOOD PRESSURE: 90.73 (range 86.88-95.5) mmHg	Number screened: NR Number enrolled: 30	Withdrawn: 6 Lost to follow up: zero reported Analyzed: 24

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Rutkowski 2004 Poland no trial name Fair	Percent decrease in proteinuria from baseline: L: -28.17% B: -20.19% L+B: -45.54% Significantly greater reduction in proteinuria was seen in L+B vs. L (p = 0.009) Significantly greater reduction in proteinuria was seen in L+B vs. B (p < 0.001) 16 patients showed maximal reduction in proteinuria in L+B 4 patients showed maximal reduction in proteinuria in B 4 patients showed maximal reduction in proteinuria in L Antiproteinuric effect of L was greater than that of B numerically, but that difference was not statistically significant (p = 0.093). There were no statistically significant differences in blood pressures achieved between different treatment arms. No significant changes in serum creatinine or 24 hr creatinine clearance values were noted during the study. P values and 95% CI NR.	N/A

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Rutkowski 2004 Poland no trial name Fair	Subgroup analysis for participants delineated by amount of baseline proteinuria: >2 gm/d: 3.06 +/- 0.23 gm/d to 1.41 +/- 0.23 gm/d <2 gm/d: 1.2 +/- 0.17 gm/d to 0.9 +/- 0.16 gm/d Those with proteinuria >2gm/d showed significantly greater reduction in proteinuria compared to those with <2gm/d for all therapies (p < 0.001 for combination therapy, p = 0.026 for Losartan, and p = 0.019 for Benazpariil).	Method to assess NR Pre-specified that patients could be withdrawn for any of the following reasons: withdrawal of consent, noncompliance with therapy, hyperkalemia (potassium > 6 mEq/L), worsening renal function (defined as serum creatinine level increase by greater than 50% confirmed on 2 occasions), cough on ACE-I therapy, and "any other severe adverse event."	3 patients noted symptoms consistent with hypotension (SYSTOLIC BLOOD PRESSURE recorded at <100 in two of these three); of these two, one was on Losartan and one was on combination therapy. Serum potassium values were reportedly no greater than 6 mEq/L for any treatment arm. 2 patients noted dry cough on ACE-I.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Rutkowski 2004 Poland no trial name Fair	Total withdrawals: 6 Withdrawals due to adverse events: 5 (most not specified by treatment group) -2 for hypotension (one in L and one in L+B) -1 for allergic reaction to Losartan -1 for cough on ACE-I -1 for pregnancy One participant chose to withdrawn for personal reasons.		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Segura 2003 Spain No trial name Fair	Study design: randomized, parallel group open-label Setting: NR Duration: 6 months	Inclusion criteria: Diagnosis of primary renal disease Presenting BP >140/90 mmHg Proteinuria >1.5 gm/d On therapy with ACE-I alone or with other anti-hypertensive drugs for at least 3 mo prior to enrollment CrCL >30 ml/min Exclusion criteria: NR	Types of CKD: NR Biopsy proven? NR Degree of proteinuria: >1.5 gm/d required. Baseline proteinuria ranged from 3.8-4.6 gm/d. Proteinuria was measured via 24 hour urine collection.	Stage of CKD: not explicitly addressed. CrCl >30 ml/min required Mean CrCL at baseline ~75 ml/min CrCl measured via 24 hr urine collection

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Segura 2003 Spain No trial name Fair	After discontinuation of prior ACE-I therapy, participants were randomly assigned to one of the following: [B] Benazepril 10-20 mg/d ** [V] Valsartan 80mg/d; increased to 160mg/d after 2 weeks [B+V] Benazepril 10-20 mg/d** for 4 weeks, after which Valsartan 80mg/d was added. # **Benazepril dose was dependent on CrCl; CrCl <50 ml/min received only 10mg/d. # In B+V, Valsartan was increased from 80 mg/d to 160mg/d if needed. Presumably, authors are referring to "if needed" for blood pressure control.	Run in: NR Washout: NR	Blood pressure goal was <140/90 mmHg. If BP was not achieved with study medication alone, then additional medications could be added. Additional medications could include: loop diuretics Doxazosin β-blockers	Primary end point: not explicitly stated. Primary aim: to investigate in daily clinical practice the effects of monotherapy with an ACE-I or ARB up-titrated to maximal recommended doses, and to compare the effect of maximum monotherapy vs. combination therapy on proteinuria. Visits were completed at baseline and at 7 days, 1 month, 3 months, and 6 months. Measurements done at each visit included: blood pressure serum labs 24 hour urine for CrCl and proteinuria

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Segura 2003 Spain No trial name Fair	Mean age: B: 49.8 +/- 16.5 years V: 49.7 +/- 12.4 years B+V: 47.9 +/- 15.2 years Gender (male/female): B: 8/4 V: 8/4 B+V: 10/2 Ethnicity: NR	Mean SYSTOLIC BLOOD PRESSURE: B: 154 +/- 16 mmHg V: 152 +/-21 mmHg B+V: 149 +/- 15 mmHg Mean CrCl: B: 72 +/- 25 ml/min V: 74 +/- 23 ml/min B+V: 68 +/- 29 ml/min Proteinuria: B: 3.8 +/- 2.4 gm/d V: 4.6 +/- 3.4 gm/d B+V: 4.1 +/- 2.4 gm/d	Number screened: NR Eligible: NR Enrolled: 36	Number withdrawn: NR Lost to follow up: NR Analyzed: 36

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Segura 2003 Spain No trial name Fair	Mean change in proteinuria (and mean calculated percent decline): B: 0.5 +/- 1.7 gm/d (-13%) V: 1.2 +/- 2 gm/d (-26%) B+V: 2.5 +/- 1.8 gm/d (-61%) p < 0.05 comparing B to B+V per Figure 2 in this report; p value V vs. B and V vs. B+V NR but presumably not significant as not reported as significant in Figure 2. 95% CI NR. Change in CrCl: NR BP reduction was noted to be similar between the three groups, but SYSTOLIC BLOOD PRESSURE was significantly lower in V compared to B at 3 and 6 months.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Segura 2003 Spain No trial name Fair	NR	NR	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Segura 2003 Spain No trial name Fair	NR		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Song 2003 Korea no trial name Fair	Study design: double-blind, randomized, crossover Setting: outpatient clinics Duration: not specifically stated; 41 weeks based on treatment groups, run-in, and wash-out.	Inclusion criteria: Ramipril therapy of >5mg/d for at least 6 mo Blood pressure <130/80 CrCl 25-90 ml/min/1.73m2 24 hr urine for proteinuria with >1 gm/d Exclusion criteria: IgA nephropathy patients who had required steroids or cytotoxic therapy in 6 mo prior History of proven cardiac or vascular disease Uncontrolled diabetes Malignancies	Types: IgA nephropathy (IgA) Diabetic nephropathy (DM) (Biopsy proven) Proteinuria ? 1 gm/d required Baseline proteinuria ~4 gm/d	Stage of CKD not specifically addressed. CrCl required to be between 25-90 ml/min Baseline CrCl was 59-60 ml/min/1.73m2 for IgA and Diabetic nephropathy. CrCl calculated as mean of CrCl from 2 24-hr urine collections.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Song 2003 Korea no trial name Fair	R = Ramipril (dose ranged 5-7.5 mg/d) - taken at baseline by participants C = Candesartan (4mg/d; if tolerated, increased to 8 mg/d at 12 weeks) P = placebo Participants were randomized to: R+C for 16 weeks, 1 week washout, then R+P for 16 weeks or R+P for 16 weeks, 1 week washout, then R+C for 16 weeks	8 week run-in with Ramipril alone 1 week wash-out between cross-over arms	Not clearly reported. 15 of 34 patients were on additional BP meds when on Ramipril alone (prior to randomization). 2 patients are mentioned who required "additional diuretic."	Primary endpoint not specifically stated. Aim stated to be to examine therapeutic effect of dual blockade of RAS in participants with diabetic nephropathy and IgA nephropathy. 24 hour urine protein excretion and total urine Tumor growth factor (TGF)-beta were measured as surrogate markers of renal injury. Two 24-hr urine collections and serum lab collections were done during 16th week of each cross-over arm. Mean of lab values used to define: CrCl Creatinine Proteinuria

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Song 2003 Korea no trial name Fair	Mean age: 34 +/- 5 years Female: Male ratio: 19:13 Ethnicity: NR	Duration of Ramipril treatment prior to randomization: 10 +/- 3 months among IgA 13 +/- 4 months among DM Serum creatinine during Ramipril run-in: IgA: 1.4 +/- 0.1 mg/dL DM: 1.4 +/- 0.1 CrCl during Ramipril run-in: IgA: 60.3 +/- 4.6 ml/min/1.73 m2 DM: 59.4 +/- 2.7 ml/min/1.73 m2 24 hr urine protein during Ramipril run-in: IgA: 4 +/- 0.2 gm/d DM: 4.1 +/- 0.3 gm/d	108 screened (41 IgA, 67 DM) 34 eligible/enrolled (14 IgA, 20 DM)	Withdrawals: 2 Lost to follow-up: none reported Analyzed: 32

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Song 2003 Korea no trial name Fair	Changes in proteinuria between groups by treatment and type of renal disease: R: (baseline) IgA: 4 +/- 0.2 gm/d; DN: 4.1 +/- 0.3 gm/ R+C: IgA: 3.5 +/- 0.3 gm/d (p < 0.05 compared to R and R+P among IgA); DN: 4 +/- 0.2 gm/d (p not significant compared to R and R+P among DN) R+P: IgA: 3.9 +/- 0.2 gm/d; DN: 4.2 +/- 0.3 gm/d Mean % change in 24 hr urine protein excretion: IgA: 95% CI 1.2 to 23.5, p < 0.05; showed a significant reduction in proteinuria for R+C vs R+P among IgA R+C: -12.3 +/- 4.5%; R+P: 0.1 +/- 3% DN: 95% CI -6.8 to 13.5, p reported as not significant; no significant difference in proteinuria for R+C vs R+P among DN R+C: -0.8 +/- 4.7%; R+P: 1.3 +/- 4.7% Greater reduction in proteinuria in R+C among IgA patients compared to DM patients (p < 0.05). Changes in CrCl between groups by treatment and type of renal disease (ml/min/1.73m2): R: (baseline) IgA: 60.3 +/- 4.6; DN: 59.4 +/- 2.7 R+C: IgA: 62.4 +/- 5.2; DN: 56.9 +/- 3.9 R+P: IgA: 63.8 +/- 5.3; DN: 60.2 +/- 4.3 No significant differences reported between groups, p values and 95% CI NR. No statistically significant difference in mean arterial blood pressure between groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Song 2003 Korea no trial name Fair	NR	NR	At candesartan dose of 4mg, no adverse effects were reported. At candesartan dose of 8 mg, patients reported the following: 5 patients; dizziness 3 patients; increase in serum potassium 1 patient; increase in serum creatinine 1 patient; increase in serum potassium and creatinine 1 patient; "refusal" Among those with side effects: 2 received increased diuretic dose (presumably for high potassium) 1 received potassium-binding resin Remaining adverse effects resolved with lowering candesartan dose.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Song 2003 Korea no trial name Fair	Total withdrawals: 2 Withdrawals due to adverse effects: 2 Both among Diabetic nephropathy participants. -1 withdrawal for azotemia/hyperkalemia -1 withdrawal for hypotension *Treatment group not specified* Withdrawals due to reason other than adverse effects: none reported	All outcomes in this paper were shown by type of renal disease (IgA or DM); no combined outcomes for all patients together were reported.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Tylicki 2002 Poland no trial name Fair	Study design: prospective, randomized trial Setting: NR Duration: 3 months	Inclusion criteria: Age 18-70 Biopsy proven primary glomerulonephritis Systolic blood pressure 120-160 mmHg Diastolic blood pressure 80-100 mmHg Daily proteinuria No ACE-I or ARB for 4 weeks prior to enrollment Creatinine <2 mg/dL Exclusion criteria: Use of steroids or immune suppression within 6 mo prior to enrollment IgA nephropathy Nephrotic syndrome	Types of CKD: Mesangial glomerulonephritis Mesangiocapillary glomerulonephritis Membranous nephropathy Focal segmental glomerulonephritis Biopsy proven: yes Degree of proteinuria: specified only as daily Per baseline characteristics, mean proteinuria ranged from 2.2 - 3.3 mg/d between groups.	Stage of CKD: not specifically stated Creatinine <2 required. Creatinine clearance ranged from 90-96 ml/min between groups at baseline. Creatinine clearance was measured via mean of two 24-hr collections

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Tylicki 2002 Poland no trial name Fair	Participants were randomized to: (L) Losartan 25mg/d (n = 17) (E) Enalapril 10 mg/d (n = 17) (L+E): Losartan 25mg/d and Enalapril 10mg/d (n = 15) Participants were followed in these groups for 3 months.	NR	NR	Primary end point not specifically stated. Stated goal was to compare Losartan, Enalapril, and the combination of the two in a low doses known to equivalently lower blood pressure to examine the effects of these medications on proteinuria, renal function, and metabolic profile. Reported outcomes included: -systolic and diastolic blood pressure -CrCl -Urinary protein excretion -lipid profile Evaluations were completed at: -baseline -1 week after initiation of treatment -3 months Evaluations consisted of: -blood pressure measurements -serum laboratory measurements -two 24 hr urine collections (the results of which were averaged to obtain CrCl and proteinuria values)

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Tylicki 2002 Poland no trial name Fair	Mean age: L: 41.2 +/- 11.8 years E: 44.1 +/- 10.1 years L+E: 36.6 +/- 13.1 years Gender (male/female): L: 7/10 E: 12/5 L+E: 11/4 Ethnicity: NR Race: all Caucasian	24 hr urine protein excretion at baseline: L: 2.13 gm/d E: 2.64 gm/d L=E: 3.29 gm/d Serum creatinine at baseline: L: 1.05 mg/dL /dL E: 1.27 mg/dL L+E: 1.2 mg/dL CrCl at baseline: L: 90.8 ml/min E: 94.2 ml/min L+E: 95.9 ml/min Systolic blood pressure at baseline: L: 138.09 mmHg E: 134.02 mmHg L+E: 139.33 mmHg Diastolic blood pressure at baseline: L: 88.7 mmHg E: 87.4 mmHg L+E: 89.3 mmHg	Number screened: NR Number eligible: NR Number enrolled: 51	Number withdrawn: 2 Number lost to follow-up: zero Number analyzed: 49

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Tylicki 2002 Poland no trial name Fair	Change in CrCl: -greater decline in E (-15.2%) vs. L (percent decline NR), but not significant (p = 0.09, 95% CI NR) -greater decline in L+E (-14.3%) vs. L (percent decline NR), but not significant (p = 0.08, 95% CI NR) Urine protein excretion declined significantly in all groups. Reduction in proteinuria was as follows: L: 25.35% E: 45.1% L+E: 65.96% Reduction in proteinuria for L vs. E did not show a statistically significant difference. p-value, 95% CI NR. Reduction in proteinuria for L+E vs. either as mono-therapy showed a significant difference (p = 0.009), 95% CI NR. Diastolic blood pressure was lowered statistically more in those on combination therapy.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Tylicki 2002 Poland no trial name Fair	NR	NR	1 allergic reaction to study medication was reported (treatment group not specified).

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Tylicki 2002 Poland no trial name Fair	Total withdrawals: 2 Withdrawals due to adverse events: 1 (allergic reaction to study medication) Withdrawals due to reasons other than adverse events: 1 (development of nephrotic syndrome requiring steroids)		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Tylicki 2005 Poland no trial name Fair	Study design: single-center, prospective, open, randomized trial Setting: outpatient nephrology clinic Duration: 12 months for initial study; additional 3 months for those who completed 12-month protocol.	Inclusion criteria: Age 18-65 Biopsy-proven primary glomerulonephritis (non-IgA only) Serum creatinine < 2 mg/dL Stable proteinuria BP ≤ 150-95 No ACE-I or ARB for minimum of 4 weeks prior to enrollment Exclusion criteria: Steroid or immune suppression within6 months of enrollment. IgA nephropathy Nephrotic syndrome	Types of CKD: Mesangial glomerulonephritis Mesangiocapillary glomerulonephritis Membranous nephropathy (Biopsy proven disease) Proteinuria at baseline ranged from 1.89-2.25 gm/d	Stage of CKD was not specifically addressed. Serum creatinine ranged from 1.04 - 1.27 mg/dL CrCl per baseline table ranged from 90.48-100.17 ml/min CrCl and proteinuria were determined from the mean values from two 24-hr urine collections.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Tylicki 2005 Poland no trial name Fair	Participants were randomized to one of the following: L = Losartan 25mg/d (n = 19) E = Enalapril 10 mg/d (n = 14) Each treatment group lasted 12 months. Those in L who completed the 12 mo protocol then had Losartan dose increased to 50mg/d for an additional 3 months.	NR	NR	Primary end point: urine protein excretion evaluated as a marker of glomerular damage. Secondary end points included urinary N-acetyl-beta-D-glucoasminidase excretion and blood pressure. Assessment of creatinine, CrCl, and proteinuria was done upon entry, at 12 mo. Creatinine, CrCl, and proteinuria assessment was repeated at 15 mo if patients in L completed additional 3 mo of therapy with higher dose Losartan. CrCl and proteinuria were measured as means of two values obtained from two 24-hr urine collections. Serum creatinine measured via standard techniques.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Tylicki 2005 Poland no trial name Fair	Mean age: L: 41.2 E: 43.7 Gender (male/female): L: 8/11 E: 11/3 Ethnicity: NR	Serum creatinine at baseline: L: 1.04 mg/dL E: 1.27 mg/dL CrCl at baseline: L: 90.48 ml/min E: 100.17 ml/min 24 hr protein excretion: L: 1.89 gm/d E: 2.25 gm/d Hypertension (BP 140-150/90-95 mmHg): L: 9 E: 4	Number screened: NR Number enrolled: 40	Withdrawals: 7 Lost to follow-up: zero reported (4 patients "resigned" from study - unclear if they were followed). Analyzed: 33

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Tylicki 2005 Poland no trial name Fair	Urinary protein excretion (baseline to post treatment): L: 1.89 +/- 0.27 to 1.27 +/- 0.22 (p < 0.05 change in urine protein compared to baseline) E: 2.25 +/- 0.3 to 1.33 +/- 0.27 (p < 0.05 change in urine protein compared to baseline) No significant difference between groups was noted, p values NR. Percent decrease in proteinuria: L: 32.8% (p < 0.029 post-treatment compared to baseline) E: 40.9% (p < 0.041 post-treatment compared to baseline) CrCl (baseline to post treatment): L: 90.48 +/- 5.86 to 94.4 +/- 6.53 ml/min (no significant change from baseline) E: 100.17 +/- 10.46 to 99.9 +/- 14.25 ml/min (no significant change from baseline) No significant changes in systolic blood pressure or diastolic blood pressure were noted among L or E groups.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Tylicki 2005 Poland no trial name Fair	Percent decrease in urine protein excretion based on lower or higher Losartan doses: L 25mg/d: 32.8% L 50 mg/d: 40.7% p comparing groups reported as not significant Change in urine protein excretion with Losartan in participants delineated by baseline proteinuria (baseline to post treatment): <1.5 gm/d: 0.81 gm/d to 0.95 gm/d (no significant difference from baseline, p value NR). >1.5 gm/d: 2.86 gm/d to 1.57 gm/d (p < 0.002 post treatment vs. baseline) Antiproteinuric effect of Losartan was more evident in participants who were normotensive (p < 0.041).	NR	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Tylicki 2005 Poland no trial name Fair	Total withdrawals: 7 Withdrawals due to adverse events: 1 *one withdrawal for allergic reaction to Losartan* Withdrawals due to reasons other than adverse effects:6 -4 patients resigned from the study -1 female patient was withdrawn for pregnancy -1 patient in E was withdrawn for development of nephrotic syndrome		

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Yilmaz 2007 Sweden no trial name Fair	Study design: controlled, head to head Setting: outpatient nephrology clinic Duration: 3 months	Inclusion criteria: GFR 30-59 ml/min/1.73m2 Proteinuria 1-2 gm/d Hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) First-referral to nephrology clinic No current treatment Exclusion criteria: Diabetes BMI >30 Cholesterol >200mg/DL or triglycerides >150 mg/dL Abnormal EKG (ischemic ST-T alterations or voltage criteria for Left ventricular hypertrophy (LVH)) History of myocardial infarction or coronary revascularization Nephrotic syndrome Elevated liver enzymes (AST or ALT ?40 U/L)	Types of CKD: Focal segmental glomerulosclerosis (primary or secondary) IgA nephropathy Membranous nephropathy Membranoproliferative glomerulonephritis Hypertensive Nephrosclerosis Minimal Mesangial proliferation Biopsy proven: yes Degree of proteinuria: 1-2 gm/d required. Per baseline characteristics, mean was 1.5 gm/d.	Stage of CKD: not specifically stated Method of defining CKD: GFR via modfied diet in renal disease (MDRD) equation GFR 30-59 ml/min/1.73m2 required Mean GFR at baseline ranged from 39-44 ml/min/1.73m2.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Yilmaz 2007 Sweden no trial name Fair	Patients were stratified into 2 groups by age, gender, and BMI: [R] Ramipril 5mg/d (n = 32) [V] Valsartan 160mg/d (n = 34) Patients remained in these treatment groups for 3 months A control group of 36 healthy participants was also defined for purposes of biochemical assessments done as part of this study.	Run-in: NR Washout: NR	NR	Primary end point not specifically stated. Main aim stated to be to investigate whether the beneficial effects of the renin-angiotensin-aldosterone system blockade in CKD has any relation to the alternation of asymmetric dimethylarginine levels. Reported results included: GFR Proteinuria Blood pressure (systolic and diastolic) Lipid profiles dimethylarginine (symmetric and asymmetric), Larginine, c reactive protein Fasting serum glucose Homeostasis model assessment The above serum and urine assessments were completed at baseline and after the study intervention.

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Yilmaz 2007 Sweden no trial name Fair	Mean age: 47.1 +/- 6.2 years Gender: 34 men, 32 women Race: Caucasian **these variables reported only for group as a whole, not for treatment groups.**	Estimated GFR at baseline: R: 44 +/- 11.8 ml/min/1.73 m2 V: 39.8 +/- 11.5 ml/min/1.73 m2 Proteinuria at baseline: R: 1.49 +/- .29 gm/d V: 1.49 +/- 0.41 gm/d Systolic blood pressure at baseline: R: 154.8 +/- 7.8 mmHg V: 151.6 +/- 7.0 mmHg Diastolic blood pressure at baseline: R: 94.6 +/- 2.9 mmHg V: 91.4 +/- 2.7 mmHg	Number screened: 318 Number eligible: NR Number enrolled: 80	Number withdrawn: 14 Number lost to follow-up: NR Number analyzed: 66

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Yilmaz 2007 Sweden no trial name Fair	Pre and post GFR by group: R: baseline 44 +/- 11.8; 3 mo 41.9 +/- 11.67 ml/min/1.73 m2 V: baseline 39.8 +/- 11.5; 3 mo 38.5 +/- 11.5 ml/min/1.73 m2 Not noted to be a statistically significant difference between groups, p-value and 95% CI NR Pre and post proteinuria levels by group: (calculation of mean percent change) R: baseline 1.49 +/- 0.29 gm/d; 3 mo 0.70 +/- 0.22 gm/d (-53%) V: baseline 1.48 +/- 0.41 gm/d; 3 mo 0.96 +/- 0.36 gm/d (-38%) Reduction in proteinuria was more significant in R than V, p = 0.002, 95% CI NR. Reduction in systolic blood pressure was significantly more in R vs. V (p = 0.007) Reduction in diastolic blood pressure was significantly more in R vs. V (p < 0.001)	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Yilmaz 2007 Sweden no trial name Fair	NR	NR	Adverse effects occurred as follows: 8 in group R 6 in group V *Specific effects experienced were not delineated by treatment group. Cough: 5 Hyperkalemia; value not specified: 7 Non-compliance (listed by authors as adverse event): 2

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Yilmaz 2007 Sweden no trial name Fair	Total withdrawals: 14 Withdrawals due to adverse effects: 14 Withdrawals due to reason other than adverse effects: zero	The control group in this study played a role in comparing levels of asymmetric dimethylarginine.	

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart disease (CHD)

SN abstractions

Author Year Country Trial Name (Quality Score)	Study Design Setting Follow-up interval	Eligibility criteria Inclusion criteria Exclusion criteria	Proteinuric CKD -Types -Biopsy proven? -Degree of proteinuria	Level of CKD -Stages -Method of defining CKD
Zanabli 2004 US no trial name Poor	Study design: Open-label crossover Setting: outpatient clinics Duration: not explicitly stated; 12 weeks based on treatment groups and wash-out periods	Inclusion criteria: History of treatment with ACE-I or ARB Serum creatinine 1.2-4 mg/dL Serum potassium >4.4 in of two most recent lab checks Age 18-70 Exclusion criteria: Uncontrolled Hypertension or HF Dialysis History of ACE-I/ARB allergy On changing dose of β-blockers, NSAIDS, or diuretics On potassium sparing diuretics On potassium supplements History of ventricular arrhythmia Serum potassium >6 Current hospitalization Women of childbearing age who are pregnant, breast-feeding, or not on contraceptives.	Types of CKD: NR Proteinuria: NR	Baseline renal function: NR Post treatment CrCl ranged from 31.9-33.5 ml/min CrCl assessed with 24 hr urine collection

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Zanabli 2004 US no trial name Poor	Participants were not randomized; therapy was given as follows: [Lis] Lisinopril: 5mg/d for 2 weeks, then 10 mg/d for 2 weeks THEN [Los] Losartan: 50 mg/d for 2 weeks then 100 mg/d for 2 weeks	Run-in: 2 week period prior to starting Lisinopril treatment group Washout: 2 week period between treatment with Lisinopril and Losartan -no ACE-I/ARB during run-in or washout	Amlodipine allowed for elevated blood pressure Not stated if other non-ACE-I/ARB antihypertensives were stopped as part of the study.	Primary endpoint not specifically stated. Aim reported to be to investigate side effect of hyperkalemia in ACE-I vs. ARB. 24 hr urine collections were completed after each study phase (weeks 2, 6, 8, and 12).

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Zanabli 2004 US no trial name Poor	Age: 39-68 Gender: 3 men, 4 women Ethnicity: NR	Baseline characteristics NR, but initial "wash-out" showed lab values pre-therapy as: Mean creatinine: 2.3 mg/dL Mean CrCl: 32.3 ml/min	Number screened: NR Number eligible: 30 Number enrolled: 9	Withdrawn: 2 Lost to follow-up: zero reported Analyzed: 7

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Results	Results: Quality of life; healthcare utilization
Zanabli 2004 US no trial name Poor	CrCl: During Lisinopril therapy: 32.5 ml/min During Losartan therapy: 33.5 ml/min Creatinine: During Lisinopril therapy: 2.4 mg/dL During Losartan therapy: 2.4 mg/dL No blood pressure data reported.	N/A

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Population subgroup analyses	Method of adverse events assessment	Adverse Events Reported
Zanabli 2004 US no trial name Poor	NR	Information reportedly collected on medication side effects at each subsequent visit. Timeline of follow-up visits not explicitly stated.	NR

Evidence Table 10. Data abstraction of nondiabetic chronic kidney disease trials

ACE/ARB: Coronary heart

SN abstractions

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments	Comments, internal use
Zanabli 2004 US no trial name Poor	Total withdrawals: 2 *both withdrawn for inability to comply with scheduled phlebotomy appointments. Withdrawals due to adverse events: zero reported	Primary goal of study was to investigate changes in potassium among patients with CKD on ACE-I/ARB. Types of CKD, level of CKD, and whether or not proteinuric at baseline was not specifically stated.	

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Randomization adequate?	Method of handling carry-over effects (Washout, Analysis, Not Reported (NR), None, Unclear)	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Outcome assessors masked?
Agarwal 2001 US	Method NR	Washout	Method NR	Yes	Yes	NR
Bakris 2000 US	No. Randomization was 1:1.	Washout	Method NR	Yes	Yes	No
Campbell 2003 Italy	Method NR	Analysis	Method NR	Yes	Yes	No
Chrysostomou 2006 Australia	Yes (simple randomization via hospital pharmacy dept)	None (not cross-over)	Yes (allocation per clinical pharmacists of hospital pharmacy - not otherwise associated c study)	Yes (groups did have different amts of protein and HTN at the beginning of trial, but not statistically significant).	Yes	Yes
Esnault 2005 France	Yes (Youden square design and allocation to one of 3 treatment sequences)	Washout and analysis	Method NR	Yes	Yes	No
Ferrari 2002 Switzerland	No (sealed envelopes)	Washout	Method NR	Yes	Yes	NR

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Care provider masked?	Patient masked?	Reporting: a) attrition b) crossovers c) adherence d) contamination	Post-randomization exclusions	Overall withdrawal rate: differential, high (>20%), if yes, explain
Agarwal 2001 US	NR	Yes	a) yes b) no c) no d) no	No	No/No
Bakris 2000 US	No	No	a) yes b) no c) no d) no	No	No/No
Campbell 2003 Italy	No	No	a) yes b) no c) no d) no	No	No/No
Chrysostomou 2006 Australia	Yes	Yes	a) yes b) no c) yes d) no	No	No/No
Esnault 2005 France	No	No	a) yes b) no c) no d) no	No	No/No (withdrawal 10%)
Ferrari 2002 Switzerland	No (envelopes opened after initial baseline period)	Yes	a) yes b) no c) no d) no	No	No/No

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Loss to follow-up: differential/high	Maintenance of comparable groups	Intention-to-treat (ITT) analysis	Funding	Quality Rating	Reason for quality rating if POOR.
Agarwal 2001 US	NR (one withdrawal, not specifically called a loss-to-follow-up)	Yes	No (1 of 17 or 5% not included)	Funded by Losartan specific grant; Merck	FAIR	Kept as Fair
Bakris 2000 US	NR (reason for withdrawals not stated)	Yes	No (2 of 27 or 5.4% not included)	NR	FAIR	Tempting to rate as "poor" because only reported GFR and no mention of proteinuria.
Campbell 2003 Italy	No/No	Yes	Unable to determine	NR	FAIR	
Chrysostomou 2006 Australia	No/No	Yes	Yes (for initial 3 and 6 mo analysis)	Not specifically reported, but ramipril was provided free of charge per Sonofi-Aventis.	FAIR	Kept as Fair and not "good" because of very small sample size (n = 41)
Esnault 2005 France	No/No	Yes	Yes	NR	FAIR	
Ferrari 2002 Switzerland	No/No	Yes	No (1 of 11 or 9% not included)	Supported in part by the Swiss national foundation for scientific research. Drugs supplied by Bristol-Myers Squibb and Sanofi-Synthelabo.	FAIR	

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Randomization adequate?	Method of handling carry-over effects (Washout, Analysis, Not Reported (NR), None, Unclear)	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Outcome assessors masked?
Hannedouche 2001 France	No. Randomization was 2:1 - not reported in further detail.	None (not cross-over)	NR (mechanism for allocation NR)	Yes	Yes	NR
Hou 2007 China	Yes (computer generated number based on blocks of 8 · distributed by study coordinator)	NR (not cross-over)	NR (mechanism for allocation NR)	yes	yes	yes
Kahvecioglu 2007 Turkey	No (not randomized)	None (not cross-over)	NR (mechanism for allocation NR)	Yes	Yes	No
Kim 2003 Korea	Method NR	NR	Method NR	Yes (cross-over, so overall group acted as its own control; subgroups of IgA and DM were significantly different in terms of age)	Yes	NR
Laverman 2002 The Netherlands	No (participants weren't randomized; meds were distributed in random order to each participant)	Washout	No (not blinded - each participant self-administered meds - no additional info given).	Yes	Yes	No

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Care provider masked?	Patient masked?	Reporting: a) attrition b) crossovers c) adherence d) contamination	Post-randomization exclusions	Overall withdrawal rate: differential, high (>20%), if yes, explain
Hannedouche 2001 France	Yes	Yes	a) yes b) no c) yes d) no	Yes; CRL for inclusion was initially 20-70 ml/min and was then changed to 30-80 ml/min. 1 patient was excluded after this change for CrCl 20-30 and 3 were included for CrCl 70-80.	No/No (withdrawal rate 16%)
Hou 2007 China	no	no	a) yes b) no c) no d) no	No	Yes/No (more withdrawals in ACE compared to ARB groups; overall withdrawal rate 14%)
Kahvecioglu 2007 Turkey	No	No	a) yes b) no c) no d)no	No	No/Yes (32% withdrawal rate)
Kim 2003 Korea	Yes	Yes	a) yes b) no c) no d) no	No	a) no (withdrawals not specified by group) b) no
Laverman 2002 The Netherlands	No	No	a) yes b) no c) no d) no	No	No/No

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Loss to follow-up: differential/high	Maintenance of comparable groups	Intention-to-treat (ITT) analysis	Funding	Quality Rating	Reason for quality rating if POOR.
Hannedouche 2001 France	No/No	Yes	Yes	NR	FAIR	
Hou 2007 China	No/No	yes	Yes	National nature and sciences grant for major projects, people's liberation army grant for major clinical research, national 11th 5-years plan foundation.	GOOD	
Kahvecioglu 2007 Turkey	NR/NR (loss to follow up not broken down by treatment groups).	Yes	No (10 of 31 or 32% not included)	NR	POOR	Very high withdrawal rate.
Kim 2003 Korea	No/No	Yes (cross-over study)	No (2 of 43 or 4.6% not included)	NR	FAIR	Kept as fair - overall group was similar at baseline, only subgroups differed and were analyzed separately.
Laverman 2002 The Netherlands	No/No	Yes	No (1 of 10 or 10% not included)	Funded by a grant from the Dutch Kidney Foundation.	FAIR	

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Randomization adequate?	Method of handling carry-over effects (Washout, Analysis, Not Reported (NR), None, Unclear)	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Outcome assessors masked?
Luno 2002 Spain	Yes (randomized with blocks of 6; codes kept in sealed envelopes at each center).	None (not cross-over)	Method NR	Yes	Yes	No
Matsuda 2003 Japan	NR (reported only as "randomly assigned" without further info).	NR (not cross-over)	NR (mechanism for allocation NR)	Yes	Yes	NR
Mori-Takeyama 2008 Japan	No (randomized by odd vs even last digit of patient ID number)	None (not cross-over)	Method NR	Yes	Yes	No
Nakao 2003 Japan COOPERATE primary paper	Yes (computer generated randomization vi permuted blocks of 6, distributed via sealed envelopes)	None (not cross-over)	Yes (specially prepared, sealed drug boxes per pharmacy.	Yes	Yes	Yes
Nakao 2003 Japan COOPERATE sub-study on ambulatory blood pressure analysis.	Yes (computer generated randomization vi permuted blocks of 6, distributed via sealed envelopes)	None (not cross-over)	Yes (specially prepared, sealed drug boxes per pharmacy.	Yes	Yes	Yes

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Care provider masked?	Patient masked?	Reporting: a) attrition b) crossovers c) adherence d) contamination	Post-randomization exclusions	Overall withdrawal rate: differential, high (>20%), if yes, explain
Luno 2002 Spain	No	No	a) yes b) no c) no d) no	No	No/No
Matsuda 2003 Japan	NR	NR	a) No b) No c) No d) No	No	NR/NR
Mori-Takeyama 2008 Japan	No	No	a) yes b) no c) no d) no	No	No/No
Nakao 2003 Japan COOPERATE primary paper	Yes	Yes	a) yes b) no c) yes d) no	No	a) no b) no
Nakao 2003 Japan COOPERATE sub-study on ambulatory blood pressure analysis.	Yes	Yes	a) yes b) no c) yes d) no	No	a) no b) no

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Loss to follow-up: differential/high	Maintenance of comparable groups	Intention-to-treat (ITT) analysis	Funding	Quality Rating	Reason for quality rating if POOR.
Luno 2002 Spain	No/No	Yes	Yes	Supported by a grant from Astra Zeneca Pharmaceuticals.	FAIR	
Matsuda 2003 Japan	NR/NR (withdrawals and loss to follow-up NR)	Yes	NR (since no withdrawals are reported and they do not state if ITT, I can't tell)	NR	FAIR	
Mori-Takeyama 2008 Japan	NR	NR	No (9 of 86 or 10% were not included)	NR	FAIR	
Nakao 2003 Japan COOPERATE primary paper	No/No	Yes	Yes	Funded by a grant from the Progressive Renal Disease Research Projects from the Ministry of Health, Labor, and Welfare in Japan.	POOR	This trial has been officially retracted by the primary publication due to investigation which revealed that it was not double-blind, that a statistician may not have been involved, and that sample chart review was unable to verify authenticity of any of the patient data.
Nakao 2003 Japan COOPERATE sub-study on ambulatory blood pressure analysis.	No/No	Yes	No (7 of 92 or 7.6% were not included)	NR	POOR	See above.

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Randomization adequate?	Method of handling carry-over effects (Washout, Analysis, Not Reported (NR), None, Unclear)	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Outcome assessors masked?
Remuzzi 1999 Italy	Method NR	None (not cross-over)	Method NR	No (levels of systolic blood pressure and proteinuria were higher in Irbesartan group at baseline)	Yes	No
Renke 2004 Poland	Method NR	None (not cross-over)	Method NR	No (more proteinuria in combination therapy group; reported as not statistically significantly different, no p-values reported)	Yes	No
Renke 2005 Poland	Method NR	Analysis	Method NR	Yes	Yes	No
Ruilope 2000 Spain	Method NR (only reported 3:2 distribution)	None (not cross-over)	Method NR	No (more proteinuria in one group, one group had higher percentage age >65).	Yes	NR
Russo 2001 Italy	Method NR	Washout	Method NR	Yes	Yes	NR
Rutkowski 2004 Poland	Method NR	Analysis	Method NR	Yes	Yes	No

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Care provider masked?	Patient masked?	Reporting: a) attrition b) crossovers c) adherence d) contamination	Post-randomization exclusions	Overall withdrawal rate: differential, high (>20%), if yes, explain
Remuzzi 1999 Italy	No	Yes	a) No b) No c) No d) No	No	Unable to determine (withdrawals not reported)
Renke 2004 Poland	No	No	a) yes b) no c) no d) no	No	No/No
Renke 2005 Poland	No	No	a) yes b) no c) yes d) no	No	No/Yes (20% withdrawal rate)
Ruilope 2000 Spain	NR	NR	a) yes b) no c) no d) no	No	No/No
Russo 2001 Italy	NR	NR	a) yes b) no c) no d) no	No	No/Yes (49% withdrawal rate)
Rutkowski 2004 Poland	No	No	a) yes b) no c) no d) no	No	Unable to determine (withdrawals not reported by groups)

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Loss to follow-up: differential/high	Maintenance of comparable groups	Intention-to-treat (ITT) analysis	Funding	Quality Rating	Reason for quality rating if POOR.
Remuzzi 1999 Italy	Unable to determine (loss to follow-up NR)	No (incomparable groups from the beginning)	Unable to determine	Partially supported by a research grant from Sanofi Withrop.	POOR	Incomparable groups at baseline by SBP and proteinuria levels; no mention of withdrawals. Adverse events not reported.
Renke 2004 Poland	Unable to determine (loss to follow-up NR)	Yes	No (2 of 54 or 3.7% were not included)	Medical University of Gdansk	FAIR	Groups uneven with more protein in one group at baseline. Although numbers of analysis not shown, study text reports that these differences were not statistically significant.
Renke 2005 Poland	NR/No (loss to follow-up and withdrawals not reported by treatment groups)	Yes	No (6 of 30 or 20% were not included)	Drugs were provided by Fournier Poland and ADAMED.	FAIR	Baseline characteristics are arguably reported and similar because cross-over design allows each participant to act as own control.
Ruilope 2000 Spain	No/No	Yes	No (1 of 109 or 0.9% were not included)	NR	FAIR	
Russo 2001 Italy	No/No	Yes	No (9 of 19 or 47% were not included)	NR	POOR	Very high withdrawal rate.
Rutkowski 2004 Poland	Unable to determine (loss to follow-up NR)	Yes	No (6 of 30 or 20% were not included)	Funding unclear; Drugs provided by Fournier Poland and ADAMED.	FAIR	

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Randomization adequate?	Method of handling carry-over effects (Washout, Analysis, Not Reported (NR), None, Unclear)	Allocation concealment adequate?	Groups similar at baseline?	Inclusion criteria specified?	Outcome assessors masked?
Segura 2003 Spain	Method NR	None (not cross-over)	Method NR	Yes (more proteinuria in Valsartan group; analysis not reported but text reports "no differences between groups")	Yes	NR
Song 2003 Korea	Method NR	Washout	Method NR	Yes	Yes	NR
Tylicki 2002 Poland	Method NR	None (not cross-over)	Method NR	Yes	Yes	No
Tylicki 2005 Poland	No (1:1 randomization)	None (not cross-over)	Method NR	Yes	Yes	No
Yilmaz 2007 Sweden	No (not randomized)	None (not cross-over)	Method NR	NR	Yes	No
Zanabli 2004 US	No (not randomized)	Washout	Method NR	NR	Yes	NR

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Care provider masked?	Patient masked?	Reporting: a) attrition b) crossovers c) adherence d) contamination	Post-randomization exclusions	Overall withdrawal rate: differential, high (>20%), if yes, explain
Segura 2003 Spain	No	No	a) No b) No c) No d) No	No	Unable to determine (withdrawals not reported)
Song 2003 Korea	NR	Yes	a) yes b) no c) no d) no	No	No/No
Tylicki 2002 Poland	No	No	a) yes b) no c) no d) no	No	No/No
Tylicki 2005 Poland	No	No	a) yes b) no c) no d) no	No	No/No (Withdrawal rate 17%) Most withdrawals not reported by treatment group.
Yilmaz 2007 Sweden	No	No	a) yes b) no c) no d) no	No	No/No (withdrawal 17.5%)
Zanabli 2004 US	No	No	a) yes b) no c) no d) no	No	No/Yes (2 of 9 withdrew; 22% of all participants).

Evidence Table 11. Quality assessment of chronic kidney disease trials

Author, Year Country	Loss to follow-up: differential/high	Maintenance of comparable groups	Intention-to-treat (ITT) analysis	Funding	Quality Rating	Reason for quality rating if POOR.
Segura 2003 Spain	Unable to determine (loss to follow-up NR)	yes	Unable to determine (because withdrawals and loss to follow up are NR)	NR	FAIR	
Song 2003 Korea	No/No (no loss to follow up reported)	Yes	No (2 of 54 or 6% not included)	NR	FAIR	
Tylicki 2002 Poland	No/No	Yes	No (2 of 51 or 4% not included)	Partially supported by grant from Polish committee for scientific research. Drugs provided by Merck.	FAIR	
Tylicki 2005 Poland	No/No (no loss to follow up reported)	Yes	No (7 of 40 or 17.5% not included)	Partially sponsored by Polish committee for Scientific Research via Medical University of Gdansk.	FAIR	
Yilmaz 2007 Sweden	No/No	NR (group characteristics not clearly defined)	No (14 of 80 or 17.5% not included)	Supported by GATA research center	FAIR	
Zanabli 2004 US	No/No (no loss to follow up reported)	Yes (cross-over study)	No (2 of 9 or 22% not included)+	NR	POOR	Significant loss of 2 patients out of 9 total. No statistical numbers given for CrCl changes.

Evidence Table 12. Evidence profile of chronic kidney disease trials: Losartan compared with enalapril monotherapy

							Summary of Findings	
Quality Assessment							Results by study, Relative effect	Quality of the evidence for each outcome
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations		
Changes in renal function-proteinuria								
Renke 2004 n = 54	RCT	Fair	Consistent	Direct	Imprecise	One trial did not provide statistical analysis between groups.	NSD between groups.	Low
Tylicki 2002 n = 51	RCT	Fair					NSD between groups.	
Tylicki 2005 n = 40	RCT	Fair					NSD between groups.	
Changes in renal function-creatinine clearance								
Renke 2004 n = 54	RCT	Fair	Consistent	Direct	Imprecise	Two of three trials only reported no significant change in CrCl from baseline; no analysis between groups.	NSD between groups.	Very Low
Tylicki 2002 n = 51	RCT	Fair					NSD between groups.	
Tylicki 2005 n = 40	RCT	Fair					NSD between groups.	
Overall withdrawals								
Renke 2004 n = 54	RCT	Fair	Consistent	Direct	Imprecise		NSD between groups.	Low
Tylicki 2002 n = 51	RCT	Fair					NSD between groups.	
Tylicki 2005 n = 40	RCT	Fair					NSD between groups.	

Evidence Table 13. Evidence profile of chronic kidney disease trials: Losartan compared with benazapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
End stage renal disease								
Hou 2007 n = 360	RCT	Good	n/a	Direct	Precise		NSD between therapy groups	Moderate
Changes in renal function-proteinuria								
Hou 2007 n = 360	RCT	Good	Consistent	Direct	Imprecise		NSD between groups	Low
Rutkowski 2004 n = 30	Randomized open cross-over	Fair					NSD between groups	
Changes in renal function-creatinine clearance								
Renke 2005 n = 30	Randomized open cross-over	Fair	Consistent	Direct	Imprecise		NSD between groups	Low
Rutkowski 2004 n = 30	Randomized open cross-over	Fair					NSD between groups	
Overall withdrawals								
Hou 2007 n = 360	RCT	Good	Inconsistent	Direct	Imprecise	One trial (Hou) noted increased risk for withdrawal due to cough in those on Benazapril. The other two studies did not reflect that.	Higher rate of withdrawal due to cough	Low
Renke 2005 n = 30	Randomized open cross-over	Fair					NSD between groups	
Rutkowski 2004 n = 30	Randomized open cross-over	Fair					NSD between groups	
Total withdrawals due to any adverse event								
Hou 2007 n = 360	RCT	Good	Inconsistent	Direct	Imprecise	Percent withdrawals due to adverse is similar between groups.	Higher rate of withdrawal among those on Benazapril.	Moderate
Specific harm-hyperkalemia								
Hou 2007 n = 360	RCT	Good	n/a	Direct	Precise	Very small number of events overall.	NSD between groups	Moderate
Specific harm-acute kidney injury								
Hou 2007 n = 360	RCT	Good	n/a	Direct	Precise	Very small number of events overall.	NSD between groups	Moderate

Evidence Table 13. Evidence profile of chronic kidney disease trials: Losartan compared with benazapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Specific harm-cough								
Hou 2007 n = 360	RCT	Good	n/a	Direct	Precise	Of note, one other study reported cough with ACEI, but did not delineate of ACEI monotherapy or as part of combo therapy arm of that trial.	Incidence of cough ranged from 16-18% in the two ACEI arms of this trial, versus zero in the two AIIRA arms of this trial.	Moderate
Withdrawals due to specific harms								
Hou 2007 n = 360	RCT	Good	n/a	Direct	Precise	Of note, the two other trials reported withdrawals due to adverse effects, but did not delineate those withdrawals by treatment groups.	23-26% withdrawal rate due to adverse events for ACEI versus 6% for AIIRA.	Moderate

Two trials did not report withdrawals or adverse events by treatment group.

Evidence Table 14. Evidence profile of chronic kidney disease trials: Valsartan compared with benazepril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Changes in renal function-proteinuria								
Campbell 2003 n = 24	Randomized cross-over group study	Fair	Consistent	Direct	Imprecise		NSD between groups	Low
Segura 2003 n = 36	Randomized parallel group study	Fair					NSD between groups	
Changes in renal function-creatinine clearance								
Campbell 2003 n = 24	Randomized cross-over group study	Fair	n/a	Direct	Imprecise		NSD between groups	Very low
Overall withdrawals								
Campbell 2003 n = 24	Randomized cross-over group study	Fair	n/a	Direct	Imprecise	Reported zero withdrawals	NSD between groups	Very low
Specific harm-hyperkalemia								
Campbell 2003 n = 24	Randomized cross-over group study	Fair	n/a	Direct	Imprecise	Specifically reported zero hyperkalemic events overall.	NSD between groups	Very low

Evidence Table 15. Evidence profile of chronic kidney disease trials: Valsartan compared with ramipril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Changes in renal function- serum creatinine								
Esnault 2005 n = 18	Randomized cross-over trial	Fair	n/a	Direct	Imprecise		NSD between groups	Very Low
Changes in renal function-estimated GFR								
Yilmaz 2007 n = 66	Controlled head to head trial	Fair	n/a	Direct	Imprecise		NSD between groups	Very Low
Changes in renal function-proteinuria								
Esnault 2005 n = 18	Randomized cross-over trial	Fair	Inconsistent	Direct	Imprecise	In the trial where ACEI was superior, blood pressures were also lower in those on ACEI	NSD between groups	Low
Yilmaz 2007 n = 66	Controlled head to head trial	Fair					Proteinuria was lowered more with ACEI than AIIRA (p = 0.02), but blood pressure control was not equivalent.	
Specific harm-hypotension								
Esnault 2005 n = 18	Randomized cross-over study	Fair	n/a	Direct	Imprecise	Specifically notes only that no hypotension events occurred in either group.	NSD between groups	Very Low

Withdrawals were not delineated by treatment groups. One trial reported adverse events each group, but then did not specify which adverse events for which group.

Evidence Table 16. Evidence profile of chronic kidney disease trials: Losartan compared with enalapril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Changes in renal function-proteinuria								
Renke 2004 n = 54	RCT	Fair	Inconsistent	Direct	Imprecise	Both trials showed some unequal blood pressure control between groups.	NSD between groups	Low
Tylicki 2002 n = 51	RCT	Fair					Greater reduction in proteinuria with combination versus either monotherapy.	
Changes in renal function-creatinine clearance								
Renke 2004 n = 54	RCT	Fair	Consistent	Direct	Imprecise		NSD between groups	Low
Tylicki 2002 n = 51	RCT	Fair					NSD between groups	

Total withdrawals not reported by treatment groups. Adverse events not reported by treatment groups.

Evidence Table 17. Evidence profile of chronic kidney disease trials: Losartan in combination with benazepril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Changes in renal function-proteinuria								
Renke 2005 n = 30	Randomized cross-over trial	Fair	Consistent	Direct	Imprecise		Combination therapy lowered proteinuria more than monotherapy.	Low
Rutkowski 2004 n = 30	Randomized cross-over trial	Fair					Combination therapy lowered proteinuria more than monotherapy.	
Changes in renal function-creatinine clearance								
Renke 2005 n = 30	Randomized cross-over trial	Fair	Consistent	Direct	Imprecise		NSD between groups	Low
Rutkowski 2004 n = 30	Randomized cross-over trial	Fair					NSD between groups	

Withdrawals and adverse events were not delineated by treatment groups.

Evidence Table 18. Evidence profile of chronic kidney disease trials: Valsartan in combination with benazepril

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Changes in renal function-estimated GFR								
Campbell 2003 n = 24	Randomized cross-over trial	Fair	n/a	Direct	Imprecise		Increase in GFR was noted for those on combination therapy compared to monotherapy.	Very Low
Changes in renal function-proteinuria								
Campbell 2003 n = 24	Randomized cross-over trial	Fair	Inconsistent	Indirect	Imprecise	One trial used half-dose therapy for the combination therapy arm; the other used full-dose therapy for the combination therapy arm.	Combination therapy lowered proteinuria more than monotherapy.	Very Low
Segura 2003 n = 36	RCT	Fair					Combination therapy lowered proteinuria more only compared to Benazepril and not Valsartan monotherapy.	
Changes in renal function-creatinine clearance								
Campbell 2003 n = 24	Randomized cross-over trial	Fair	n/a	Direct	Imprecise		NSD between groups	Very Low
Specific harm-hyperkalemia								
Campbell 2003 n = 24	Randomized cross-over trial	Fair	n/a	Direct	Imprecise	No hyperkalemic events occurred in either group.	NSD between groups	Very Low

Evidence Table 19. Evidence profile of chronic kidney disease trials: Ramipril with candesartan compared with ramipril alone

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Changes in renal function-proteinuria								
Kim 2003 n = 43	Randomized cross-over trial	Fair	Consistent	Direct	Imprecise	One trial initially showed combination therapy lowered proteinuria more than mono, but that difference was found to be unique to subgroup.	Combination therapy lowered proteinuria more than monotherapy for IgA patients, but not for Diabetic nephropathy patients.	Low
Song 2003 n = 34	Randomized cross-over trial	Fair					Combination therapy lowered proteinuria more than monotherapy for IgA patients, but not for Diabetic nephropathy patients.	
Changes in renal function-creatinine clearance								
Kim 2003 n = 43	Randomized cross-over trial	Fair	Consistent	Direct	Imprecise		NSD between groups	Low
Song 2003 n = 34	Randomized cross-over trial	Fair					NSD between groups	

Withdrawals and adverse events were not delineated by treatment groups.

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Andersen 2000 Denmark	Crossover design Single center: Steno Diabetes Center, Copenhagen Double-blind	Inclusion: Type 1 diabetes; diabetic nephropathy; GFR>60 mL/min/1.73 m^2; office blood pressure > 145/85 mm Hg; age between 18 and 75 years Exclusion: Malignant hypertension, congestive heart failure. myocardial infarction or stroke within the last 3 months	Losartan 50 mg Losartan 100 mg Enalapril 10 mg Enalapril 20 mg Placebo x 2 months

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Andersen 2000 Denmark	Run-in: NR Washout: NR	All antihypertensive medication, including diuretics, withdrawn for ≥ 4 wks Furosemide given to 5 patients to prevent peripheral edema	GFR: measured at 8:00 a.m. after a single IV injection of 3.7 MBq ^{51}Crethylenediaminetetraacetic acid (EDTA) by determining the radioactivity in venous blood samples taken 180, 200, 220, and 240 minutes after the injection; results standardized for 1.73 m^2 body surface area, using the patients surface area at the start of the study; mean coefficient of variation in GFR of each patients from day to day was 4% Albuminuria: determined by enzyme-linked immunosorbent assay (ELISA), as the geometric mean of 3 consecutive 24-hour urine collections, completed immediately before each visit Creatinine: measured by high-performance liquid chromatography (normal range 4.1 to 6.4%; Variant; Bio-Rad Laboratories, Hercules, CA, USA)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Andersen 2000 Denmark	42±2 years 62% male Ethnicity NR	Diabetes duration (years): 33±2 Albuminuria (mg/24 hr): 1156 (643-2080) GFR (ml/min/1.73 m^2): 90±6

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Andersen 2000 Denmark	NR/NR/16	0/0/16

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Andersen 2000 Denmark	Losartan 50 mg vs losartan 100 mg vs enalapril 10 mg vs enalapril 20 mg: GFR (ml/min/1.73 m2): 91±6 vs 89±6 vs 89±6 vs 87±61, NS Urinary albumin (mg/24 hr): 775 (445-1349) vs 651 (377-1126) vs 631 (340-1173) vs 477 (251-910); NSD between losartan 100 mg and enalapril 20 mg, other comparisons NR Serum creatinine (μmol/L): 94±6 vs 92±7 vs 96±5 vs 89±6, NS	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Andersen 2000 Denmark	"No patients reported side-effects that could be related to the study medication"	0/0	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Barnett 2004/Barnett 2006 Northern Europe DETAIL	Parallel, noninferiority design Multicenter: 39 centers in Northern Europe Double-blind	Inclusion: Male or female; white or Asian; 35 to 80 years of age; type 2 diabetes treated by diet, diet plus oral hypoglycemic drugs (≥ 1 year), or insulin preceded by treatment with oral agents (≥ 1 year); onset of diabetes after age 40 and BMI > 25 for diabetics treated with insulin; mild-to-moderate hypertension (resting BP < 180/95 mm Hg after ≥ 3 mos of ACEI therapy; normal renal morphology; UAE rate (mean of 3 consecutive overnight values) between 11 and 999 μg per minute, with 2 values > than 10 μg per minute; HbA1c < 12%; serum creatinine < 1.6 per deciliter (141 μmol per liter); GFR > 70 ml/min/1.73 m2 Exclusion: Any condition other than cardiovascular disease	Telmisartan 40 mg QD x 4 wks, then forced titration to 80 mg QD Enalapril 10 mg QD x 4 wks, then forced titration to 20 mg QD x 5 years Dose of study drug could be reduced after 2 months, but subsequent increase not permitted

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Barnett 2004/Barnett 2006 Northern Europe DETAIL	Run-in: None Wash-out: Antihypertensive medication continued during 1 month screening period; but stopped at time of randomization	Additional antihypertensive medication (not an ACEI or AIIRA) was allowed after 2 months if resting SBP > 160 mm Hg or resting DBP > 100 mm Hg Telmisartan/enalapril (% patients) Diuretics: 52%/51% Beta blockers: 39%/39% Calcium channel blockers: 46%/46% Other antihypertensive agents: 35%/35% Aspirin: 37%/41% Statins: 42%/41%	Primary Outcome: Change in GFR (determined by measurement of the plasma clearance of iohexol) after 5 years (clinically significant difference predefined as difference of ≥ -10.0 ml/min/1.73 m^2) Secondary Outcomes: Annual changes in GFR, urinary albumin excretion (determined by rate nephelometry, with the use of timed overnight samples obtained on three consecutive nights), serum creatinine, rates of clinical events (end-stage renal disease, myocardial infarction, stroke, and congestive heart failure), all-cause mortality; adverse event rates; laboratory abnormalities

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Barnett 2004/Barnett 2006 Northern Europe DETAIL	Telmisartan vs enalapril 61.2±8.5 vs 60.0±9.1 years 72.5% vs 73.1% male 98.3% vs 98.5% White race	Telmisartan vs enalapril BMI: 30.8±4.4 vs 30.6±5.1 SBP (mm Hg): 152.6±16.6 vs 151.6±15.8 DBP (mm Hg): 85.4±8.8 vs 85.9±7.8 Duration of HTN (median years and range): 8.0 (0-34) vs 5.5 (0-49) Duration of diabetes (median years and range): 8.0 (0-25) vs 8.0 (0-37) History of CV disease (% subjects): 49.2% vs 48.5%) GFR (ml/min/1.73 m^2): 91.4±21.5 vs 94.3±22.1 Serum creatinine (mg/dl): 1.02±0.21 vs 0.99±0.20 Median (range) UAE rate (μg/min): 46.2 (4-1011) vs 60.0 (9-969) Microalbuminuria (% subjects): 81.7% vs 81.5%) Macroalbuminuria (% subjects): 18.3% vs 17.7%

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Barnett 2004/Barnett 2006 Northern Europe DETAIL	NR/NR/250	82 (33%)/2 (0.8%)/216 (86%)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Barnett 2004/Barnett 2006 Northern Europe DETAIL	Telmisartan vs enalapril: Mean change in GFR (ml/min/1.73 m^2): -17.9 vs -14.9; difference= -3.0 (95% CI -7.6 to 1.6); lower boundary of -7.6 > predefined value of -10, indicating telmisartan was not inferior Serum creatinine (mg/dl): 0.10 vs 0.10; difference=0 (95% CI -0.66 to 0.65) Kidney failure/required dialysis: 0 vs 0 Increase in serum creatinine to > 2.3 mg/dL (200 μmol/L): 0 vs 0 Stroke: 6 (5.0%) vs 6 (4.6%); P=NR Congestive heart failure: 9 (7.5%) vs 7 (5.4%); P=NR Nonfatal MI: 9 (7.5%) vs 6 (4.6%); P=NR Deaths: 6 (5.0%) vs 6 (4.6%); P=NR Cardiovascular event-related deaths: 3 (2.5%) vs 2 (1.5%); P=NR	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Barnett 2004/Barnett 2006 Northern Europe DETAIL	Telmisartan vs enalapril: Any adverse event: 115 (96%) vs 130 (100%)	Overall withdrawals: 38 (32%) vs 44 (34%); *P*=NR Withdrawals due to adverse events: 20 (17%) vs 30 (23%); *P*=NR	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Cetinkaya 2004 Turkey	Parallel design Setting NR Blinding NR	Diabetic nephropathy with proteinuria > 300 mg/day	Enalapril 10 mg (Group 1) OR Losartan 50 mg/day (Group 2) x 12 weeks Followed by: Combination therapy with enalapril 10 mg plus losartan 50 mg/day (Group 3) OR Double dose monotherapy with enalapril 20 mg or losartan 100 mg (Group 4) x 12 weeks
Deyneli, 2006 Turkey	Parallel design Multicenter: Outpatient clinics at Marmara University Hospital Endocrine and Internal Medicine	Inclusion: Male and female patients with type 2 diabetes diagnosed after age 30, mild to moderate essential hypertension; macroalbuminuria Exclusion: Secondary hypertension, history of malignant hypertension, myocardial infarction, cerebrovascular disease, heart failure, treatment with antiaggregants, steroids or other drugs that might affect BP, serum creatinine>200mmol/L, UTI and other systemic disorders.	Enalapril: 5-20mg/day Losartan: 50-100mg/day Duration: 6 weeks dose titration phase; 24 weeks maintenance phase

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Cetinkaya 2004 Turkey	NR/NR	NR	Serum creatinine measured at weeks 4, 12, 16 and 24 Proteinuria was measured by the sulfosalicylic method at weeks 12 and 24
Deyneli, 2006 Turkey	Run-in: NR Washout: NR	Oral antidiabetic drugs and insulin	Urinary albumin excretion measured using nephelometric method

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Cetinkaya 2004 Turkey	54.72±7.72 years 54.5% male Race NR	Body weight (kg): 68.16±9.97 Proteinuria (g/day): 4.82±1.11 Creatinine clearance (ml/min/1.73 m^2): 65.3±10.1 $HbA1_c$: 6.9±1.3
Deyneli, 2006 Turkey	52.3 yrs 25% male Ethnicity: NR	Enalapril vs Losartan BMI (kg/m2): 28.6 (SD 8.8) vs 29.3 (SD 5.3) Diabetes duration (yrs): 4.7 (SD 3.2) vs 4.6 (SD 3.7) Diabetic medication: Oral antidiabetic drugs 91.7% in each group, 8.3% in each group HbA1c(%): 6.5 (SD 0.5) vs 6.4 (SD 0.6) Albuminuria (mg/d): 83.5(SD 51) vs 80.1 (SD 52)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Cetinkaya 2004 Turkey	NR/NR/22	NR/NR/NR
Deyneli, 2006 Turkey	NR/NR/24	1/NR/NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Cetinkaya 2004 Turkey	Proteinuria (g/day) at endpoint: Group 1=3.17±0.69; Group 2=3.21±0.71; Group 3=2.36±0.40; Group 4=3.09±0.56 % decrease in proteinuria (g/day): Group 1+2=33% vs Group 3=51% (*P*<0.05) OR vs Group 4=37% (*P*=NR) Serum creatinine (mg/dl) at endpoint: Baseline=1.78±0.42 vs Group 1+2=2.0±0.52 (*P*<0.05); Group 3=2.08±0.63 (*P*<0.05); Group 4=2.10±0.55 (*P*<0.05)	Recorded at quarterly visits
Deyneli, 2006 Turkey	Enalapril vs Losartan Change in UAE at 24 weeks 117.5 (SD 7.4) vs 19.3 (SD 8.4), p<0.005 for change from baseline for both groups	Monitoring spontaneous reports of AE and pill counts, 24 hr urine and fasting venous blood samples

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Cetinkaya 2004 Turkey	NR	NR;NR	
Deyneli, 2006 Turkey	Enalapril vs Losartan Deaths: 0 vs 0 Cardiovascular events: 0 vs 0	Total withdrawals Enalapril: 1, Losartan:0 Withdrawals due to AE: Enalapril: 0, Losartan: 0	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Igarashi 2006 Japan	Parallel design Single center: Yamagata University Hospital outpatient clinic Blinding NR	Inclusion: Type 2 diabetes and nephropathy (American Diabetes Association criteria); age ≥ 20 years; HbA_{1c} < 8%; SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg; persistent urinary protein excretion > 0.5 g/24 hr Exclusion: Type 1 diabetes; nondiabetic renal disease; malignant or secondary hypertension, MI or cerebrovascular event within previous 6 months; chronic hepatic disease; history of allergic reaction to drugs, especially ACE inhibitors	Doubled ACEI: Enalapril 10 mg ACEI + ARB: Enalapril 5 mg plus losartan 50 mg
Jacobsen 2003 "Additive effect of…" Denmark	Crossover design Single center: Steno Diabetes Center, Copenhagen Double-blind	Inclusion: Diabetic nephropathy was diagnosed clinically based on persistent albuminuria > 300 mg/24 H in 2 of 3 consecutive determinations, presence of diabetic retinopathy, and no other kidney or renal tract disease; insulin-dependent from time of diagnosis and received at least 2 daily injections of insulin; diabetic diet (45-55% carbohydrates; 30-35% fat, 15-20% protein) without restriction in sodium or protein intake Exclusion: Plasma potassium > 4.8 mmol/L, pregnancy, no use of contraceptives, age < 18 yr; alcohol or medicine abuse; inability to understand patient information; contraindication to treatment with ACEI or ARB; SBP < 100 mm Hg; GFR < 30 ml/min; heart failure; myocardial infarction; or coronary bypass within the last 6 months	Placebo, Benazepril 20 mg, Valsartan 80 mg, or Benazepril 20 mg plus valsartan 80 mg x 8 weeks

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Igarashi 2006 Japan	Run-In: Enalapril 5 mg for 12 weeks (observational period) Washout=2-4 weeks	Other antihypertensive agents including calcium antagonists, alpha or beta-receptor blockers, or diuretics	Total protein, albumin, creatinine
Jacobsen 2003 "Additive effect of…" Denmark	Run-in: 4-week, single-blind, placebo period	All antihypertensive medication withdrawn at screening visit, except loop diuretics	Primary Endpoint: Albuminuria Secondary Endpoints: GFR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Igarashi 2006 Japan	ACEI+ARB/Doubled ACEI: Age: 63.5±2.5/63.9±2.7 69% male (overall) Race NR	ACEI+ARB/Doubled ACEI: Duration of diabetes (years): 14.8±2.0/13.8±2.0 BMI (kg/m^2): 25.7±1.8/26.0±1.1 HbA1c (%): 7.21±0.26/7.18±0.24 Creatinine (mg/dl): 0.97±0.09/0.77±0.05 Urinary protein excretion (g/day): 1.83±0.50/1.78±0.51 Diabetic retinopathy (No/simple/proliferative): 2/5/6 vs 2/5/6
Jacobsen 2003 "Additive effect of…" Denmark	43± 7 72% male 100% white	Duration of diabetes (years): 30±7 Duration of diabetic nephropathy (years): 10±6 Retinopathy (# background/proliferative): 6/12 Smokers (# no/yes): 12/6 Albuminuria (mg/24 h): 362 (80-2628) Number of antihypertensive agents (median): 2 (2-3) Previous treatment with ACE-I/ARB (# yes/no): 18/0 Median dose of furosemide (mg/d): 40 (20-250)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Igarashi 2006 Japan	NR/28/26 (2 excluded due to cough during run-in period)	0/0/26
Jacobsen 2003 "Additive effect of…" Denmark	60/22/20	2/NR/18

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Igarashi 2006 Japan	Creatinine clearance (ml/min at week 0/after 12-week run-in/week 24): ACE+ARB=77.3±8.9/91.8±10.0/83.2±8.9 vs Doubled ACEI=73.8±7.5/79.5±9.0/80.1±8.1; *P*=NR % of week 12 urinary protein excretion (g/day): ACEI+ARB=60.1±9.5% vs Doubled ACEI=99.3±11.2%; *P*<0.05	NR
Jacobsen 2003 "Additive effect of…" Denmark	Albuminuria; geometric mean, 95% CI/% reduction (mg/24 h): placebo=701 (490 to 1002), dual blockade=138 (91 to 208)/80% (75% to 84%), *P*<0.01 vs any monotherapy, benazepril=239 (169 to 345)/65% (56% to 72%), valsartan=225 (146 to 345)/65% (56% to 72%), benazepril and valsartan were equally effective GFR (ml/min per 1.73 m2): placebo mean (SEM)=82 (7); mean changes (95% CI): benazepril=3 (-1 to 7), valsartan=4 (-1 to 8), dual blockade=10 (6 to 14), *P*<0.01 vs any monotherapy P-creatinine (reported in publication as μmol/L, but converted to mg/dL): placebo mean (SEM)=1.30 (0.08); mean changes (95% CI): benazepril=-0.01 (-0.09 to 0.07), valsartan=0.02 (-0.06 to 0.10), dual blockade= -0.10 (-0.18 to -0.02), *P*=NS vs any monotherapy	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Igarashi 2006 Japan	NR	Overall withdrawals: None Withdrawals due to adverse events: None	
Jacobsen 2003 "Additive effect of…" Denmark	Transient hypotension: dual blockade=6 (33%) vs benazepril=2 (11%) vs valsartan=0; *P*=NR Treatment for anemia: 0 in any group	Overall withdrawals: dual blockade=0, benazepril=2 (11%), valsartan=0, *P*=NR Withdrawals due to adverse events: dual blockade=0, benazepril=2 (11%), valsartan=0, *P*=NR	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Jacobsen 2003 "Dual blockade of…" Denmark	Crossover design Single center: Steno Diabetes Center, Copenhagen Double-blind	Inclusion: Diabetic nephropathy was diagnosed clinically based on persistent albuminuria > 300 mg/24 H in 2 of 3 consecutive determinations, presence of diabetic retinopathy, and no other kidney or renal tract disease; insulin-dependent from time of diagnosis and received at least 2 daily injections of insulin; diabetic diet (45-55% carbohydrates; 30-35% fat, 15-20% protein) without restriction in sodium or protein intake Exclusion: Plasma potassium > 4.8 mmol/L, pregnancy, no use of contraceptives, age < 18 yr; alcohol or medicine abuse; inability to understand patient information; contraindication to treatment with ACEI or ARB; SBP < 100 mm Hg; GFR < 30 ml/min; heart failure; myocardial infarction; or coronary bypass within the last 6 months	Irbesartan 300 mg Placebo x 8 weeks

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Jacobsen 2003 "Dual blockade of…" Denmark	Run-in: NR Washout: NR	Study medication was added to usual antihypertensive treatment, including enalapril 40 mg, which all patients had received for > 3 months prior to the study Total number of antihypertensive drugs (1/2/3/4): 5/12/6/1 Total number of patients receiving diuretics (thiazide/furosemide): 8/11 Number of patients receiving calcium channel blockers: 6 Number of patients receiving statins: 10	Primary Endpoint: Albuminuria Secondary Endpoints: GFR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Jacobsen 2003 "Dual blockade of…" Denmark	Age, years, mean (SD): 42 (9) 71% male Race NR	Duration of diabetes, years, mean (SD): 31 (9) Duration of diabetic nephropathy (years): 13 (5) Retinopathy (# background/proliferative): 5/19

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Jacobsen 2003 "Dual blockade of…" Denmark	NR/NR/24	0/0/24

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Jacobsen 2003 "Dual blockade of…" Denmark	Comparison: Enalapril alone vs dual blockage Values represent mean (SEM), unless otherwise specified Albuminuria (mg/24 hr): 519 (95% CI 342, 789) vs 373 (224, 622; mean difference (95% CI)= -25% (-34, -15); *P*<0.001 GFR (mL/min/1.73 m2): 65 (5) VS 63 (5); mean difference -3 (-1, 7), *P*=0.222 Plasma creatinine (reported in μmol/L, converted to mg/dL): 1.51 (0.08) vs 1.57 (0.08); mean difference 0.04 (-0.04, 0.15), *P*=0.290	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Jacobsen 2003 "Dual blockade of…" Denmark	Overall adverse events: NR Transient hypotension: 17% vs 0%, P=NR Increase in plasma potassium to > 5.2mmol/L: 4% vs 4% Need for treatment for anemia: 0 vs 0	Overall withdrawals: 0 Withdrawals due to adverse events: 0	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Ko 2005 China	Parallel design Single center: Department of Medicine of Alice Ho Miu Ling Nethersole Hospital, Hong Kong Blinding NR	Inclusion: Chinese patients with type 2 diabetes aged 30 to 80 Exclusion: Uncontrolled hypertension (sitting BP > 200/115 mm Hg); history of myocardial infarction, cerebrovascular accident, uncontrolled congestive heart failure within the previous 6 months, significant renal impairment (plasma creatinine ≥ 1.70 mg/dL)	Valsartan 80 mg Enalapril 5 mg

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Ko 2005 China	Run-in: 2-weeks, treatment NR Washout NR	Patients were allowed to continue other drugs (e.g., antidiabetic drugs) at the same dosage as before they enrolled in the study	Creatinine, 24-hour urinary albumin, regression of albuminuria (conversion of macroalbuminuria to microalbuminuria or normoalbuminuria or the conversion of microalbuminuria to normoalbuminuria), microabuminuria (24-hour UAE of 30 to 300 mg/d or spot urinary ACR readings of 3 to 30 mg/mmol), macroalbuminuria (24-hour UAE of 300 mg/d or spot urinary ACR readings of ≥ 30 mg/mmol

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Ko 2005 China	Age, years (mean ± SD): 61.0±11.1 40.5% male 100% Chinese	All values expressed as mean ± SD, except where indicated Duration of diabetes, years: 9.6±6.1 Hypertension diagnosis (% patients): 100% Duration of hypertension, years: 6.6±5.1 BMI, kg/m2: 25.3±2.8 HbA1c, %: 7.6±1.7 Creatinine (mg/dL): 0.95±0.36 24-hour urinary albumin, mg/d: 70.4x/÷7.5

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ko 2005 China	NR/NR/42	1/1/42

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Ko 2005 China	Valsartan vs enalapril: Creatinine (mg/dL): End of study: 0.94±0.38 vs 1.10±0.66; *P*=0.343 Percentage change: -3.4%±15.2% vs 55.5%±201.8%, *P*=0.190 24-hour urinary albumin, mg/d End of study: 39.3 x/÷ 6.6 vs 83.9 x/÷ 9.4; *P*=0.270 Percentage change: -6±11 vs -5±36; *P*=0.906 Spot urinary albumin creatinine ratio (mg/mmol): End of study: 4.6x/÷6.6 vs 12.8x/÷7.4 *P*=0.161 Percentage change: -8±131 vs 34±192, *P*=0.453 Regression of albuminuria: 2 (9.5%) vs 2 (10%); *P*=NR Microalbuminuria (baseline/end of study): 10 (45.5%)/8 (38.1%), *P*=0.977 vs 9 (45.0%)/9 (45.0%), *P*=0.663 Macroalbuminuria (baseline/end of study): 3 (13.6%)/3 (14.3%), *P*=0.361 vs 5 (25.0%)/6 (30.0%), *P*=0.235	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Ko 2005 China	Cough: enalapril=7 (35%) vs valsartan=0, *P*=0.003 Any adverse event: enalapril=9 (45.0%) vs valsartan=3 (13.6%), *P*=0.015	Total withdrawals: enalapril=0, valsartan=1 (4.5%); *P*=NR Withdrawals due to adverse events: None	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Lacourciere 2000 Canada	Parallel design Multicenter: 8 clinical centers	Inclusion: Male and female outpatients with type 2 diabetes mellitus diagnosed at 30 years of age or later, mild to moderate essential hypertension (sitting DBP 90 to 115 mm Hg) and early nephropathy characterized by a UAE rate 20 to 350 μg/min without evidence of urinary tract infection Exclusion: Evidence or suspicion of renovascular disease, history of malignant hypertension, SBP > 210 mm Hg, cerebrovascular accident in the previous 12 months or current transient ischemia attacks, myocardial infarction within the previous 12 months, clinically significant arteriovenous (AV) conduction disturbances and/or arrhythmias, unstable angina, history of heart failure, serum creatinine ≥ 2.26 mg/dL, serum potassium ≥ 5.5 mmol/L or ≤ 3.5 mmol/L, drug or alcohol abuse, pregnancy, breast feeding, and ineffective contraception	Losartan 50 mg (mean=86.3 mg) Enalapril 5 mg (mean=16.0 mg) x 12 months Week 4: Losartan 50 mg maintained Enalapril 5 mg titrated to 10 mg if sitting DBP was > 85 mm Hg Week 8: Uncontrolled subjects (sitting DBP > 85 mm Hg) of both groups had medication doubled Week 12: Subjects with sitting DBP > 85 mm Hg were given add-on HCTZ 12.5 mg titrated to 25 mg Thereafter: Additional antihypertensive agents other than ACEI, AIIRA, or CCB were prescribed to achieve goal BP Week 20: Subjects with sitting DBP > 100 mm Hg were withdrawn

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Lacourciere 2000 Canada	Washout of current antihypertensive medications, other than beta blockers and nitrates was 7 days (14 days for ACE inhibitors) Run-in: 2- to 4-week, single-blind placebo run-period, at end of run-in, subjects with sitting DBP of 90 to 115 mm Hg and increased UAE were randomized	Excluded: oral corticosteroids, concomitant use of agents that may affect BP, except beta blockers and nitrates used in the treatment of stable angina	Albuminuria and GFR performed at weeks 4, 12, 28 and 52

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Lacourciere 2000 Canada	Age, years, mean (SD): Losartan=59.2 (9.2), Enalapril=57.8 (10.5) 81% male Caucasian: 99 (96%) Oriental=3 (3%) Black=1 (1%)	Losartan/enalapril, values mean (SD) unless otherwise noted: Weight, kg: 92.4 (17.2)/91.5 (19.8) Mean duration of diabetes, years: 9.2 (7.6)/12.6 (8.4, *P*=0.031 Mean age at diabetes diagnosis, years: 49.7 (10.7)/45 (10.6); *P*=0.039 Mean UAE, mg/day, geometric mean: 92.3/106.4

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Lacourciere 2000 Canada	NR/NR/103	11 (11%)/NR/98 (95%)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Lacourciere 2000 Canada	Losartan/enalapril at 52 weeks: Albuminuria, mg/day,: 59.8 vs 48.2; *P*=NS after adjustment for significant treatment-by-center interaction, unadjusted *P*=0.026 GFR, mL/min, % decline: 9% vs 9%; *P*=NS	Assessed by monitoring spontaneous reports of adverse experiences at each visit

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Lacourciere 2000 Canada	Total clinical adverse experiences: no significant differences, data NR Treatment-related cough: enalapril=14% vs losartan=0%, *P*=0.006	Withdrawals due to adverse events: losartan=2 (3.8%, dyspnea, urticaria) vs enalapril=1 (2.0%, cough), *P*=NR Overall withdrawals: losartan=6/52 (11.5) vs enalapril=5/51 (9.8%), *P*=NR	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Lim 2007 Singapore	Crossover design Single, secondary care institution Single-blind, all investigators/endpoint observers were blinded	Inclusion: Type 2 diabetes mellitus, diagnosed according to the American Diabetes Association Expert Committee recommendation in 1997; albuminuria, defined as urinary spot albumin over creatinine ratio of ≥ 30 mg/g on two separate occasions without concomitant confounding reasons such as urinary tract infection, congestive cardiac failure, febrile illness, uncontrolled blood glucose (HbA1c > 10%), and immediate postexercise period Exclusion: Previous treatment with ACE inhibitor or ARB, uncontrolled hypertension (SPB > 180 mm Hg or DBP > 105 mm Hg), uncontrolled dyslipidemia (triglycerides > 5 mM or total cholesterol > 8 mM), major diabetes complications such as bypass surgery for coronary artery disease or peripheral vascular disease, any other serious chronic disease requiring active treatment or women of child-bearing potential not using an effective form of birth control	Losartan 50 mg Quinapril 20 mg x 4 weeks

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Lim 2007 Singapore	Run-in NR Washout between periods of 4 weeks	Other antihypertensive agents including HCTZ, calcium channel blockers and beta blockers	Serum creatinine, urinary albumin/creatinine ratio

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Lim 2007 Singapore	Age, mean (SD): 52 (10) years 66% male 61% Chinese 34% Malays 5% Indian	Overall: Duration of diabetes, mean (SD): 8 (14) years Concomitant antihypertensive medications: None: 30 (73%) HCTZ: 2 (5%) Calcium channel blockers: 3 (7%) Beta blockers: 3 (7%) Dual agents (calcium channel blockers and beta blockers): 3 (7%) Losartan/Quinapril: Weight, kg: 73.1±18.1/74.0±17.3 HbA1c (%): 8.4±1.9/8.4±1.6 Serum creatinine, mg/dL: 0.86±0.20/0.86±0.23 Urinary albumin/creatinine ratio, mg/g: 471±153/550±170

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Lim 2007 Singapore	NR/NR/41	0/0/NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Lim 2007 Singapore	Losartan vs quinapril: Serum creatinine, mg/dL: 0.87±0.23 vs 0.87±0.21; *P*=NR Urinary albumin/creatinine ratio, mg/g: Endpoint value: 378±124 vs 501±146; *P*=NR Reduction, mean±SE: -93±82 vs -49±65, *P*=0.025	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Lim 2007 Singapore	Overall adverse events: NR Increase in serum potassium, mM, before/after: 4.3±0.4/4.4±0.4, *P*=NR vs 4.2±0.4/4.4±0.4, *P*=0.01	Overall withdrawals=0 Withdrawals due to adverse events=0	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Matos 2005 Brazil	Crossover design Single center Open-label	Inclusion: age > 40 years; SBP > 140 mm Hg or any value if currently using antihypertensive drugs; proteinuria ≥ 0.5 mg/24h and < 3.0 g/24h; creatinine clearance ≥ 40 mg/min/1.73 m^2; serum potassium < 5.0 mEq/l, no evidence of cause other than diabetes for the renal involvement Exclusion: malignant hypertension; uncontrolled glycemia (HbA1c ≥ 9%), recurrent urinary tract infection, severe peripheral vascular disease, stroke or myocardial infarction within the previous 6 months, and previous side effects associated with any drug class to be used, but mainly intolerance to ACEI	Perindopril 8 mg, Irbesartan 300 mg, or combination of the above x 16 weeks

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Matos 2005 Brazil	Run-in: 8 weeks for adjustment to glycemic control and substitution of antihypertensives for diuretics, clonidine, and/or hydralazine Washout: 4 weeks between periods	All patients received diuretics throughout the study (HCTZ 25-50 mg or furosemide 40-160 mg); hydralazine 100-200 mg and clonidine 0.2-0.6 mg were sequentially introduced to maintain BP under 140/90 by end of run-in period	Primary endpoint/sample size calculation: Reduction in proteinuria Other endpoints: creatinine, GFR evaluated at baseline and at the end (week 16) of each treatment period

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Matos 2005 Brazil	Age, years, median (range): 54 (40-73) 25% male 50% white 50% nonwhite	Values are expressed as median (range) or frequency, unless otherwise noted: Years of diabetes diagnosis: 11 (1 to 20) Years of hypertension diagnosis: 10 (1 to 30) Retinopathy (proliferative/nonproliferative/none): 7 (35%) /10 (50%) /3 (15%) BMI, kg/m2: 30 (24 to 39) Smoker (yes/no): 1 (5%)/19 (95%) Proteinuria (g/24h): 0.9 (0.5 to 2.2) GFR, ml/min/1.73 $m^{2,}$ mean±SEM: 67±7 Additional hypotensive drugs, %, perindopril vs irbesartan vs dual therapy, start/end None: 0/6.7 vs 6.7/6.7 vs 6.7/6.7 Diuretic: 53.3/40.0 vs 33.0/40.0 vs 40.0/53.3 Hydralazine+diuretic: 6.7/6.7 vs 13.3/6.7 vs 6.7/6.7 Clonidine+diuretic: 6.7/13.3 vs 13.3/6.7 vs 13.3/0 Hydralazine+clonidine: 33.0/33.0 vs 33.0/40.0 vs 33.0/33.0

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Matos 2005 Brazil	NR/NR/20	5 (25%)/0/NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Matos 2005 Brazil	Perindopril vs irbesartan vs combined therapy: Proteinuria, mg/d, geometric mean (95% CI) Start/endpoint: 829 (537-1280)/545 (288-1029) vs 996 (686-1445)/773 (478-1248) vs 966 (681-1369)/644 (393-1085) % change: -34% (-53% to -9%) vs -22% (-45% to 9%) vs -33% (-49% to -12%); *P*=NS GFR, ml/min/1.73 m2, mean±SEM: 64±7 vs 67±6 vs 64±6, P=NR Creatinine, mg/dl, start/end: 1.1±0.1/1.2±0.1 vs 1.2±0.1/1.2±0.1 vs 1.1±0.1/1.2±0.1, *P*=NR	Hyperkalemia: data were censored by the end of treatment period of when a potassium-restricted diet was indicated (last value carried forward)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Matos 2005 Brazil	None reported	Total withdrawals: NR for each group separately Withdrawals due to hyperkalemia (# patients): perindopril=0, irbesartan=1, combined therapy=1	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Mogensen 2000 Australia, Denmark, Finland, Israel	Multicenter Double-blind Parallel	Inclusion: Type 2 diabetes, aged between 30 and 75, previously diagnosed hypertension and microalbuminuria (urinary albumin creatinine ratio 2.5 to 25 mg/mmol); DBP 90 to 110 mm Hg after two and four weeks of placebo, respectively Exclusion: BMI ≥ 40 kg/m2; SBP > 200 mm Hg; non-diabetic cause of secondary hypertension; cardiovascular event in the past six months: serum creatinine concentration ≥ 130 x6dmol/l in women and ≥ 150 x6d mol/l in men; serum potassium concentration > 5.5 mmol/l; glycated hemoglobin concentration (HbA1c) > 10%, pregnancy or potential pregnancy and breast feeding	Group 1: Candesartan 16 mg x 24 weeks Group 2: Lisinopril 20 mg x 24 weeks Group 3: Candesartan 16 mg x 12 weeks, then combination therapy with candesartan 16 mg/lisinopril 20 mg x 12 weeks Group 4: Lisinopril 20 mg x 12 weeks, then combination therapy with candesartan 16 mg/lisinopril 20 mg x 12 more weeks

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Mogensen 2000 Australia, Denmark, Finland, Israel	Run-in: 4 weeks of placebo treatment Washout: NR	HCTZ 12.5 mg once daily: Candesartan (group 1)=6 (10.6%) vs lisinopril (group 2)=6 (9.4%) vs combination (groups 3 and 4): 6 (8.9%)	Albumin: Creatinine ratio

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Mogensen 2000 Australia, Denmark, Finland, Israel	Age, years, mean ± SD: candesartan=59.7±9.9, lisinopril=59.9 (9.0), combination=59.8±8.7 65.0% male Ethnicity NR	Candesartan (group 1) vs lisinopril (group 2) vs combination (groups 3 and 4): BMI, kg m^2: 31.0±4.2 vs 29.6±3.7 vs 30.2±4.2 Duration of hypertension, years: 8.3±8.9 vs 7.9±8.1 vs 9.7±9.3 Duration of diabetes, years: 10.0±7.7 vs 8.3±7.0 vs 9.1±7.7 Urinary albumin: creatinine ratio, mg/mmol: 7.2±1.1 vs 5.9±1.2 vs 5.6±1.1 Serum creatinine, mg/dl: 1.0±0.2 vs 1.0±0.2 vs 0.9±0.2 Creatinine clearance, µmol/l: 103.5±38.4 vs 96.8±28.9 vs 98.4±32.9

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Mogensen 2000 Australia, Denmark, Finland, Israel	NR/NR/199	55 (27.6%)/ NR/144 (72.4%)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Mogensen 2000 Australia, Denmark, Finland, Israel	Adjusted mean reduction in urinary albumin: creatinine ratio, % (95% CI), adjusted for center, treatment, baseline value, weight, and DBP change: candesartan= -24% (0 to -43%), lisinopril= -39% (-20% to -54%), combination= -50% (-36% to -61%) Adjusted mean difference: combination vs candesartan: -34% (-3% to -55%), *P*=0.04; combination vs lisinopril= -18% (+20 to -44%), *P*=NS	Tolerability was assessed by using spontaneously reported adverse events, recorded in response to an open question or observed by the investigator at each visit

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Mogensen 2000 Australia, Denmark, Finland, Israel	"Slight increases of doubtful clinical significance" of potassium in the combination group, mean: +0.30 mmol/l Decrease in creatinine clearance, mean, ml/sec: lisinopril= -0.835, combination= -0.0735, candesartan= not affected	Candesartan vs lisinopril vs combination therapy Overall withdrawals, n (% patients): 17 (25.7%) vs 18 (28.1%) vs 18 (26.9%) Withdrawals due to any adverse event: 2 (3.0%) vs 5 (7.8%) vs 1 (1.5%) Withdrawal due to dizziness, feeling weak or both: 2 (3.0%) vs 2 (3.1%) vs 1 (1.5%) Discontinuation due to cough: 0 vs 3 (4.7%) vs 0	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Muirhead N, 1999 Canada	RCT (double-blind, parallel-group) Multicenter (4 centers in Canada)	Inclusion: ≥18 years of age; type 2 diabetes mellitus and incipient diabetic neuropathy (defined as an albumin excretion rate between 20 and 300 μg.min with GFR ≥60 mL/min per 1.73 m^2 at visit 1); women of childbearing potential using an effective method of birth control not based on estrogen/progesterone; patients being treated with ACE inhibitors or calcium channel blockers provided they discontinued treatment for at least 28 days before randomization Exclusion: Patients with "brittle" diabetes or a history of noncompliance with medical regimens; patients who experienced symptomatic hypotension, who progressed to hypertension, or who experienced serious adverse experiences were discontinued from the trial	Valsartan 80 mg 1x/day Valsartan 160 mg 1x/day Captopril 25mg 3x/day Placebo 52 weeks

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Muirhead N, 1999 Canada	Washout: 28 day washout period for patients receiving ACE inhibitors of calcium channel blockers Run-in: NR	Glycemic control was maintained during the study by means of the patients' customary treatment Use of antihypertensive medication (except diuretics and beta-blockers), estrogen replacement therapy, or thyroid medication <6 months before entry into the trial was prohibited.	Patients were assessed clinically at baseline and at 6, 12, 26, 38, and 52 weeks of treatment AER and GFR were assessed at baseline and after 12, 26, 38, and 52 weeks of treatment AER was measured from a 24-hour urine sample by means of a radioimmunoassay, and GFR was determined by measuring the clearance of ^{99}Tc DTPA

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Muirhead N, 1999 Canada	Valsartan 80mg/Valsartan 160mg/Captopril/Placebo Age (years): 53.7±9.5/58.3±9.5/56.7±10.0/55.5±11.3 Gender (%male): 71.0/58.1/72.4/90.3 Ethnicity (%): White: 87.0/100.0/82.8/90.3 Black: 0/0/3.4/0 Asian: 6.5/0/6.9/3.2 Other: 6.5/0/6.9/6.5	Valsartan 80mg/Valsartan 160mg/Captopril/Placebo Body weight (kg): 97.8±20.2/96.7±25.0/89.1±16.7/93.6±18.7 Antihypertensive medication use (% yes): 32.3/29.0/37.9/54.8 AER (μg/min): 60.5/58.1/40.9/64.0 GFR (mL/min per 1.73m^2): 101.5/83.1/88.1/86.7

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Muirhead N, 1999 Canada	NR/NR/122	19/NR/103

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Muirhead N, 1999 Canada	Geometric means of change from baseline in AERs (μg/min) for the intent-to-treat population (all randomized patients with at least 1 post baseline AER measurement): Valsartan 80mg/Valsartan 160mg/Captopril/Placebo Baseline: 60.0/58.1/40.9/63.3 End point: 43.3/45.8/30.1/74.8 End point/baseline ratio: 0.72/0.79/0.73/1.18 Geometric means of change from baseline in GFRs (mL/min per 1.73 m^2) for the intent to treat population: Valsartan 80mg/Valsartan 160mg/Captopril/Placebo Baseline: 102.4/83.1/89.5/83.2 End point: 95.0/74.3/89.9/76.8 End point/baseline ratio: 0.927/0.894/1.005/0.923 Contrast between treatments for the end point/baseline ratio in AERs for the intent-to-treat population: Contrast mean/95% CI/P-value Valsartan 80mg vs Placebo: 0.593/0.386 to 0.911/0.018 Valsartan 160mg vs Placebo: 0.652/0.431 to 0.986/0.043 Captopril vs Placebo: 0.566/0.370 to 0.868/0.009 Valsartan 80mg vs Captopril: 1.048/0.681 to 1.612/0.831 Valsartan 160mg vs Captopril: 1.151/0.760 to 1.743/0.503	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Muirhead N, 1999 Canada	Valsartan 80mg/Valsartan 160mg/Captopril/Placebo Patients with AEs (%): 80.6/87.1/96.6/82.8 Patients with trial-drug related AEs (%): Patients with ≥1 trial-drug related AE: 9.7/22.6/34.5/13.8 Dry cough: 3.2/9.7/20.7/3.4 Diarrhea: 0/3.2/3.4/0 Dizziness: 0/0/10.3/3.4 Dyspepsia: 0/0/3.4/0 Gastrointestinal disorder: 3.2/0/0/0 Headache: 0/3.2/0/3.4 Postural hypotension: 3.2/0/0/0 Migraine: 0/0/0/3.4 Nausea: 0/3.2/0/3.4 Pyuria: 3.2/0/0/0 Upper respiratory tract infection: 0/0/3.4/0 Vertigo: 0/0/3.4/0 Abnormal vision: 0/3.2/0/0	19/4 (1 aneurysm/cerebrovascular disorder in the valsartan 80mg group; 1 uncontrolled hypertension in the valsartan 160mg group; 1 bolt hemorrhages and 1 dry cough in the captopril group)	

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Parving 2008 International AVOID	Multinational Randomized Double-blind	Inclusion: Patients with hypertension who were 18 to 85 years of age and who had type 2 diabetes and nephropathy (defined by an early-morning urinary albumin-to-creatinine ratio of >300 mg/g or >200 mg/g in patients receiving therapy targeted at blockade of the renin-angiotensin-aldosterone system) Exclusion: Nondiabetic kidney disease, a urinary albumin-to-creatinine ratio of more than 3500 mg/g, an eGFR rate of < 30 mg/min/1.73 m^2, chronic urinary tract infection, a serum potassium level > 5.1 mmol/l, severe hypertension, major cardiovascular disease within the previous 6 months	Aliskiren 150 mg x 3 months, then 300 mg x 3 more months OR Placebo

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Parving 2008 International AVOID	Run-in: 3-month discontinuation of all renin angiotensin aldosterone system blocking drugs, except for beta blockers and open-label losartan 100 mg was initiated plus additional antihypertensive therapy aimed at achieving a target BP of < 130/80 mm Hg Washout: NR	Antihypertensive drugs received during double-blind period, aliskiren vs placebo, n (% patients): Calcium channel blocker: 157 (52.2%) vs 180 (60.4%) Beta blocker: 109 (36.2%) vs 121 (40.6%) Thiazide diuretic: 99 (32.9%) vs 102 (34.2%) Loop diuretic: 93 (30.9%) vs 99 (33.2%) Alpha-blocker: 46 (15.3%) vs 38 (12.8%) Centrally acting agent: 28 (9.3%) vs 21 (7.0%) Angiotensive receptor blocker: 1 (0.3%) vs 0 Angiotensin converting enzyme inhibitor: 0 vs 0	Primary endpoint: Percentage reduction in the early-morning urinary albumin-to-creatinine ratio from baseline to the end of the study (24 weeks) Other endpoints: Reduction of 50% or more in albuminuria, mean rate of decline in eGFR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Parving 2008 International AVOID	Aliskiren vs placebo: Age, years: 59.8±9.6 vs 61.8±9.6, *P*=0.009 71.2% male 86.8% White 8.3% Black 1.8% Asian 3.0% Other	Aliskiren vs placebo: BMI, kg/m2: 33±7 vs 32±6 Known duration of diabetes, years: 13.2±8.4 vs 14.9±8.7, *P*=0.02 Medical History, n (% patients): Angina: 24 (8%) vs 20 (6.7%) Coronary artery disease: 24 (8.0%) vs 25 (8.4%) Myocardial infarction: 19 (6.3%) vs 15 (5.0%) Stroke: 9 (3%) vs 12 (4%) Diabetic neuropathy: 55 (18.3%) vs 49 (16.4%) Diabetic retinopathy: 65 (21.6%) vs 82 (27.5%) Dyslipidemia: 74 (24.6%) vs 72 (24.2%) Current smoking: 61 (20.3%) vs 53 (17.8%) Urinary albumin-to-creatinine ratio, geometric mean (95% confidence interval): 513 (463-569) vs 553 (502-609) Urinary albumin excretion rate, µg/min: geometric mean (95% confidence interval): 495 (440-557) vs 520 (469-576) Serum creatinine Men: 1.3±0.5 vs 1.3±0.4 Women: 1.1±0.4 vs 1.1±0.5 Estimated GFR, ml/min/1.73 m^2: 68.5±25.7 vs 66.8±24.5 Serum potassium, mmol/l: 4.5±0.5 vs 4.5±0.5

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Parving 2008 International AVOID	1892/805 entered run-in/599 randomized	75 (12.5%)/1 (0.01%)/599

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Parving 2008 International AVOID	Overall percentage reduction in the early-morning urinary albumin-to-creatinine ratio for aliskiren vs placebo: -20% (95% confidence interval -9% to -30%), *P*<0.001 - After adjustment for change in SBP: -18% (95% CI, -7% to -28%), *P*=0.002 - No differences among subgroups based on sex, race, age (below vs at or above median), urinary albumin-to-creatinine ratio (below vs at or above median), eGFR (below vs at or above median), SBP or DPB (below vs at or above median), or glycated hemoglobin (below vs at or above median) Reduction of 50% or more in albuminuria, % patients: aliskiren=24.7% vs placebo=12.5%, *P*<0.001 Mean rate of decline in eGFR, ml/min/1.73 m2: aliskiren= -2.4 (95% CI -1.1 to -3.7) vs placebo= -3.8 (95% CI -2.5 to -5.1), *P*=0.07	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Parving 2008 International AVOID	Aliskiren vs placebo, n (% patients), *P*=NR for all, except where indicated Overall adverse events: 201 (66.8%) vs 200 (67.1%) Any serious adverse event: 27 (9.0%) vs 28 (9.4%) Death: 0 vs 2 (0.7%) Serious adverse events occurring in > 1 patient: Pneumonia: 2 (0.7%) vs 3 (1.0%) Peripheral edema: 2 (0.7%) vs 1 (0.3%) Congestive heart failure: 2 (0.7%) vs 1 (0.3%) Limb abscess: 2 (0.7%) vs 0 Gastroenteritis: 2 (0.7%) vs 0 Acute renal failure: 2 (0.7%) vs 0 Angina pectoris 1 (0.3%) vs 2 (0.7%) Cellulitis: 1 (0.3%) vs 2 (0.7%) Adverse events in ≥ of either group: Headache: 18 (6.0%) vs 11 (3.7%) Nasopharyngitis: 18 (6.0%) vs 15 (5.0%) Dizziness: 15 (5.0%) vs 10 (3.4%) Hyperkalemia: 15 (5.0%) vs 17 (5.7%) Peripheral edema: 13 (4.3%) vs 23 (7.7%) Hypotension: 12 (4.0%) vs 3 (1.0%) Diarrhea: 9 (3.0%) vs 8 (2.7%) Influenza: 9 (3.0%) vs 7 (2.3%) Nausea: 8 (2.7%) vs 5 (1.7%) Gastroenteritis: 7 (2.3%) vs 1 (0.3%) Cough: 5 (1.7%) vs 7 (2.3%) Serum potassium <3.5 mmol/l: 15 (5.0%) vs 11 (3.7%) > 5.5 mmol/l: 41 (13.7%) vs 32 (10.8%) ≥ 6.0 mmol/l: 14 (4.7%) vs 5 (1.7%), *P*=0.06	Aliskiren vs placebo Total withdrawals: 42 (13.9%) vs 33 (11.1%) Withdrawal due to adverse event: 17 (5.6%) vs 19 (6.4%) Withdrawal due to serious adverse event: 9 (3.0%) vs 8 (2.7%)	Other adverse events reported in ≤ 2% available in Table 3 of publication

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Study Design Setting	Inclusion/Exclusion Criteria	Interventions Duration
Song 2006 Korea	Crossover design Multicenter Double-blind	Inclusion: Type 2 diabetes, defined by WHO criteria; overt nephropathy, already been administered either 5 mg or more of ramipril or 8 mg or more of candesartan without complications; 24-h urinary protein excretion rate > 1.0 g/24h; creatinine clearance 30 to 59 ml/min/1.73 m2; blood pressure maintained at < 140/90 mmHg with or without additional antihypertensives for at least 3 months prior to the study Exclusion: history of noticeable side effects or hypersensitivity to ACE inhibitors or ARBs, age < 18 years, pregnant women, serum potassium > 5.5 mmol/l, absence of retinopathy, presence of nondiabetic renal disease, renal artery stenosis, type IV renal tubular acidosis, morbid cardiac, vascular diseases or malignancy, or uncontrolled diabetes	Ramipril 10 mg, Candesartan 16 mg, or combination of ramipril 5 mg plus candesartan 8 mg x 16 weeks
Tutuncu 2001 Turkey	Parallel design Single center (Clinic) Blinding : NR	Inclusion: Normotensive type 2 diabetic patients with documented microalbuminuria defined as urinary albumin excretion of 30-3000 mg/day or 20-200mg/min in at least 3 consecutive 24-hour urinary albumin excretion determinations Exclusion-: Type 1 diabetes, hypertension, secondary diabetes, thyroid disease, alcoholism, renal insufficiency not related to diabetes, chronic liver disease, overt carcinoma and treatment with insulin	Enalapril 5mg Losartan 50mg Combination of enalapril and losartan 12 months

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Song 2006 Korea	Run-in: 8 weeks to ensure the safety of ramipril or candesartan and the efficacy of the agents in maintaining BP within the goal of <140/80 mmHg Wash-out: 8 weeks between treatment periods	Other antihypertensive drugs, including calcium channel blockers, alpha or beta blockers and/or diuretics were added if necessary to achieve the BP goal during the study period	Serum creatinine, serum albumin, creatinine clearance, 24-h urinary protein excretion
Tutuncu 2001 Turkey	Run-in: NR Washout: NR	NR	HBA1c, lipid profile, blood pressure, urinary albumin excretion rates At 3 month intervals for 12 months

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Age Gender Ethnicity	Other population characteristics; values are given as mean ± SD, unless otherwise noted
Song 2006 Korea	Age, years: 49±8 52% male 100% Korean	BMI, kg/m2: 21.0±2.4 Duration of diabetes, years: 8±3 24-h urinary protein excretion, g/24-h: 42.±2.1 Duration of ramipril or candesartan, months: 11±5 Creatinine, mg/dl: 1.8±0.2 Albumin, g/dl: 3.0±0.4 Creatinine clearance, ml/min/1.73 m^2: 40.6±4.1 24-h urinary protein excretion, g/24-h: 4.1±1.9 Total number of antihypertensives, 1/2/3/4/5, # patients (%): 5 (24%)/7(33%)/5 (24%)/3 (14%)/1 (5%) Antihypertensives, # patients (%): Diuretics: 9 (43%) Calcium channel blockers: 12 (57%) Beta Blockers: 6 (28%) Alpha antagonists: 4 (19%)
Tutuncu 2001 Turkey	Age, years: 55.6 Gender: NR Ethnicity: NR	Enalapril 5mg (Group 1) Losartan 50mg (Group 2) Combination of enalapril and losartan (Group 3) Group 1 vs Group 2 vs Group 3 BMI, kg/m (SD): 30.27 (3.84) vs 28.32 (3.27) vs 28.15(1.59) Duration of diabetes, years (SD): 7.75(6.39) vs 6.9(5.02) vs 8.44(5.44) Retinopathy: 2 (5.8%) vs 1 (2.9%) vs 0 (0%) Neuropathy: 0 (0%) vs 2 (5.8%) vs 1 (2.9%) Coronary heart disease: 2(5.8%) vs 1 (2.9%) vs 0 (0%) HbA1c % (beginning of study): 7.63 (0.86) vs 7.75 (0.88) vs 7.49 (0.89) Mean daily blood pressure mmHg (beginning of study): 115/75 (8/1) vs 115/80(7/2) vs 120/75 (6/1)

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Song 2006 Korea	NR/NR/25	4 (16%)/0/21
Tutuncu 2001 Turkey	NR/NR/37	3/NR/34

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Results, values are given as mean±SD or geometric mean (range), unless otherwise noted	Method of adverse events assessment
Song 2006 Korea	Ramipril 10 mg vs candesartan 16 mg vs combination therapy (ramipril 5 mg plus candesartan 8 mg) Creatinine, mg/dl: 1.9±0.2 vs 1.9±0.2 vs 1.9±0.3, *P*=NR Albumin, g/dl: 3.0±0.4 vs 3.1±0.4 vs 3.1±0.4, *P*=NR Creatinine clearance, ml/min/1.73 m^2: 40.7±5.3 vs 39.0±7.1 vs 39.2±6.1, *P*=NR 24-h urinary protein excretion, g/24-h: 3.5±1.8 vs 3.3±2.0 vs 2.9±1.4, *P*<0.05 for combination therapy vs ramipril and candesartan single therapy	NR
Tutuncu 2001 Turkey	Group 1 vs Group 2 vs Group 3 % of patients with normalization of UAER (<30mg/day) 83.3% vs 66.6% vs 70%, p=NS among 3 groups at baseline or end of study	NR

Evidence Table 20. Data abstraction of diabetic nephropathy trials

Author Year Country Trial Name (Quality Rating)	Adverse Events Reported	Total withdrawals; withdrawals due to adverse events	Comments
Song 2006 Korea	Ramipril 10 mg vs candesartan 16 mg vs combination therapy (ramipril 5 mg plus candesartan 8 mg), *P*=NR for all events Any adverse events: 3 (14.3%) vs 4 (19.0%) vs 4 (19.0%) Hypotension: 0 vs 1 (4.8%) vs 2 (9.5%) Malaise/fatigue: 0 vs 1 (4.8%) vs 0 Abnormal vision: 0 vs 0 vs 0 Hyperkalemia (> 6.0 mEq/l): 1 (4.8%) vs 0 vs 2 (9.5%) Azotemia (change in serum creatinine > 30%): 1 (4.8%) vs 2 (9.5%) vs 0 Cough: 1 (4.8%) vs 0 vs 0 Allergic reaction: 0 vs 0 vs 0 GI trouble: 0 vs 0 vs 0	Total withdrawals: NR for each group separately Withdrawals due to adverse events: Ramipril=1 (5%) vs candesartan=1 (5%), *P*=NR	
Tutuncu 2001 Turkey	None of the subjects experienced any drug related AE including cough, hypoglycemia, hypotension, dizziness, fatigue or malaise	NR, NR	

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	If no, explain	Inclusion criteria specified?
Andersen 2000	Method not described	Method not described	NR		Yes
Barnett 2004	Method not described	Yes	Yes		Yes
Cetinkaya 2004	Method not described	Method not described	NR		Yes
Deyneli 2006	Yes	No	Unclear	U group creatine clearance 102.6 vs. 115.9 for L group; UNAG 10.4 vs. 7.7. No analysis provided	Yes
Igarashi 2006	No	Method not described	Yes		Yes
Jacobsen 2003 (Dual blockade)	Method not described	Yes	NR		Yes

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Exclusion criteria specified?	Were outcome assessors blinded?	Were the care providers blinded?	Were the patients blinded?	Was attrition reported?	Were crossovers reported?	Was adherence reported?	Was contamination reported?	How were potential carry-over effects handled in crossover trials?
Andersen 2000	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	No	No	analysis
Barnett 2004	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	No	No	No	washout
Cetinkaya 2004	No	NR	NR	NR	No	No	No	No	none
Deyneli 2006	Yes	NR	No	No	Yes	No	Yes	No	none
Igarashi 2006	Yes	NR	NR	NR	Yes	No	No	No	none
Jacobsen 2003 (Dual blockade)	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	Yes	No	analysis

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Were overall withdrawals high or differential?	If yes, describe	Was loss to follow up high or differential?	If yes, describe	Did the article report an ITT, or provide sufficient data to calculate it?	If not, describe	Were there any post-randomization exclusions?	If yes, describe
Andersen 2000	No		No		Yes		No	
Barnett 2004	Yes	Overall withdrawal rate of 33% (82/250)	No		No	Excluded 14% (34/250) from LOCF analysis	No	
Cetinkaya 2004	Unable to determine		Unable to determine		Unable to determine		Unable to determine	
Deyneli 2006	No		No		No	Excluded 2/26 (8%)	No	
Igarashi 2006	No		No		Unable to determine		No	
Jacobsen 2003 (Dual blockade)	No		No		Yes		No	

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	What was the funding source?	Overall Rating
Andersen 2000	Merck	Fair
Barnett 2004	Boehringer	Fair
Cetinkaya 2004	NR	Poor
Deyneli 2006	Turkish Diabetes Foundation	Fair
Igarashi 2006	None declared	Fair
Jacobsen 2003 (Dual blockade)	P. Carl Petersens Foundation, Danish Diabetes Association, Sanofi-Synthelabo	Good

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	If no, explain	Inclusion criteria specified?
Jacobsen 2003 (Additive effect…)	Yes	Yes	NR		Yes
Ko 2005	Method not described	No	Yes		Yes
Lacourciere 2000	Method not described	Method not described	No	Losartan group: higher diastolic blood pressure and shorter duration of diabetes with diagnosis of diabetes at later age	Yes
Lim 2007	Method not described	Method not described	Yes		Yes
Matos 2005	Method not described	Method not described	NR		Yes

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Exclusion criteria specified?	Were outcome assessors blinded?	Were the care providers blinded?	Were the patients blinded?	Was attrition reported?	Were crossovers reported?	Was adherence reported?	Was contamination reported?	How were potential carry-over effects handled in crossover trials?
Jacobsen 2003 (Additive effect…)	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	Yes	No	analysis
Ko 2005	Yes	NR	NR	NR	Yes	No	No	No	washout
Lacourciere 2000	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	No	No	none
Lim 2007	Yes	Yes	No	No	Yes	No	No	No	washout
Matos 2005	Yes	NR	No	No	Yes	No	Yes	No	washout

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Were overall withdrawals high or differential?	If yes, describe	Was loss to follow up high or differential?	If yes, describe	Did the article report an ITT, or provide sufficient data to calculate it?	If not, describe	Were there any post-randomization exclusions?	If yes, describe
Jacobsen 2003 (Additive effect…)	No		No		No		No	
Ko 2005	No		No		Yes		No	
Lacourciere 2000	No		No		No	Excluded 5 (5%)	No	
Lim 2007	No		No		Unable to determine		No	
Matos 2005	Yes	5/20 (25%) withdrawn	No		Unable to determine		No	

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	What was the funding source?	Overall Rating
Jacobsen 2003 (Additive effect…)	P. Carl Petersens Foundation, Danish Diabetes Association, Novartis	Fair
Ko 2005	NR	Fair
Lacourciere 2000	Merck	Fair
Lim 2007	Investigator-initiated, with no industry support	Fair
Matos 2005	Center of Studies Americo Piquet Carneiro, a non-profile organization, not related to the pharmaceutical industry	Poor

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	If no, explain	Inclusion criteria specified?
Mogensen 2000	Method not described	Method not described	Yes		Yes
Muirhead 1999	Method not described	Method not described	No	(1) fewer females in placebo group (8%) compared to valsartan 80 mg (29%), valsartan 160 mg (42%) and captopril 28%); (2) lower albumin excretion rate (µg/min) for captopril (40.9) compared to valsartan 80 mg (60.5), valsartan 160 mg (58.1) and placebo (64.0)	Yes
Parving 2008	Yes	Method not described	Yes		Yes
Song 2006	Method not described	Method not described	NR		Yes
Tutuncu 2001	Method not described	Method not described	Yes		Yes

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Exclusion criteria specified?	Were outcome assessors blinded?	Were the care providers blinded?	Were the patients blinded?	Was attrition reported?	Were crossovers reported?	Was adherence reported?	Was contamination reported?	How were potential carry-over effects handled in crossover trials?
Mogensen 2000	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	No	No	none
Muirhead 1999	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	No	No	N/A
Parving 2008	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	No	No	none
Song 2006	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	No	No	washout
Tutuncu 2001	Yes	NR	NR	NR	Yes	No	No	No	NR

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	Were overall withdrawals high or differential?	If yes, describe	Was loss to follow up high or differential?	If yes, describe	Did the article report an ITT, or provide sufficient data to calculate it?	If not, describe	Were there any post-randomization exclusions?	If yes, describe
Mogensen 2000	Yes	55 (27.6%) withdrew at 12 week visit, mostly due to DBP was below 80 mm Hg	No		No	Excluded 55/199 (27.6%)	No	
Muirhead 1999	Yes	Overall=16%; valsartan 80 mg=23%, valsartan 160 mg=3%, captopril=14%, placebo=23%	No		No	Excluded 7/122 (6%)	No	
Parving 2008	No		No		Unable to determine		No	
Song 2006	No		No		No	Excluded 4/25 (16%)	No	
Tutuncu 2001	No		No		No	Excluded 3/37 (8%)	No	

Evidence Table 21. Quality assessment of diabetic nephropathy trials

Author	What was the funding source?	Overall Rating
Mogensen 2000	AstraZeneca	Fair
Muirhead 1999	Novartis	Poor
Parving 2008	Novartis	Fair
Song 2006	NR	Fair
Tutuncu 2001	NR	Fair

Evidence Table 22. Evidence profile of diabetic nephropathy trials: Losartan compared with enalapril in adults

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Overall withdrawals								
Andersen 2000 N=16	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Moderate
Lacourciere 2000 N=103	RCT	Fair					NSD between groups	
Deyneli 2006 N=26	RCT	Fair					NSD between groups	
Albumin								
Andersen 2000 N=16	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Low
Deyneli 2006 N=26	RCT	Fair					NSD between groups	
GFR								
Andersen 2000 N=16	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Low
Lacourciere 2000 N=103	RCT	Fair					NSD between groups	
Serum creatinine								
Andersen 2000 N=16	RCT	Fair	Consistent	Direct	Imprecise	None	NSD between groups	Low
Cetinkaya 2004 N=22	RCT	Poor					NSD between groups	
Deaths or cardiovascular events								
Deyneli 2006 N=26	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	Very Low
Creatinine clearance								
Deyneli 2006 N=26	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	Very Low
Regression of microalbuminuria to normoalbuminuria								
Tutuncu 2001 N=34	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	Very Low

Evidence Table 22. Evidence profile of diabetic nephropathy trials: Losartan compared with enalapril in adults

Quality Assessment							Summary of Findings	
Study	Design	Quality	Inconsistency	Indirectness	Imprecision	Other considerations	Results by study, Relative effect	Quality of the evidence for each outcome
Proteinuria								
Cetinkaya 2004 N=22	RCT	Poor	N/A	Direct	Imprecise	None	NSD between groups	Very Low
Cough								
Lacourciere 2000 N=103	RCT	Fair	N/A	Direct	Imprecise	None	Significantly lower incidence with losartan	Very Low
Overall adverse events								
Lacourciere 2000 N=103	RCT	Fair	N/A	Direct	Imprecise	None	NSD between groups	Very Low

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Design	Total N Subject recruitment	Inclusion criteria	F/U period	Setting	Population Age (mean (SD) Sex (% female) Race/ethnicity	Intervention drug
ACE-I							
Captopril							
Chalmers 1992 Scotland	Single-group cohort, open label, post-marketing	67698 GPs report information on all their patients on captopril for HT; post-marketing surveillance	Patients on captopril for HT	Median F/U 6m Total 39,635 pt-years	General practice	HT Age: 60.4 (11.3) y 57% female	Captopril, dosage NR
Gonzalez-Perez 2004 Sweden	Cohort with nested case-control	3708 breast cancer cases; 18478 controls; total on ACE about 1000 Subjects and controls from National Practitioner Database in UK	Females 30-79 years of age; had computerized prescription at least 1y prior to entry; incident cases of breast cancer from database also	NR (NR how long (recruitment period 1/1995-12/2001)	GP offices	HT Age: NR	Captopril, enalapril, lisinopril Dosages NR

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Other allowed HT medications	Total withdrawals Withdrawals due to AEs	AE assessment	Adverse events
ACE-I				
Captopril				
Chalmers 1992 Scotland	NA	75% of patients completed the study WD due to AEs: 8.2%	GPs reported AEs to a centralized agency	Angioedema: 16 pts; after median 28d (7-306) Hypotension: 2.8/1000 (more common in >70y) Heamatological disorders: 15 pts WD due to heam disorders; 11 leucopenia; 4 thrombocytopenia; none persisted after WD; several cases had other likely causes Liver disease: 9 patients WD; all had other likely causes; 3 deaths from liver failure (not suspected to be related to drug) Deaths: 1.1%; this rate was 80% of expected rate (in general populations) and 4% more than expected rate of CV deaths in general populations Renald failure: listed as cause in 21 deaths; all had underlying disease
Gonzalez-Perez 2004 Sweden	NR	NA (case-control)	Incident cases of breast cancer, validated approach from UK database	Incidence breast cancer among current users of ACE-I vs non-users: Captopril Usage <2y: OR 1.1 (95% CI, 0.6 to 2.0) Usage >2y: OR 0.8 (95% CI, 0.5 to 1.3) Enalapril Usage <2y: OR 0.9 (95% CI, 0.6 to 1.4) Usage >2y: OR 0.7 (95% CI, 0.5 to 1.1) Lisinopril Usage <2y: OR 0.8 (95% CI, 05 to 1.2) Usage >2y: OR 0.7 (95% CI, 0.7 to 1.6)

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	AEs among subgroups	Comments
ACE-I		
Captopril		
Chalmers 1992 Scotland	WD rates were higher in >70y and in females (10.4% in females >70y)	
Gonzalez-Perez 2004 Sweden	NR	Incidence breast cancer among users of anti-HT drugs vs non-users: OR 1.0 (95% CI, 0.9 to 1.1)

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Design	Total N Subject recruitment	Inclusion criteria	F/U period	Setting	Population Age (mean (SD) Sex (% female) Race/ethnicity	Intervention drug
DeBianco 1991 US	Single-group cohort, open label, prospective	6669 with data (7658 started the trial) Data from a trial; subjects apparently selected by participating GPs	Inclusion criteria: >18y; HF NYHA class II or III; no prior captopril; on diuretic +/- digoxin	8w	Office	HF: mild-to-moderate Age:	Captopril: start at 12.5 mg tid, titrate up to 15 mg tid Mean dosage: 65 mg QD
Cilazapril							
Rosenthal 1996 Germany	Single-group cohort, open label, prospective, multicenter	33841 Private practice physicians in Germany asked to record results of 4m of treatment in up to 5 patients	HT, not otherwise specified (33447/33841 had HT, NR what remaining patients had)	mean 109d	General practice	HT Age: 58.6Y (NR) Diabetes: 5037/33841	Cilazapril: start at 1.25 mg qd, increase to 2.5 to 5 mg qd; 0.5 mg to 2.5 mg qd in elderly or with impaired renal function Median dosage at end of observation period: 2.5 mg qd
Enalapril							
Messner 1995	Single-group cohort, multicenter	17546 NR	Inclusion criteria: >18y; HF stabilized with diuretic and/or digitalis therapy Exclusion criteria: on vasodilator; Cr>150 mmol/L: Na <130 meq/L; SGP <110 mm Hg; pregnant or nursing	3m	GP offices	HF: mild-to-moderate Age: 70y (10.5) Sex: 50.4% female Race: 99.3% Caucasian NYHA class II 67%, class III 33%	Enalapril: start 2.5 mg qd for 3d; 5 mg qd for 3d; 10 mg qd for 7d, then 20 mg qd Mean daily dosage 16 mg Run-in period: 1-3w; stability observed; diuretic dosage reduced by 1/2

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Other allowed HT medications	Total withdrawals Withdrawals due to AEs	AE assessment	Adverse events
DeBianco 1991 US	NR	Total WDs: 14.8% Of patients with AEs, 4.9% withdrew	NR	AEs (1 or more) in 18.1% of patients Total AEs: 1983 in 1386 patients) Deaths: 3.0%, causes NR Most common AEs: dizziness (2.4%), nausea (1.4%), cough (1.1%), hypotension (1.2%) Postural hypotension: <1%
Cilazapril				
Rosenthal 1996 Germany	Various; 14.4% took concomitant HT medications	Total WD: 6.7% WD due to AEs: 3.7%	GPs reported serious AEs on a form, reported to central agency	Overall rate of AEs: 7.3%; 3.8% of total population considered to have drug-related AE Severe AEs (not defined): 0.6% of total population; none felt to be related to treatment Deaths: 44 patients (12 cardiac, 10 cerebral) Hypotension (not defined): approximately 0.2% (graphical data)
Enalapril				
Messner 1995	Diuretic; digitalis	Total WDs: 3.3% WD due to AEs: 1.4%	Patients asked to report any AE; investigator completed a case report	Overall adverse event rate: 5.6% Hypotension: 0.34% Postural hypotension: 0.3% Hyperkalemia: 0.13% Death: 127/17,546 (0.72%); none felt related to drug Worsening HF: 95/17,546 (0.54%); none felt related to drug MI: 0.10% Pulmonary embolism: 0.08%

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	AEs among subgroups	Comments
DeBianco 1991 US	NR	
Cilazapril		
Rosenthal 1996 Germany	NR	Rate of cough: 1.5% (most frequently reported AE)
Enalapril		
Messner 1995	NR	Cough: 1.7% Creatinine: increase 10.9 to 11.1 mg/d, P=0.0001

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Design	Total N Subject recruitment	Inclusion criteria	F/U period	Setting	Population Age (mean (SD) Sex (% female) Race/ethnicity	Intervention drug
Lisinopril							
Thorp 2005 US	Retrospective cohort	18977 prescribed lisinopril; 13166 had pre and post Cr levels Computerized database of HMO medical records	Patients taking lisinopril between 7/2000 and 6/2002; >40y	6m	US HMO	Various indications Age: reported by stratum Sex; 49.5% female Race: NR DM and/or CHD: 53.8%	Lisinopril; dosage NR
Perindopril		o					
Speirs 1998 France	Post-marketing surveillance	47351 From GP offices across France; physicians selected up to 10 patients per practice	Adults with nonaccelerated HT and DBP 95-115 mmg Hg Exclusion: pregnancy, breast-feeding, secondary HT, history of stroke, MI, or unstable angina in last 3m;hepatic, renal, or other serious disease	12m	GP offices	HT Age: 60.9 (NR) 53% women Diabetes: 14%	Perindopril: started at 2 (>70y) to 4 mg and titrated up to 8 mg

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Other allowed HT medications	Total withdrawals Withdrawals due to AEs	AE assessment	Adverse events
Lisinopril				
Thorp 2005 US	NA	NA: only subjects with pre and post Cr levels were examined	Pre and post lisinopril serum creatinine levels within 6m of initial prescription	Rise in serum Cr from ≤ 1.2 mg/dl to >2.5 mg/dL: 31 patients (0.2%) Rise in serum Cr from ≤ 1.2 mg/dl to >1.2 mg/dl: 6.8% In N=31: possible contributors to increase in Cr: CHF (9/31), dehydration 7/31, infection 4/31 In N=31, "most patients" had decrease from rise in subsequent 6m to <2.5 md/dL ESRD: 0 cases Deaths: 3 patients
Perindopril				
Speirs 1998 France	Diuretics	Total WD: 4008/47,351 (8%) WD due to AEs: 6.3% female, 3.5% male	Case report forms	Overall rate of AEs: men 14.2%, women 17.8% Deaths: 190 (0.4%)' 27 due to MI; 26 due to stroke Hospital admissions: 255 Renal dysfunction: men 0.14%, women 0.17%; 3 cases of CKD referred for hemodialysis (2 had renal artery stenosis) Angioedema: men 0.004%, women 0.02% Serious allergic reaction: men 0.02%, women 0.01%; 3 cases were pancytopenia which started after perindopril started Hematologic disturbance: men 0.02%, women 0.004% Serious allergic reaction: men 0.02%, women 0.01% Hypotension: men 0.29%, women 0.4%; 1 case related to nonfatal stroke

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	AEs among subgroups	Comments
Lisinopril		
Thorp 2005 US	In N=31, 11 had no DM or CAD; 20 had one or both	
Perindopril		
Speirs 1998 France	WD due to AEs: no difference across age and sex groups except for WD due to renal insufficiency which increased with age; rate highest in men >80y	Cough: 11.3% in women, 7.8% in men

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Design	Total N Subject recruitment	Inclusion criteria	F/U period	Setting	Population Age (mean (SD) Sex (% female) Race/ethnicity	Intervention drug
Trandolapril							
Tytus 2007 Canada	Single-group cohort, open label, prospective, multicenter	Enrolled: 2096 Completed 14-w titration period: 1683 Recruited from randomly-selected primary care practices; NR how provider selected patients	Stage 1 to 2 HT, no prior HT treatment or HT uncontrolled on current monotherapy with a diuretic or calcium channel blocker Exclusion criteria: on steroids, secondary HT, clinically significant CVD	26w	Primary care clinics in Canada	HT (newly treated or uncontrolled on current first-line medications) Age: 56.6(12.6) (years)	Trandolapril: 1 mg qd, titrated up to 4 mg qd
ARBs							
Irbesartan							
Bramlage 2004 Germany	Single-group cohort, open label, prospective, multicenter	17,284; 16,600 "could be used in the analysis" GPs selected patients for treatment with irbesartan; study period 10/2002 to 6/2003	>=18y, with HT and type 2 diabetes	3m	German GP offices	HT and DM2 Age: 62.2 (10.7)	Irbesartan 300 mg qd (Aprovel 300) or combined with HCTZ 12.5mg qd (CoAprovel 300)
Schrader 2007 Germany	Post-marketing surveillance; prospective, multi-center	14200 Physicians collected data on patients they elected to treat with irbesartan	Adults with uncontrolled HT	Up to 9m	General practice	Uncontrolled HT, with or without metabolic syndrome Age: 62 (10.8) y Diabetes: 31.1% Metabolic syndrome: 65.4%	Irbesartan 75 to 300 mg daily or irbesartan/HCTZ 150/12.5 or 300/12.5 mg qd

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Other allowed HT medications	Total withdrawals Withdrawals due to AEs	AE assessment	Adverse events
Trandolapril				
Tytus 2007 Canada	Verapamil 240 mg qd, diuretic Excluded: beta-blockers, another ACE-I	Total WD during 14-w titration period 413/2096 (19.7%) WD during remaining 12w: 33/1683 (2%) WD due to serious AE: 19 (0.9%) WD due to nonserious AE: 169 (8.1%) (cough, nausea, headache)	Treating physician asked about AE at each visit and determined if AE causally related to drug	Total of 343 AEs attributed to study drugs in 252 patients (15.3%) Serious AEs: pregnancy, cerebral aneurysm, diabetic crisis, TIA, carcinoma, others (rates NR) None attributed to trandolapril
ARBs				
Irbesartan				
Bramlage 2004 Germany	HCTZ allowed, other HT drugs as needed	Data available on 16,600/17,284 (96.0%); no other details	Collected by GPs; no other details	62 AEs noted in 48 patients (0.3% of total); 2 serious AEs: terminal renal insufficiency "not related to study medication" and tremor "likely related" No deaths during study
Schrader 2007 Germany	As needed; no restrictions	Total WD: NR WD due to AEs: NR	GPs reported serious AEs on a form, reported to central agency	Overall AE rate: 0.62% (141 events in 88 patients) Number of patients (n=14,200) Serious AEs (not defined): 34 patients (0.24%) (not all were listed in table or described) Deaths: 16 over 9-m F/U Cardiogenic shock: 1 Cerebral infarction: 1 Gastrointestinal hemorrhage: 1 MI: 2

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	AEs among subgroups	Comments
Trandolapril		
Tytus 2007 Canada	NR	
ARBs		
Irbesartan		
Bramlage 2004 Germany	Included subjects had DM2; no other subpopulations examined	
Schrader 2007 Germany	NR	

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Design	Total N Subject recruitment	Inclusion criteria	F/U period	Setting	Population Age (mean (SD) Sex (% female) Race/ethnicity	Intervention drug
Losartan							
Mann 1999 UK	Post-marketing surveillance	14522 Data from prescription event monitoring database; forms sent to physicians who prescribed the drug	Physician completed drug AE form for patients' first prescription	Patients on drug at least 6m	GP offices	HT or HF Age: 63.5 (12.1) y Sex: 59.3% female	Losartan
Olmesartan							
Schmidt 2008 Germany	Single-group cohort, open label, multicenter, prospective	4252 Physicians collected data on patients they elected to treat with irbesartan	Adults with HT treated in GP offices	6w; mean 44.1d (SD 21.7)	General practice	Mild-to-moderate HT Age: 62.5 (11.9) Diabetes: 20.9% CHD: 16.4% HF: 9.9% Renal failure: 3.4%	Olmesartan 10 to 40 mg qd; mean dosage 19.9 (7.1) mg
Telmisartan							
Schumacher 2008 Italy	Retrospective cohort derived from the Micardis project database, which includes results from 30 double-blind and 20 open-label clinical studies	5013 for telmisartan monotherapy in RCTs; 5907 in open-label studies NR, likely varied across included studies	Adults with HT; varied somewhat across studies	Varied across studies: 7d to 2y; mean duration in double-blind studies 67d	NR	HT Age: double-blind studies: 55.9 (11.2) open-label studies:56.3 (11.3) Race: double-blind: 90.0% non-black, 10.0% black	Telmisartan 20-160 mg +/- HCTZ 6.25 to 25 mg qd or placebo

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Other allowed HT medications	Total withdrawals Withdrawals due to AEs	AE assessment	Adverse events
Losartan				
Mann 1999 UK	NA	Survey response rate 60%; additional 7.8% had no event data; useful information obtained on 14,522 subjects Total WD: 17.5% after 6m WD due to AEs: 5.1%	Prescription event monitoring system	303 adverse drug reactions (defined as attributed to the drug by the GP) (including dizziness, headache, malaise, nausea, cough, etc) Incidence density per 1000 patient-months: month 1; month 2-5 Cardiac failure: 53; 115 Renal dialysis: 13; 2 Number of cases: Angioedema: 8 Renal failure and electrolyte abnormalities: researchers unable to differentiate from pre-existing disease Death: 363; none attributed to losartan (Table 5 lists causes)
Olmesartan				
Schmidt 2008 Germany	As needed; no restrictions	Total WD: NR WD due to AEs: NR	GPs reported serious AEs on a form, reported to central agency	Overall AE rate: 0.66% Serious AEs (not defined): 2 patients: circulatory collapse and aortic bypass surgery
Telmisartan				
Schumacher 2008 Italy	Other HT medications allowed in most studies	Treatment discontinuations due to AEs in double-blind studies: 0.33 PPY (4.4%) with placebo, 0.14 PPY (2.6%) with monotherapy; in open-label studies 0.07 PPY (4.0%)	AEs were spontaneously reported by the patient or detected by the investigator	AEs PPY in double-blind (open label) studies: monotherapy 2.03 (37.4%) (0.65, 49.6%), placebo 2.73 (36.1%) Serious AEs: monotherapy 0.07 (1.2%) (0.07, 4.4%)), placebo 0.09 (1.2%); NSD between active treatment groups in double-blind studies Open-label studies, events PPY with monotherapy MIs: 0.004, (0.3%) Deaths: overall 0.004 PPY with monotherapy Hepatobiliary laboratory abnormalities: <0.05% with monotherapy

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	AEs among subgroups	Comments
Losartan		
Mann 1999 UK	Incidence density higher for >76y vs <76 (P<0.05) for cough, dizziness, edema, nausea/vomiting	
Olmesartan		
Schmidt 2008 Germany	NR	Dizziness most common AE (0.19%) Text resembles Schrader 2007
Telmisartan		
Schumacher 2008 Italy	The incidences of all-cause AEs PPY were lower in patients >65y than <65y; serious AEs were higher in older group	AEs occurring at >1% in double-blind studies: headache, dizziness, fatigue; cough, peripheral edema, erectile dysfunction occurred at 0.3% or less in double-blind studies, 0.7% or less in open-label studies

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Design	Total N Subject recruitment	Inclusion criteria	F/U period	Setting	Population Age (mean (SD) Sex (% female) Race/ethnicity	Intervention drug
Valsartan							
Biswas 2002 UK	Single-group cohort, open label, prospective	12881 GPs completed questionnaire on dispensed prescriptions	Patients with prescriptions dispensed between 12/96 and 11/98	At least 6m after start of drug	GP offices	HT (assumed as was indication) Age: men 61.1(12.1); women 65.4 (12.5) 59% females	Valsartan: dosage NR

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	Other allowed HT medications	Total withdrawals Withdrawals due to AEs	AE assessment	Adverse events
Valsartan				
Biswas 2002 UK	NA	Return rate on questionnaires: 55% WD at 6m F/U: 19.9%	GPs completed questionnaire on dispensed prescriptions; adverse drug reactions were reviewed in detail and additional questionnaire sent to the GP	Total AEs: 295 events in 209 (1.5%) of patients Most common reasons for WD due to AEs: malaise (0.3%), dizziness (0.1%) Deaths: 1.5% (78/85 due to CVD or cancer) Angioedema: 0.03% Abnormal liver function tests: 0.2% (1 case of jaundice and 1 of hepatitis improved after stopping the drug) Hyperkalemia: 0.13% Hyponatremia: 0.12% Spontaneous bleeding: hematuria, hemoptysis, ect: 59 cases; unclear if related to drug

Evidence Table 23. Data abstraction of major harms in cohort studies

Study Country	AEs among subgroups	Comments
Valsartan		
Biswas 2002 UK	NR	