Drug Class Review
on
Angiotensin II Receptor Antagonists

Final Report Update 1 Evidence Tables

February 2006

Original Report Date: September 2004
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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We would like to acknowledge Shannon Rhodes, MSPH who reviewed the evidence tables on the original report.

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(1) Author, Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2043	Schrader, 2005 Germany, Austria MOSES (Fair)	RCT, PROBE, multicenter	HTN requiring treatment and history of cerebrovascular event (transient ischemic attack [TIA, focal neurological deficit attributable to ischemia resolving within 24 hours], ischemic stroke, cerebral hemorrhage), documented by either cranial computed tomography or magnetic resonance scan (within 24 months prior to inclusion)	Eprosartan 600 mg once daily Nitrendipine 10mg once daily Mean follow-up 2.5 years
2019	Yamamoto, 2003 Japan (Poor)	Open-label	Age 35 to 81 with uncomplicated mild to moderate HTN, receiving DCCB as only anithypertensive	Candesartan 8mg or 12mg once daily (8mg dose increased to 12mg if SBP not reduced > 20 mm Hg and DBP reduced > 10 mm Hg) Follow-up 3 months

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
2043	None	Dose could be adjusted or combination therapy initiated (recommended to start with diuretic, then beta-blocker, then alpha-blockers or centrally acting agents) to achieve target sitting SBP < 140 mm Hg and DBP < 90 mm Hg	Primary endpoint was composite all-cause mortality and number cardiovascular and cerebrovascular events (including recurrent events); secondary endpoints were all single components of the primary endpoint and assessment of functional capacity (modified Rankin Scale [0 to 5; best=0] and Barthel Index [0 to 100; best=100] and cognitive function (Mini Mental Status Exam). Clinic visits at 3, 6, and 9 weeks, and 3, 6, 12, 18, 24, 36, and 48 months; ABPM and MMSE at 12, 24, and 48 months; Rankin Scale and Bartel Index at 24 and 48 months
2019	None	Not specified	Objective to compare effect on QOL after switching from DCCB to candesartan. QOL assessed by 37 item questionnaire: general health (10 items); work and housework (3 items); daily life (5 items); sleeping (4 items); psychological well-being (4 items); intelligence (2 items); sex life (3 items); cooperation (1 item); social activity (2 items); self-control (2 items); activity (1 item). Four point scale used to assess physical symptoms (1=definite, 4=absent). QOL assessed before and after 3 months candesartan

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2043	Mean age 68 54% male Ethnicity not specified	Stroke 61% TIA 27% Prolonged reversible ischemic neurological deficit 6% Intracerebral hemorrhage 5.5% DM 37% CHD 26% Hyperlipidemia 53% Renal disease 5% Baseline BP: Eprosartan 150.7±18.5/87.0±10.8 mm Hg Nitrendipine 152.0±18.2/87.2±9.6 mm Hg	Number screened not reported/1405 eligible/1352 enrolled	53 withdrew consent/3 without known vital status/ 26 lost to fu/1352 analyzed
2019	Mean age 63 51% male Ethnicity not specified	DM 29% Cardiac disease 3% Cerebrovascular disease 5% Hyperlipidemia 29% Renal disease 2% Baseline BP 142.4±11.5/84.9±5.8 mm Hg	Number screened not reported/number eligible not reported/100 enrolled	None withdrawn/none lost to fu/100 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
2043	**Primary endpoint (cerebrovascular and CV events and nonCV death)** Incidence density per 100 person years (ID) Eprosartan vs. nitrendipine: ID ratio 0.79 (95% CI 0.66-0.96; P=0.014) NNT=13 (95% CI 8-37)	**Secondary endpoints** Fatal and nonfatal cerebrovascular events Eprosartan vs. nitrendipine: ID ratio 0.75 (95% CI 0.58-0.97; P=0.026) Fatal and nonfatal CV events Eprosartan vs. nitrendipine: ID ratio 0.75 (95% CI 0.55-1.02; P=0.061)	Assessed by investigator at each examination
2019	QOL main objective: Significant improvement candesartan vs DCCB: General symptoms (P<0.001) Physical symptoms (P<0.001) Work and satisfaction (P<0.001) Sleep scale (P<0.001) Emotional state (P<0.001) Cognitive function (P<0.001) Sexual function (P<0.001) Life satisfaction (P<0.01) Vigor (P<0.05) Overall (P<0.001)	QOL General symptoms sub-items: Significant improvement candesartan vs DCCB: Headache, dull headache (P<0.001) Dizziness, fainting (P<0.01) Shoulder stiffness (P<0.001) Palpitation (P<0.001) Facial flushing (P<0.001) Numbness (P<0.001)	Monitored throughout the study

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2043	Dizziness/hypotension Eprosartan 12.9% Nitrendipine 10.6% Pneumonia Eprosartan 10.8% Nitrendipine 11.4% Metabolic disorder Eprosartan 5.5% Nitrendipine 5.9%	53 withdrew consent; withdrawals due to adverse events not reported
2019	No adverse laboratory events reported; significant decrease in TC compared to baseline (217.2±30.3 vs. 202.5±25.9 mg/dl; P<0.0001)	Reported that all patients completed the study

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(16) Comments
2043	Mean BP at final visit/study end: eprosartan 137.5±16.7/80.8±8.9 mm Hg; nitrendipine 136.0±15.6/80.2±8.8 mm Hg. Monotherapy: eprosartan 34.4%, nitrendipine 33.1%; combination therapy: eprosartan 65.6%, nitrendipine 66.9%. Mean dose at end of study in patients who remained on study drug: eprosartan 623±129.3 mg; nitrendipine 16.2±7.9 mg. No significant differences in mean values before and at end of study of cognitive or functional capacity.
2019	Baseline values to determine if increased candesartan dose warranted based on BP reductions not defined; 93 patients received 8mg, 7 received 12mg candesartan (mean follow-up BP 130.0±5.5/76.6±6.4 mm Hg; P<0.01 vs. baseline on DCCB)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(1) Author, Year Country Trial Name (Quality Score)		(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
944	Tedesco, 1999 Country not stated (Fair)		RCT	Age 30 to 73 with uncomplicated mild to moderate HTN (DBP 90-114 mm Hg on nonpharmacologic therapy)	Losartan 50mg once daily or HCTZ 25mg once daily Mean follow-up 2.2 years
283	Dahlof, 1997 Sweden, Australia, Finland Study (Fair)	LOA	RCT, multicenter	Mild to moderate HTN (DBP 90-115 mm Hg)	Losartan 50mg once daily (if DBP > 90 mm Hg, increased to 100mg); losartan 50mg (if DBP > 90 mm Hg, add HCTZ 12.5mg); amlodipine 5mg once daily (if DBP > 90 mm Hg, increased to 10mg); adjustment occurred at 6 weeks Follow-up 12 weeks

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
944	Two weeks double-blind nonpharmacologic therapy	Not specified	Objective to examine long-term changes in QOL [assessed by 46 item questionnaire appropriate for HTN including symptomatic physical well-being, psychologic well-being, activity, perception of effects of treatment on lifestyle, including social participation, performance, and satisfaction at work; scored disability as a Health Index on a continuum from 0 (death) to 1 (perfect health), and cognitive function [by Sandoz Clinical Assessment Geriatric (SCAG) and Mini-Mental State Examination (MMSE)], and to compare the antihypertensive effect of losartan vs. HCTZ; patients stratified by age (< 60years vs. ≥ 60years). Patients assessed at baseline and 26 months
283	1 week wash-out/4 week placebo run-in	Not specified	Objective to compare effect on QOL [assessed by the psychological general well-being (PGWB) index, 22 item questionnaire (22-132 points) with 6 domains (anxiety, depressed mood, positive well-being, self-control, general health, vitality)], BP and drug tolerability. Patients completed a questionnaire at home on the day before visits during weeks -4, 0, 6, and 12 (given to investigator in sealed envelope)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
944	Mean age 55 (losartan 23 patients < 60 years, 19 ≥ 60 years vs. HCTZ 13 patients < 60 years, 14 ≥ 60 years) 52% male Ethnicity not specified	Duration of HTN 5 years (significantly longer in patients ≥ 60 years, P<0.001 losartan, P<0.01 HCTZ), education 9 years	Number screened not reported/number eligible not reported/69 enrolled	None withdrawn/none lost to fu/69 analyzed
283	Mean age 58 53% male 99% white	16-23% CVD, 6-7% DM, 39-41% musculoskeletal diseases, 25-26% neurologic and psychiatric disorders, 20-22% respiratory diseases	Number screened not reported/number eligible not reported/898 enrolled	75 did not complete the study/number lost to fu not reported/787 analyzed for QOL

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
944	QOL main objective: mean (sd) losartan baseline 0.90(0.08) vs. 26 months 0.96(0.06) (P<0.01; 95% CI -0.08 to -0.02), < 60 years (P<0.003), ≥ 60 years (P<0.02); HCTZ baseline 0.89(0.07) vs. 26 months 0.94(0.08) (P<0.02; 95% CI -0.09 to -0.01), < 60 years (NS), > 60 years (P<0.05)	Reported that ANOVA for BP, MMSE, SCAG, QOL showed a significant difference losartan vs. HCTZ (P<0.001)	Not reported
283	QOL main objective: total score (after 12 wks) losartan 110.0 vs. 107.5 baseline (P<0.001), losartan + HCTZ 109.8 vs. 108.1 baseline (P=0.002), amlodipine 108.7 vs. 108.2 baseline; improvement in PGWB score in 60% losartan monotherapy, 54% losartan + HCTZ, 50% amlodipine (losartan vs. amlodipine P=0.011) NNT=9 (95% CI 5-30) for losartan monotherapy vs amlodipine	QOL main objective (continued): losartan monotherapy significantly improved anxiety, depressed mood, positive well-being, vitality; losartan + HCTZ signifcantly improved anxiety, general health, vitality; none of the 6 domains were significantly improved with amlodipine	Monitored at each visit by asking one general (Y/N) question and 24 (Y/N) on specific symptoms; spontaneous reporting

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
944	No complaints of cough or complications in sexual performance; no adverse laboratory events reported	Reported that all patients completed the study
283	Any discomfort: 22.5% losartan monotherapy, 23.5% losartan + HCTZ, 33.1% amlodipine (P=0.002 amlodipine vs. baseline); dizziness upon standing: 10.1% losartan monotherapy (P=0.028 vs. baseline), 17.1% losartan + HCTZ (P=0.001 vs. baseline), 33.1% amlodipine (P=0.002 amlodipine vs. baseline); no difference in global symptom score (0-24) between groups	94% on losartan monotherapy, 92% on losartan + HCTZ, 89% on amlodipine did not complete the study; 2% on losartan monotherapy, 5% on losartan + HCTZ, 8% on amlodipine withdrew due to adverse experiences (P=0.01 amlodipine vs. losartan monotherapy)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(16) Comments
944	Differences in SCAG, MMSE, 24hr SBP and 24hr DBP all statistically significantly improved at the end of the trial vs. baseline for patients on losartan as well as those in each age subgroup (significant improvement for HCTZ in 24hr SBP and 24hr DBP, and in patients < 60 years). 80% of patients on losartan and 50% patients on HCTZ were satisfied with their therapy and chose to continue
283	All treatment groups significantly reduced SBP and DBP vs. baseline (P<0.001)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(1) Author, Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
941	Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Multicenter	Male and female outpatients aged 20 to 80 years with primary hypertension and a history of ACE-inhibitor-induced cough	Candesartan 8 mg once daily Enalapril 10 mg once daily Placebo 8 weeks or when patient reported dry cough

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
941	1-4 week enalapril challenge period Those who experienced dry cough continued to a 1-4 week placebo dechallenge period in which cough had to resolve and be absent on two consecutive visits	HCTZ (12.5 mg) if diastolic BP > 105 mm Hg	Symptom Assessment (SA) questionnaire of symptoms using 5-point Likert scale (not at all, a little, moderation, quite a bit, and extremely) Cough frequency rated using 100 mm visual analog scale (1=none of the time to 100=all of the time) Quality of life: 15 of original 24 items in the Minor Symptom Evaluation (MSE) profile for contentment, vitality and sleep; MSE uses 100-mm visual analog scale with lower end of the scale indicating positive feelings and the higher end of the scale negative feelings

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
941	60 37% male 81.2% white	BMI 29 kg m2 DBP 93 mm Hg SBP 153 mm Hg	Number screened not reported/301 eligible/156 enrolled	Number withdrawn not reported/number lost to fu not reported/154 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
941	Patients with cough (%) after 8 weeks Placebo=26.9% Candesartan=35.5% (P>0.20 vs placebo) Enalapril=68.2% (P<0.001 vs candesartan) NNT=3 (95% CI 2-6) for candesartan vs enalapril MSE profile contentment: mean difference between candesartan & placebo=7.6mm, 95% CI 0.7 to 14.4mm P=0.03 sleep and vitality: nonsignificant trends	Recorded, either from spontaneous reports by the patient, or in response to an open, nonspecific questions (such as "Have you had any health problems since we last met?"), or as observed by study personnel	

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
941	Cough Enalapril=31% Candesartan=16% Placebo=11%	Withdrawals due to adverse events Placebo=3/26(11.5%) Candesartan=5/62(8.1%) Enalapril=3/66(4.5%)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(16) Comments
941	Unable to determine percent of patients with HCTZ added in each group

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(1) Author, Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
795	Rake, 2001 U.S. (Fair)	Multicenter	Male and female patients, of at least 18 years of age, with mild to moderate hypertension and a history of ACE inhibitor induced cough; no dry cough and average sitting diastolic BP of 95-114 mm Hg at the last 2 weekly visits of the 4-5 week single-blind, placebo run-in period; development of persistent non-productive dry cough during 3-4 week single-blind period of treatment with enalapril 20 mg daily; no cough at the end of the 2-4 week placebo washout period	Eprosartan 600 mg twice daily Enalapril 20 mg once daily Placebo

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
795	4-5 week single blind placebo run-in 3-4 week single blind treatment with enalapril 20 mg 2-4 week placebo wash-out period	Not reported	Quality of life: Psychological General Wellbeing Index (PGWB) (anxiety, depressed mood, positive well-being, self-control, general health and vitality; higher scores reflect more positive well-being); sleep disturbance scale; life satisfaction; satisfaction with spouse Pulmonary Questionnaire: self-reported dry unproductive cough Completed at the beginning of the placebo run-in period, during the placebo washout phase just prior to randomizsation, and at the last visit of the double-blind treatment

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
795	56.6 52.3% male Ethnicity not reported	Diastolic BP=100.7 mm Hg Smoking history=9.1% Smoker's cough=0.7%	231 screened/number eligible not reported/136 enrolled	4(2.9%) withdrawn/0 lost to fu/132 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
795	Quality of life (mean change) *Anxiety* Placebo=(-0.49) Enalapril=0.33 Eprosartan=(-0.14) *Depression* Placebo=(-0.39) Enalapril=0.02 Eprosartan=(-0.18) *Positive well-being* Placebo=0.10 Enalapril=0.40 Eprosartan=0.12 Life satisfaction/Spouse satisfaction/Sleep disturbance=no treatment effects (data nr)	*Self-control* Placebo=(-0.05) Enalapril=(-0.02) Eprosartan=0.00 *General health* Placebo=0.63 Enalapril=(-0.38) Eprosartan=(-0.13) *Vitality* Placebo=0.36 Enalapril=0.60 Eprosartan=0.14 *PGWB Total* Placebo=0.20 Enalapril=0.94 Eprosartan=(-0.29)	Pulmonary Questionnaire: self-reported dry unproductive cough Investigator completion of pulmonary questionnaire

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
795	Self-assessed cough *Definite dry cough* Placebo=2/41(4.9%) Enalapril=5/39(12.8%) Eprosartan=1/39(2.6%) *Probably dry cough* Placebo=0 Enalapril=4/39(10.2%) Eprosartan=1/39(2.6%) *Possible dry cough* Placebo=0 Enalapril=0 Eprosartan=0 *All coughs* Placebo=2/41(4.9%) Enalapril=9/39(23.1%)(p=0.047 for eprosartan vs enalapril) Eprosartan=2/39(5.1%) Investigator reported cough Placebo=3/41(7.3%) Enalapril=11/39(28.2%)NS Eprosartan=5/39(12.8%)	Not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(16) Comments
795	

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(1) Author, Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
213	Breeze, 2001 North America, Europe, South Africa (Fair)	Multicenter	Patients aged 18 or more with sustained mild-moderate hypertension (mean sitting diastolic BP between 95 mm Hg and 114 mm Hg inclusive at 3 successive visits	Eprosartan 400-600 mg twice daily Enalapril 5-20 mg once daily Duration 26 weeks

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
213	3-5 week placebo run-in period	HCTZ 12.5-25 mg (after 12 weeks if necessary - goal not reported)	Dry unproductive persistent cough assessed by questionnaire Quality of life assessed by Psychological General Wellbeing Index (PGWB) Clinic visits at week 6, 12 and 26

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
213	55.7 56.5% male 87.2% white	Cough Status Definite=1.3% Probably=0.6%	Number screened not reported/number eligible not reported/529 enrolled	82/529(15.5%) withdrawn/number lost to fu not reported/523 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
213	PGWB scores (between treatment differences in mean change (95% CI)) *Eprosartan:Enalapril (study endpoint/monotherapy endpoint* Anxiety: -0.82(-1.55, -0.99)/-0.58 (-1.21, 0.05) Depression: -0.27(-0.64, 0.11)/-0.07(-0.40, 0.26) Positive well-being: -0.16(-0.68, 0.35)/0.24(-0.25, 0.72) Self-control: -0.50(-0.89, -0.10)/-0.09(-0.44, 0.27) General health: -0.42(-0.82, -0.02)/-0.00(-0.41, 0.41) Vitality: -0.23(-0.75, 0.30)/-0.21(-0.73, 0.31) Total: -2.48(-4.63, -0.32)/-0.79(-2.72, 1.15) Life satisfaction/sleep disturbance/job satisfaction: no between group differences (data nr)	PGWB regression analysis adjusted for baseline values Eprosartan:Enalapril (95% CI; p-value) Anxiety: -0.60(-1.28, 0.07; NS) Depression: -0.19(-0.52, 0.15; NS) Positive well-being i) baseline score ≤19: -0.42 (-0.97, 0.12; NS) ii) baseline score >19: 0.65 (-0.29, 1.60; NS) Self-control: -0.45(-0.81, -0.08; p=0.016) General health: -0.34(-0.70, 0.14; NS) Vitality i) baseline score ≤20: -0.27(-0.94, 0.39, NS) ii) baseline score >20: 0.16(-0.53, 0.85; NS) Total i) baseline score ≤119: -2.32(-4.54, -0.10; P=0.041) ii) baseline score >119: -0.99(-6.13, 4.14; NS)	Assessed by investigator using a questionnaire

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
213	Cough incidence (% patients) *Study endpoint analysis* *Definite* Eprosartan=5/247(2%) Enalapril=12/249(4.8%) *Probable/possible* Eprosartan=3/247(1.2%) Enalapril=7/249(2.8%) *Definite/Probable/possible* Eprosartan=8/247(3.2%) Enalapril=19/249(7.6%) *Monotherapy endpoint analysis* *Definite* Eprosartan=4/245(1.6%) Enalapril=15/247(6.1%) *Probable/possible* Eprosartan=1/245(0.5%) Enalapril=9/247(3.6%) *Definite/Probable/possible* Eprosartan=5/245(2.0%) Enalapril=24/247(9.7%) (p=0.001)	Total withdrawals Eprosartan=35/265(13.2%) Enalapril=47/264(17.8%) Withdrawal due to cough Eprosartan=2/265(0.7%) Enalapril=7/264(2.6%)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(16) Comments
213	Reported that open-label HCTZ added at 12 weeks was almost identical in both groups (data not shown)

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(1) Author, Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
291	De Rosa, 2002 Italy (Fair)	Single center (outpatient clinic)	Essential HTN, classified as WHO stage II (average supine DBP >90 mm Hg and/or SBP > 140 mm Hg)	Enalapril 5-20 mg once daily Losartan 12.5-50 mg once daily Titration generally occurred at 7-day intervals as tolerated if DBP was ≥ 90 mm Hg Duration 3 years

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
291	2-week placebo run-in	Not reported	Clinic visits after 1, 2, 3, and 4 weeks and every 12 weeks of the 3 year therapy QOL: symptom bother (not at all, little, moderately, quite a bit or extremely), overall health perceptions, psychologic well being, social functioning, sleep disturbance, cognitive functioning and sexual functions

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
291	54.9 50% male Ethnicity not reported	BMI 27.4 kg/m2 SBP 156.9 mm Hg DBP 102.5 mm Hg GFR 97.1 ml/min	Number screened not reported/number eligible not reported/50 enrolled	8(16%) withdrawn/2(4%) lost to fu/42 analyzed

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
291	<u>GFR change (%)</u> Losartan 12.5% increase (P<0.005 vs. baseline) Enalapril 5.3% increase (P=0.085 vs. baseline) Change in GFR: mean(sd) after 3 years of treatment in ml/min Losartan: baseline=96.5 (32.3) follow-up=108.6 (31.12) P<0.005 Enalapril: baseline=94.8 (31.1) follow-up=99.8 (19.6) P=0.085 <u>Quality of life</u> (12 weeks) Losartan=Enalapril on all domains except > bother due to cough with enalapril (12%) vs. lisinopril (2%) (P=0.01) (other data not reported)		Not reported

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
291	Incidence of bother due to cough: Losartan 2% Enalapril 12% (P=0.01)	Total withdrawals Losartan 4/26(15.4%) Enalapril 4/24(16.7%) NS Withdrawal due to adverse events Losartan 0 Enalapril 3/24(12.5%) NS

Evidence Table 1. Active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

ID	(16) Comments
291	

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2033	Trenkwalder, 2005 U.S., Canada, Europe SCOPE trial substudy (demographics, risk factors, comorbidities) (Fair)	RCT, multicenter	Age 70 to 89 with HTN (treated or untreated 160-179/90-99 mm Hg), MMSE $\geq$ 24	See SCOPE trial (Lithell, 2003) Intervention below

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2033	Open run-in (1 to 3 months) untreated or HCTZ 12.5mg BP 160-179/90-99 mm Hg	Open-label HCTZ 12.5mg (as described under SCOPE trial Interventions below) or increase, with addition of other antihypertensive agents (except ACEIs, AIIRAs); breakdown of medication classes in the subgroups not provided	Endpoints evaluated by pre-specified subgroup (age, race, DM, history of stroke, smoking) or post hoc subgroup (medium or high CV risk). Primary endpoint of first major CV event (CV death, nonfatal MI, and nonfatal stroke); secondary endpoints of first fatal and nonfatal stroke (combined and separate). Patients were followed-up at regular visits (1 and 3 months after randomization, then every 6 months)	21% 80-89 79% 70-79 36% male Ethnicity not specified

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2033	12% DM 4% previous stroke 9% current smoker 35% high CV risk	Number screened not reported/4964 randomized/4937 enrolled	27 excluded/8 lost to fu/4937 analyzed	**Primary endpoint (first major CV event)**: Previous stroke subgroup (candesartan vs. control) [Yes] RR 0.36 (95% CI 0.18-0.73); P=0.004 [No] RR 0.95 (95% CI 0.79-1.14); P=0.591 P (for interaction)=0.008 No statistically significant difference when other subgroups evaluated

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2033	**Secondary endpoints:** *First nonfatal stroke* DM (candesartan vs. control) [Yes] RR 0.84 (95% CI 0.38-1.84); P=0.664 [No] RR 0.70 (95% CI 0.50-0.98); P=0.040 Interaction between treatment and subgroups P=0.678 Previous stroke (candesartan vs. control) [Yes] RR 0.34 (95% CI 0.12-0.95); P=0.039 [No] RR 0.79 (95% CI 0.57-1.10); P=0.159 Interaction between treatment and subgroups P=0.124 *First nonfatal or fatal stroke* DM (candesartan vs. control) [Yes] RR 0.90 (95% CI 0.46-1.76); P=0.755 [No] RR 0.73 (95% CI 0.54-1.00); P=0.046 Interaction between treatment and subgroups P=0.577 Previous stroke (candesartan vs. control) [Yes] RR 0.38 (95% CI 0.15-0.99); P=0.047 [No] RR 0.82 (95% CI 0.64-1.10); P=0.184	Assessed at each visit per SCOPE trial methods	Not reported by subgroup	Not reported by subgroup

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(16) Comments
2033	

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2007	Papademetriou, 2004 U.S., Canada, Europe SCOPE trial substudy (ISH) (Fair)	RCT, multicenter	Age 70 to 89 with HTN (treated or untreated 160-179/90-99 mm Hg), MMSE $\geq$ 24; predefined subgroup of ISH (SBP > 160 mm Hg and DBP < 90 mm Hg)	Candesartan 8mg, titrated to 16mg if BP > 160/85 mm Hg or SBP < 10 mm Hg vs. randomization) vs. placebo. If BP > 160/90 mm Hg despite 16mg candesartan (or placebo) addition of open-label antihypertensive treatment was recommended (HCTZ 12.5mg or increase if patient on from baseline), then adding other antihypertensive agents besides an AIIRA or ACEI) Mean follow-up 3.6 years

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2007	Open run-in (1 to 3 months) untreated or HCTZ 12.5mg	Open-label HCTZ 12.5mg or increase, with addition of other antihypertensive agents (except ACEIs, AIIRAs); candesartan vs. control: 26% vs. 18% on study drug only, 21% vs. 15% on study drug plus HCTZ 12.5mg baseline, 36% vs. 46% increase HCTZ or 12.5mg started after baseline, 19% vs. 27% beta-blocker, 21% vs. 30% CCB; respectively	Primary endpoint: first major CV event (CV death, nonfatal MI, or nonfatal stroke); secondary endpoints: cognitive function, dementia, total mortality, CV mortality, fatal and nonfatal MI, fatal and nonfatal stroke, new-onset DM, and discontinuation of study drug due to adverse events	Mean age 77 36% male, ethnicity not specified

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2007	4.2-4.5% previous MI 3.9-4.4% previous stroke 11-13.5% DM	Number screened not reported/1518 randomized with ISH/1518 enrolled	Number excluded not reported/1 lost to fu/reported range 1512-1518 analyzed	**Primary endpoint (first major CV event)**: candesartan vs. control RR 0.89 (95% CI 0.65-1.21, P>0.20)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2007	**Secondary endpoints**: first stroke (fatal or nonfatal) RR 0.58 (95% CI 0.33-1.00, P=0.05) with candesartan vs. control; there was no significant difference in fatal stroke, nonfatal stroke, fatal or nonfatal MI, CV mortality or total mortality; no significant difference in change in MMSE score, development of dementia, or new-onset DM	Assessed at each visit per SCOPE trial methods	Most common (dizziness/vertigo, accident/injury, back pain, bronchitis) occurred in similar number in both groups	Total withdrawals not reported; candesartan vs. control: 17.3% vs. 17.6% withdrew due to adverse events

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(16) Comments
2007	Originally designed as placebo-controlled trial; only 18% patients in control group on placebo (82% received open-label antihypertensive agents); average difference in BP reduction 2.0/1.2 mm Hg favoring candesartan (P=0.064)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2002	Degl'Innocenti, 2004 U.S., Europe SCOPE trial substudy (QOL) (Fair)	RCT, multicenter	Age 70 to 89 with HTN (treated or untreated 160-179/90-99 mm Hg), MMSE $\geq$ 24 at 314 study centers	See SCOPE trial (Lithell, 2003) Intervention below

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2002	Open run-in (1 to 3 months) untreated or HCTZ 12.5mg BP 160-179/90-99 mm Hg	Open-label HCTZ 12.5mg (as described under SCOPE trial Interventions below) or increase, with addition of other antihypertensive agents (except ACEIs, AIIRAs); breakdown of medication classes in QOL subgroup not provided	Quality of life: Psychological General Wellbeing Index (PGWB): Total Score (min 22 to max 132; higher scores reflect more positive well-being); anxiety, depressed mood, positive well-being, self-control, general health, and vitality Subjective Symptom Assessment Profile (SSA-P): Seven-point scale (low value=mild symptoms); three of six dimensions used (cardiac symptoms, dizziness, peripheral/circulatory symptoms) plus 17 single items EuroQoL Health Utility Index (EuroQoL): 100-point visual analogue scale (100=best; 0=worst); physical, mental, and social functioning Completed at baseline and specific time points during clinic visits throughout study	Mean age 76 36% male, ethnicity not specified

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2002	4.2% previous MI 3.9-4.1% previous stroke 10% DM Education (10% less than primary school, 40% primary school, 44% more than primary school, 5% University)	Number screened not reported/number randomized not reported/2850 enrolled	Number excluded not reported/lost to fu not reported/2659 analyzed	PGWB Total score Candesartan vs. control Baseline: 106/106.3 Last visit: 103/101.8 Change: -4.26/-5.63 Mean: -1.37 (P=0.06) Anxiety Candesartan vs. control Baseline: 25/25.1 Last visit: 24.7/24.3 Change: -0.51/-1.01 Mean: -0.50 (P=0.01) Positive well-being Candesartan vs. control Baseline: 17/17.2 Last visit: 16.4/16.2 Change: -0.79/-1.12 Mean: -1.12 (P=0.04)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2002	SSA-P: No patient reported symptoms as moderate or above Cardic symptoms Adjusted mean difference in change Candesartan vs. control 0.07 (P=0.03) only statistically significant measure EuroQoL: Mean baseline scores high (74) Current health Adjusted mean difference in change Candesartan vs. control -2.19 (P=0.008)	Assessed at each visit	Not reported (refer to adverse events evaluated in QOL tools)	191 did not have evaluable QOL data at one or more visits; number withdrawals due to adverse events not reported

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(16) Comments
2002	

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2031	Faulhaber, 1999 Germany (Fair)	RCT, multicenter	Age 18 to 80 with HTN (treated DBP > 80 and < 100 mm Hg), stable renal insufficiency (sCr 150 to 600 µmol/L, not more than 25% change during run-in)	Valsartan 80 mg daily Placebo Duration 6 months

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2031	3 months treatment free run-in period	Continued concomitant antihypertensives except ACEIs, diuretics (furosemide allowed) for DBP > 80 and < 100 mm Hg Valsartan vs. Placebo Furosemide: 80% vs. 92.3% CCBs: 66.7% vs. 80.8% Beta-blockers: 56.7% vs. 57.7% Alpha-blockers: 30% vs. 42.3%	Primary endpoint: change from baseline in GFR Secondary endpoint: change in sCr Week 12 and 24	Mean age 55 59% male 96% white 4% oriental

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2031	Median GFR 19.5 vs. 22.0 mL/min per 1.73 m2 (valsartan vs. placebo)	Number screened not reported/56 randomized/56 enrolled	6 excluded/none lost to fu/50 analyzed for endpoints (56 for safety and tolerablity)	**Primary endpoint (GFR mL/min per 1.73 m2)** Geometric mean (baseline vs. endpoint) Valsartan (19.2 vs. 17.6) Placebo (21.2 vs. 16.5) Least squares mean endpoint/baseline ratio Valsartan (0.82) Placebo (0.74) Least squares geometric mean ratio at endpoint valsartan/placebo (1.11) 95% CI (0.77 to 1.59) P=0.577

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2031	**Secondary endpoint (sCr µmol/L)** Least squares mean change from baseline Valsartan (43.22) Placebo (47.02) Least squares mean difference at endpoint Valsartan vs. placebo (-3.80) 95% CI (-33.34 to 25.73) P=0.796	Assessed at baseline, weeks 1 and 4, and then at 4 week intervals	Placebo vs. valsartan Dizziness (7.7%, 13.3%) Increase sCr (11.5%, 10.0%) Hypotension (3.8%, 10.0%) Hyperkalemia (0.0%, 6.7%) Syncope (0.0%, 6.7%) Total events (23.1%, 46.7%)	Total withdrawals Placebo 5/26 (19.2%) Valsartan 4/30 (13.3%) Withdrawals due to adverse events Placebo 3/26 (11.5%) Valsartan 4/30 (13.3%)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(16) Comments
2031	BP reduction with valsartan statistically significantly greater with valsartan vs. placebo (adjusted mean difference DBP -7.84 mm Hg and SBP -14.27 mm Hg; P<0.002)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
15	Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	RCT, multicenter	Age 70 to 89 with HTN (treated or untreated 160-179/90-99 mm Hg), MMSE $\geq$ 24	Candesartan 8mg, titrated to 16mg if BP > 160/85 mm Hg or SBP < 10 mm Hg vs. randomization) vs. placebo. If BP > 160/100 mm Hg despite 16mg candesartan (or placebo) addition of open-label antihypertensive treatment was recommended (HCTZ 12.5mg or increase if patient on from baseline), then adding other antihypertensive agents besides an AIIRA or ACEI) Mean follow-up 3.7 years

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
15	Open run-in (1 to 3 months) untreated or HCTZ 12.5mg BP 160-179/90-99 mm Hg	Open-label HCTZ 12.5mg (as described under Interventions) or increase, with addition of other antihypertensive agents (except ACEIs, AIIRAs); candesartan vs. control: 25% vs. 16% on study drug only, 26% vs. 18% on study drug plus HCTZ 12.5mg baseline, 49% vs. 66% increase HCTZ or 12.5mg started after baseline, 17% vs. 26% beta-blocker, 18% vs. 28% CCB; respectively	Primary endpoint included major CV events (CV death, nonfatal MI, and nonfatal stroke); secondary endpoints included cognitive function (measured by MMSE), dementia, total mortality, CV mortality, fatal and non-fatal MI (combined and separate), fatal and non-fatal stroke (combined and separate), new onset DM, and discontinuation of study drug. Patients were followed-up at regular visits (1 and 3 months after randomization, then every 6 months)	Mean age 76 36% male, ethnicity not specified

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
15	4.5% previous MI, 3.9% previous stroke, 12% DM, education (10% less than primary school, 44% primary school, 40% more than primary school, 6% University)	Number screened not reported/4964 randomized/4937 enrolled	27 excluded/8 lost to fu/4937 analyzed	**Primary endpoint first major CV event (CV death, nonfatal MI, non-fatal stroke)**: candesartan group vs. control risk reduction 10.9% (95% CI -6.0-25.1, P=0.19)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
15	**Secondary endpoints**: risk of nonfatal stroke was reduced by 27.8% (95% CI 1.3-47.2, P=0.04) with candesartan vs. control; there was no significant difference in fatal, nonfatal or total MI, fatal stroke, CV mortality or total mortality; no significant difference in the adjusted change in MMSE score (decrease mean 28.5 to 28.0 with candesartan vs. 28.5 to 27.9 in the control group); no difference in cognitive decline or development of dementia; no difference in new-onset DM	Assessed at each visit (any unintended, unfavorable clinical sign or symptom, any illness or disease, or any clinically relevant deterioration in laboratory variable or other clinical test, whether or not considered treatment related)	Hypotension: candesartan (24.6%, 0.3% withdrew) vs. control (23.4%, 0.2% withdrew); dizziness/vertigo: candesartan (20.9%) vs. control (20.0%); accident/injury: candesartan (18.4%) vs. control (18.4%); back pain: candesartan (19.2%) vs. control (17.1%); bronchitis: candesartan (15.9%) vs. control (16.0%); sCr increased from 91.0 to 100.6umol/l with candesartan vs. 91.0 to 96.3 umol/l in the control group	Total withdrawals not reported; candesartan vs. control: 15% vs. 17% withdrew due to adverse events

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(16) Comments
15	Originally designed as placebo-controlled trial. Mean dose candesartan 11.6±4.0mg/day; only 16% of patients in control group were on placebo (84% received open-label antihypertensive agents); mean BP reduced to 145.2/79.9 mm Hg in the candesartan group vs. 148.5/81.6 mm Hg in the control group (mean difference in adjusted BP reduction 3.2/1.6 mm Hg favoring candesartan (P<0.001)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
30	Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Multicenter	Hypertensive patients, ranging in age from 30 to 70 years, with type 2 DM (WHO criteria), persistent microalbuminuria (defined as an albumin excretion rate of 20 to 200 µg/minute in 2 or 3 consecutive, sterile, overnight urine samples) and a sCr concentration of no more than 133 µmol/L for men and no more than 97 µmol/L for women; HTN was defined by the finding on at least 2 of 3 consecutive measurements obtained one week apart during the run-in period of a mean SBP > 135 mm Hg or mean DBP > 85 mm Hg or both	Irbesartan 150 mg once daily Irbesartan 300 mg once daily Placebo Duration 2 years

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
30	3-week run-in screening period during which all antihypertensive treatment was discontinued and replaced by placebo	Diuretics, beta blockers and nondihydropyridine CCBs	Clinic visits at weeks 2 and 4 and months 3, 6, 12, 18, 22, and 24	58 68.5% male 97.3% white

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
30	BMI 30.1 DM duration 9.7 years SBP 153 mm Hg DBP 90 mm Hg UAE 55.5 µg/min CrCl 109 ml/min	Number screened not reported/1469 eligible/611 enrolled	77(13.1%)/3(.5%)lost to fu/590 analyzed	**Primary endpoint (time to onset diabetic nephropathy)**: Irbesartan150 9.7% Irbesartan300 5.2% Placebo 14.9% Irbesartan300 vs. placebo (HR 0.30 95% CI 0.14-0.61; P<0.001) NNT=8 (95% CI 5-19) Irbesartan150 vs. placebo (HR 0.61 95% CI 0.34-1.08; P=0.08) NNT=16 (95% CI 7-83)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
30	UAE Placebo 2% decrease (P<0.0001 for placebo vs. combined irbesartan groups) Irbesartan150 24% decrease Irbesartan300 38% decrease Restoration of normoalbuminuria Placebo 21% Irbesartan150 24% Irbesartan300 34%(P=0.006 vs. placebo) CrCl change at 24 months (estimated from graph) Placebo 3.7% decrease Irbesartan150 5.4% decrease Irbesartan300 6.5% decrease NS	Not reported	Serious adverse events Placebo 22.8% Irbesartan150/300 15.4% (P=0.02) Nonfatal CV events Placebo 8.7% Irbesartan150 Not reported Irbesartan300 4.5% NS	Total withdrawals Placebo 30/201(14.9%) Irbesartan150 27/195(13.8%) Irbesartan300 20/194(10.3%) Withdrawals due to adverse events Placebo 17/201(8.4%) Irbesartan150 18/195 (9.2%) Irbesartan300 8/194 (4.1%)

Evidence table 2. Placebo/active-controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

ID	(16) Comments
30	Average BP: placebo (144/83 mm Hg); irbesartan150 (143/83 mm Hg); irbesartan300 (141/83 mm Hg) (SBP P=0.0004 placebo vs. combined irbesartan groups)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2027	Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial (Good)	RCT, multicenter	Age 50 or older with HTN (treated or untreated) mean BP 160-210/< 115 mm Hg (untreated) and CV risk factors (male, age > 50 years, verified DM, current smoking, high total cholesterol, LVH by ECG, proteinuria on dipstick and raised sCr between 150 and 265 µmol/L); and CV disease (verified coronary disease, cerebrovascular disease or peripheral arterial occlusive disease, or LVH with strain pattern)	Valsartan 80mg or amlodipine 5mg once daily with five step upward titration (step 1: valsartan 80mg or amlodipine 5mg; step 2: valsartan 160mg or amlodipine 10mg; step 3: valsartan 160mg + HCTZ 12.5mg or amlodipine 10mg + HCTZ 12.5mg; step 4: valsartan 160mg + HCTZ 25mg or amlodipine 10mg + HCTZ 25mg; step 5: other HTN drugs) to achieve target BP < 140/90 mm Hg Mean follow-up 4.2 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2027	None	Addition of other antihypertensive agents (except AIIRAs) allowed to achieve target BP; ACEIs or CCBs allowed only if clinically indicated for reasons other than HTN (patients on study medication at primary endpoint including stroke or at final visit for those without event: 15.9% on valsartan 80mg and 11.1% on 160mg; 20.8% on amlodipine 5mg and 14.5% on 10mg; HCTZ in 2.1% on valsartan 80mg and in 22.5% on 160mg; HCTZ in 4.3% on amlodipine 5mg and in 19.5% on 10mg; 23.0% in valsartan treatment group and 16.8% in amlodipine group on other combinations or drugs, respectively; 25.5% in valsartan treatment group and 23.9% in amlodipine group were classified as not on study therapy)	Primary endpoint included time to first cardiac event (composite sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or CABG, death due to HF, and death associated with recent MI on autopsy, HF requiring hospital management, nonfatal MI, or emergency procedures to prevent MI); secondary endpoints included fatal and nonfatal MI, fatal and nonfatal HF, and fatal and nonfatal stroke. Additional pre-specified endpoints included all-cause mortality and new-onset DM. Safety was monitored by an independent data and safety monitoring board. Patients were followed-up at regular visits	Mean age 67 58% male, 89% white, 4% black, 3.5% Oriental, 3% Other

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2027	CHD: 45.6% valsartan, 46.0% amlodipine; peripheral arterial disease: 13.8% valsartan, 14.0% amlodipine; stroke or TIA: 19.8% valsartan, 19.8% amlodipine; LVH with strain pattern: 5.9% valsartan, 6.1% amlodipine; previous HTN treatment: 92.7% valsartan, 92.0% amlodipine; BP 154/87 mm Hg	18,124 screened/15,313 eligible/15,245 enrolled	71 withdrawn/90 from closed sites/90 lost to fu/15,245 analyzed	**Primary endpoint (time to first cardiac event):** valsartan vs. amlodipine HR 1.04 (95% CI 0.94-1.15; P=0.49); when analyzed separately, cardiac mortality HR 1.01 (95% CI 0.86-1.18; P=0.90), cardiac morbidity HR 1.02 (95% CI 0.91-1.15; P=0.71)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2027	**Secondary endpoints:** valsartan vs. amlodipine fatal and nonfatal MI HR 1.19 (95% CI 1.02-1.38; P=0.02), fatal and nonfatal HF HR 0.89 (95% CI 0.77-1.03; P=0.12), and fatal and nonfatal stroke HR 1.15 (95% CI 0.98-1.35; P=0.08); additional pre-specified endpoints: all-cause mortality HR 1.04 (95% CI 0.94-1.14; P=0.45), and new-onset DM HR 0.77 (95% CI 0.69-0.86; P<0.0001)	Adverse events and prespecified safety outcomes were monitored throughout study	Pre-specified adverse events: peripheral edema: valsartan (14.9%) vs. amlodipine (32.9%) (P<0.0001); dizziness: valsartan (16.5%) vs. amlodipine (14.3%) (P<0.0001); headache: valsartan (14.7%) vs. amlodipine (12.5%) (P<0.0001); fatigue: valsartan (9.7%) vs. amlodipine (8.9%) (P=0.075). Reported as serious: angina pectoris: valsartan (4.4%) vs. amlodipine (3.1%) (P<0.0001); atrial fibrillation: valsartan (2.4%) vs. amlodipine (2.0%) (P=0.1197); syncope: valsartan (1.7%) vs. amlodipine (1.0%) (P<0.0001); mean potassium unchanged with valsartan (baseline 4.4±0.4 mmol/L vs. 4.4+0.5 mmol/L at study end) and decreased slightly with amlodipine (baseline 4.4+0.5 mmol/L vs. 4.2+0.5 mmol/L at study end)	Total withdrawals not reported: 37 on valsartan vs. 34 on amlodipine withdrew consent; 43 on valsartan vs. 47 on amlodipine were enrolled at sites that closed prematurely; 40 on valsartan vs. 50 on amlodipine were lost to follow-up; 911 (11.9%) on valsartan vs. 983 (12.9%) on amlodipine withdrew due to adverse events

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
2027	At the end of the study, median dose (mg/day): valsartan 151.7 (interquartile range 83.2-158.5), amlodipine 8.5 (interquartile range 5.0-9.9); mean BP at study end or final visit 139.3±17.6/79.2±9.8 mm Hg in the valsartan treatment groups vs. 137.5±15.0/77.7±9.0 mm Hg in the amlodipine treatment groups (BP reduction from baseline 15.2/8.2 mm Hg with valsartan vs. 17.3/9.9 mm Hg; P<0.0001), difference in BP reduction greater with amlodipine earlier in trial (4.0/2.1 mm Hg after 1 month compared to 2.0/1.5 mm Hg after 1 year, and approximately 1.5/1.3 mm Hg thereafter); more patients in the valsartan group received the highest dose of the study drug plus HCTZ plus other antihypertensive agents compared to the amlodipine group, with less patients on valsartan monotherapy compared to amlodipine

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2018	Kondo, 2003 Japan (Poor)	RCT, single center, open	History coronary intervention without significant coronary stenosis on angiography at 6 months	Candesartan 4mg once daily vs. standard therapy control group Mean follow-up 2 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2018	None	Continued other medications: ACEIs (candesartan 21%, control 29%); beta-blockers (candesartan 14%, control 14%); statins (candesartan 37%, control 32%); aspirin (candesartan 68%, control 67%)	Primary endpoint: composite of revascularization, nonfatal MI, or CV death; secondary endpoint: hospitalization for CV causes (worsening angina or HF); CV events diagnosed by 2 cardiologists Time period for follow-up not specified	Mean age 65 76% male, ethnicity not specified

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2018	Candesartan vs. control History MI: 67% vs. 70% Current smoker: 25% vs. 21% HTN: 48% vs. 39% DM: 27% vs. 23% HL: 51% vs. 46%	Number screened not reported/number eligible not reported/406 enrolled	9 withdrawn/none lost to fu/406 analyzed	**Primary endpoint (composite revascularization, nonfatal MI, CV mortality):** Candesartan 12/203 (5.9%) vs. control 25/203 (12.3%) RR 0.47 (95% CI 0.24-0.93; P=0.03), calculated NNT= 16 (95% CI 8, 125)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2018	**Secondary endpoints (hospitalization for CV causes):** Candesartan 9/203 (4.4%) vs. control 16/203 (7.9%) RR 0.55 (95% CI 0.24-1.23; P=0.14) **All events:** Candesartan 23/203 (11.3%) vs. control 40/203 (19.7%) RR 0.55 (95% CI 0.33-0.92; P=0.02)	Not reported	Candesartan: dizziness or lightheadedness (9 patients); no significant changes in biochemical data reported	Total withdrawals not reported; 9 patients on candesartan withdrew due to adverse events; 2 patients in control group relocated (phone fu)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
2018	No significant difference in BP at baseline or follow-up. Significant interaction with concomitant medications on events for no ACEIs (P=0.01), no beta-blockers (P=0.03), and aspirin (P=0.04) in favor of candesartan

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2000	Julius, 2004 U.S., U.K., Scandinavia LIFE trial substudy (Black patients) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) and LVH (by ECG), Sitting BP 160-120/95-115 mmHg after 1-2 weeks of placebo	Refer to Interventions LIFE trial (Dahlof, 2002) below

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
2000	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (US Black patients: 12% on losartan 50mg and 44% on 100mg required addition of HCTZ and/or other drugs; 13% on atenolol 50mg and 38% on 100mg required addition of HCTZ and/or other drugs, US Non-Black patients: 11% on losartan 50mg and 41% on 100mg required addition of HCTZ and/or other drugs; 14% on atenolol 50mg and 32% on 100mg required addition of HCTZ and/or other drugs)	Refer to Outcome Assessment LIFE trial (Dahlof, 2002) below; only composite and components of primary endpoint reported for subanalysis	Reported for US Black vs. US Non-Black: 65 vs. 67.4

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
2000	US Black vs. US Non-Black Current smoker: 25% vs. 13.2% Prior CHD: 23.1% vs. 32.4% DM: 25.4% vs. 19.6%	Not available by ethnic background/533 Black patients enrolled worldwide (523 in US)	Number withdrawn not reported/number lost to fu not reported/533 worldwide and 523 US Black patients analyzed	**Primary endpoint (composite CV mortality, fatal or nonfatal MI, fatal or nonfatal stroke):** Worldwide Black patients: losartan (n=270) vs. atenolol (n=263) 17% vs. 11% adjusted HR 1.666 (95% CI 1.043-2.661; P=0.033), calculated NNT=17 (95% CI 8, 1000); Worldwide Non-Black patients: losartan (n=4355) vs. atenolol (n=4325) 10.7% vs. 12.9% adjusted HR 0.829 (95% CI 0.733-0.938; P=0.003), calculated NNT=45 (95% CI 28, 125); US Black patients: losartan (n=264) vs. atenolol (n=259) 17.4% vs. 11.2% adjusted HR 1.665 (95% CI 1.042-2.659; P=0.033), calculated NNT=16 (95% CI 8, 400); US Non-Black patients: losartan (n=605) vs. atenolol (n=579) 11.2% vs. 14.9% adjusted HR 0.722 (95% CI 0.525-0.994; P=0.046), calculated NNT=29 (95% CI 14, 265)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2000	**Secondary endpoints (components of primary endpoint): Fatal or nonfatal stroke:** Worldwide Black patients: losartan (n=270) vs. atenolol (n=263) 8.9% vs. 4.6% adjusted HR 2.179 (95% CI 1.079-4.401; P=0.030) (no significant difference in CV death or MI). Worldwide Non-Black patients: losartan (n=4355) vs. atenolol (n=4325) fatal or nonfatal stroke 4.8% vs. 6.9% adjusted HR 0.700 (95% CI 0.586-0.836; P<0.001) (no significant difference in CV death or MI). US Black patients: losartan (n=264) vs. atenolol (n=259) 9.1% vs. 4.6% adjusted HR 2.181 (95% CI 1.080-4.403; P=0.030) (no significant difference in CV death or MI). US Non-Black patients: losartan (n=605) vs. atenolol (n=579) (no significant difference in CV death, MI, or stroke)	Not reported for subanalysis	Not reported for subanalysis	Total withdrawals (off-study drug): US Black patients losartan 33% vs. atenolol 37%, US Non-Black patients losartan 33% vs. atenolol 38%; withdrawals due to adverse events not reported

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
2000	Compared US Black vs. US Non-Black patients due to differences in baseline characteristics between US vs. overall. At last visit before primary endpoint or end of the study, mean BP US Black patients 141.7/80.6 mm Hg on losartan vs. 142.7/80.5 mm Hg on atenolol and in US Non-Black patients 140.4/77.8 mm Hg on losartan vs. 140.3/76.4 mm Hg on atenolol

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
11	Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) and LVH (by ECG)	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.8 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
11	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (18% on losartan 50mg and 48% on 100mg required addition of HCTZ and/or other drugs; 20% on atenolol 50mg and 41% on 100mg required addition of HCTZ and/or other drugs)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest, new-onset DM. CV events were reviewed by an endpoint classification committee and deaths were reported to the data and safety monitoring board. Patients were followed-up at regular visits	Mean age 67 46% male, 92% white, 6% black, 1% Hispanic, 0.5% Asian

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
11	25% any vascular disease; 13% DM	10,780 screened/9222 eligible/9193 enrolled	78 withdrawn/12 lost to fu/9193 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted HR 0.87 (95% CI 0.77-0.98; P=0.021), calculated NNT=56 (95% CI 32-217); when analyzed separately, fatal or nonfatal stroke adjusted HR 0.75 (95% CI 0.63-0.89; P=0.001) NNT=59 (95% CI 38-136) , no significant difference in CV death or MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
11	**Secondary endpoints:** losartan vs. atenolol not significantly different except new onset DM adjusted HR 0.75 (95% CI 0.63-0.88; P=0.001)	Monitored throughout study; recorded at each visit on a worksheet	Hypotension: losartan (3%) vs. atenolol (2%) (P=0.001); cough: losartan (3%) vs. atenolol (2%); angioedema: losartan (0.1%) vs. atenolol (0.2%); bradycardia (P<0.0001), cold extremities (P<0.0001), sexual dysfunction (P=0.009) occurred more frequently with atenolol vs. losartan ; potassium was unchanged with losartan (0.0±0.4mmol/L) and decreased slightly with atenolol (0.1±0.5mmol/L)	Losartan vs. atenolol: 105/4605 (2.3%) vs. 92/4588 (2.0%) withdrew for any reason (1043/4605 (23%) losartan and 1243/4588 (27%) atenolol were off study drugs); approximately 13% on losartan vs. 18% on atenolol withdrew due to adverse events (P<0.0001)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
11	At the end of the study, mean dose (mg/day): losartan 82±24, atenolol 79±26; Mean BP 144.1+17.1/81.3+9.6 mm Hg on losartan vs. 145.4+16.4/80.9+9.6 mm Hg on atenolol, adjustment for BP changes did not alter outcome

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
14	Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) trough BP 160-200/95-115 mm Hg and LVH (by ECG); focus on patients without previous coronary, cerebral, or peripheral vascular disease	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.8 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
14	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (19% on losartan 50mg and 49% on 100mg required addition of HCTZ or other drugs; 20% on atenolol 50mg and 43% on 100mg required addition of HCTZ or other drugs)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest, new-onset DM. All events were reviewed by an endpoint classification committee. Patients were followed-up at regular visits	Mean age 66 44% male, 93% white, 5% black, 1% Hispanic, 0.6% Asian

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
14	11% DM; BP 174/98 mm Hg	10,780 screened/9222 eligible/6886 of 9193 enrolled in substudy	Number withdrawn not stated/none lost to fu before endpoint occurrence/6886 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted HR 0.81 (95% CI 0.69-0.95; P=0.008), NNT=53 (95% CI 31-187); when analyzed separately, fatal or nonfatal stroke adjusted HR 0.66 (95% CI 0.53-0.82; P<0.001) NNT=54 (95% CI 35-114), no significant difference in CV death or MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
14	**Secondary endpoints:** losartan vs. atenolol not significantly different except new onset DM adjusted HR 0.69 (95% CI 0.57-0.84; P<0.001)	Monitored throughout study; recorded at each visit on a worksheet	Any adverse event: losartan (12.7%) vs. atenolol (17.3%) (P<0.001); drug-related adverse event: losartan (6.0%) vs. atenolol (10.2%) (P<0.001); serious adverse event: losartan (3.8%) vs. atenolol (4.4%) (P>0.2); serious, drug-related adverse event: losartan (0.5%) vs. atenolol (1.0%) (P=0.018)	Total withdrawals and withdrawals due to adverse events not specified; losartan 701/3402 (21%) and atenolol 866/3484 (25%) were off study drugs at the end of the trial

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
14	At the end of the study, mean dose (mg/day): losartan 82, atenolol 79; Mean BP 144.0/81.7 mm Hg on losartan vs. 145.1/81.4 mm Hg on atenolol, adjustment for BP as a time-varying covariate for the primary outcome (HR 0.822 (CI 0.684-0.988, P=0.037)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
13	Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) trough BP 160-200/< 90 mm Hg and LVH (by ECG)	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.7 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
13	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (20.6% on losartan 50mg and 41.8% on 100mg required addition of HCTZ and/or other drugs; 22.2% on atenolol 50mg and 35.4% on 100mg required addition of HCTZ and/or other drugs)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest, new-onset DM. Findings of the primary outcome were confirmed with an on-treatment approach that censored end points from patients 14 days after the drug was discontinued. Patients were followed-up at regular visits	Mean age 70 40% male, 92% white, 6% black, 1% Hispanic, 0.5% Asian

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
13	DM: 15.6% losartan, 19.8% atenolol; CHD: 23.9% losartan, 21% atenolol; CVD: 10.6% losartan, 12.9% atenolol; BP 174/83 mm Hg	10,780 screened/9222 eligible/1326 of 9193 enrolled in substudy	14 withdrawn/2 lost to fu/1326 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted RR 0.75 (95% CI 0.56-1.01; P=0.06), unadjusted RR 0.71 (95% CI 0.53-0.95; P=0.02), NNT=24 (95% CI 14-172); when analyzed separately, fatal or nonfatal stroke adjusted RR 0.60 (95% CI 0.38-0.92; P=0.02) NNT=28 (95% CI 16 - 112); CV mortality adjusted RR 0.54 (95% CI 0.34-0.87; P=0.01) NNT=27 (95% CI 16-85); no significant difference in MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
13	**Secondary endpoints:** losartan vs. atenolol not significantly different except new onset DM adjusted HR 0.62 (95% CI 0.40-0.97; P=0.04) and total mortality adjusted HR 0.72 (95% CI 0.53-1.00; P=0.046)	Monitored throughout study; recorded at each visit on a worksheet	Hypotension: losartan (4.4%) vs. atenolol (2.7%); cough: losartan (4.1%) vs. atenolol (2.9%); angioedema: losartan (0.3%) vs. atenolol (0.3%); bradycardia (P<0.001), cold extremities (P=0.05) occurred more frequently with atenolol vs. losartan; potassium decreased slightly with losartan (-0.002mEq/L) and with atenolol (-0.08mEq/L)	Losartan vs. atenolol: 9 and 5 withdrew consent (169/660 (25.5%) losartan and 216/666 (32.3%) atenolol discontinued therapy); 14.6% on losartan vs. 22.1% on atenolol discontinued therapy due to an adverse event (P<0.001); 7.1% on losartan vs. 13.5% on atenolol discontinued due to drug-related adverse event (P<0.001)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
13	At the end of the study, mean dose (mg/day): losartan 79, atenolol 76; Mean BP 146/75 mm Hg on losartan vs. 146/74 mm Hg on atenolol (DBP P=0.04), adjustment for BP did not alter outcome

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
12	Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	RCT, multicenter	Age 55 to 80 with HTN (treated or untreated) trough BP 160-200/< 90 mm Hg and LVH (by ECG), DM (most likely type 2 per study)	Losartan 50mg (with addition of HCTZ 12.5mg and subsequent titration to losartan 100mg) or atenolol 50mg (with addition of HCTZ 12.5mg and subsequent titration to atenolol 100mg) to achieve target BP < 140/90 mm Hg Mean follow-up 4.7 years

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
12	1 to 2 weeks of placebo	HCTZ (as described under Interventions); addition of other antihypertensive agents (except ACEIs, AIIRAs, beta-blockers) allowed to achieve target BP (14% on losartan 50mg and 50% on 100mg required addition of HCTZ and/or other drugs; 16% on atenolol 50mg and 46% on 100mg required addition of HCTZ and/or other drugs)	Primary endpoint included CV morbidity and mortality (composite of CV death, MI, and stroke); secondary endpoints included total mortality, angina or HF hospitalization, coronary or peripheral revascularization, resuscitated cardiac arrest. Findings of the primary outcome were confirmed by an endpoint committee. Patients were followed-up at regular visits	Mean age 67 47% male, 86% white, 11% black, 2% Hispanic, 0.8% Asian

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
12	35% any vascular disease; current smokers: 12% losartan, 15% atenolol; BP 177/96 mm Hg	10,780 screened/9222 eligible/1195 of 9193 enrolled in substudy	18 withdrew consent/4 lost to fu/1195 analyzed	**Primary endpoint (composite CV mortality, MI, stroke):** losartan vs. atenolol adjusted HR 0.76 (95% CI 0.58-0.98; P=0.031), NNT=19 (95% CI 10-141); when analyzed separately, CV mortality adjusted HR 0.63 (95% CI 0.42-0.95; P=0.028) NNT=28 (95% CI 15-236); no significant difference in fatal or nonfatal stroke, or MI

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
12	**Secondary endpoints:** losartan vs. atenolol not significantly different except total mortality adjusted HR 0.61 (95% CI 0.45-0.84; P=0.002); HF hospitalization adjusted HR 0.59 (95% CI 0.38-0.92; P=0.019)	Monitored throughout study; recorded at each visit on a worksheet	Hypotension: losartan (2%) vs. atenolol (1%); cough: losartan (4%) vs. atenolol (3%); angioedema: losartan (0.2%) vs. atenolol (0.5%); bradycardia (P<0.0001) occurred more frequently with atenolol vs. losartan; potassium increased slightly with losartan (0.05mmol/L) and was unchanged with atenolol; glucose increased slightly with both losartan and atenolol (0.05mmol/L)	Losartan vs. atenolol: 0 and 4 withdrew consent (159/586 (27%) losartan and 194/609 (32%) atenolol discontinued therapy); 0.3% on losartan vs. 2% on atenolol discontinued therapy due to a serious drug-related adverse event (P=0.065)

Evidence Table 3. Active-controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

ID	(16) Comments
12	Mean BP at last visit before primary endpoint or at end of study 146/79 mm Hg on losartan vs. 148/79 mm Hg on atenolol, adjustment for BP had little effect (data not shown). Open-label AIIRA or ACEI allowed after study drug discontinued

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
29	Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age AMI (within 0.5 to 10 days) complicated by clinical or radiologic signs of HF, LV systolic dysfunction (EF ≤ 0.35 on ECHO or contrast angiography and ≤ 0.40 on radionuclide ventriculography), or both SBP > 100 mm Hg, sCr < 2.5mg/dl	Titration by 3 months to: valsartan 160mg twice daily vs. valsartan 80mg twice daily + captopril 50mg three times daily vs. captopril 50mg three times daily (medication adjusted at investigator's discretion) Mean follow-up 2.1 years

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
29	None	ACEI or AIIRA up to 12 hours prior to randomization Baseline: beta-blockers (70%); aspirin (91%)	Primary endpoint was all-cause mortality; clinical status, study outcomes (Definitions of End Points available in Supplementary Index 1. at www.nejm.org); drug tolerance, quality of life, pharmacoeconomic variables assessed at each visit (i.e., 6 times during first year, then at 4 month intervals for the duration of the trial)	Mean age 65 69% male, 93.5% white, 2.8% black, 1% Asian, 2.8% other

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
29	35.3% LVEF, 28% previous MI, 49% Killip class II, 15% HF, 7% CABG, 7.2% PCI, 6% stroke	Number screened not reported/number eligible not reported/14,808 enrolled	105 information censored due to informed-consent process at one site/139 vital status unavailable (55 of these withdrew consent)/14,703 analyzed	**Primary endpoint (all-cause mortality):** valsartan vs. captopril: HR 1.00 (97.5% CI 0.90-1.11; P=0.98); valsartan + captopril vs. captopril: HR 0.98 (97.5% CI 0.89-1.09; P=0.73); mortality at one year estimates: 12.5% valsartan, 12.3% valsartan + captopril, 13.3% captopril

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
29	**Secondary endpoints:** valsartan vs. captopril: combined CV mortality and MI, or HF HR 0.95 (97.5% CI 0.88-1.03; P=0.20); P<0.001 for non-inferiority; valsartan + captopril vs. captopril: combined CV mortality and MI, or HF HR 0.97 (97.5% CI 0.89-1.05; P=0.37); additional comparisons of CV mortality and morbidity not statistically significant	Elicited by investigator at study visit	hypotension: valsartan (15.1%) vs. valsartan + captopril (18.2%) vs. captopril (11.9%) decreased dose (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril); valsartan (1.4%) vs. valsartan + captopril (1.9%) vs. captopril (0.8%) discontinued treatment (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril) cough: valsartan (1.7%) vs. valsartan + captopril (4.6%) vs. captopril (5.0%) decreased dose (P<0.05 valsartan vs. captopril); valsartan (0.6%) vs. valsartan + captopril (2.1%) vs. captopril (2.5%) discontinued treatment (P<0.05 valsartan vs. captopril)	renal causes: valsartan (4.9%) vs. valsartan + captopril (4.8%) vs. captopril (3.0%) decreased dose (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril); valsartan (1.1%) vs. valsartan + captopril (1.3%) vs. captopril (0.8%) discontinued treatment (P<0.05 valsartan + captopril vs. captopril) hyperkalemia: valsartan (1.3%) vs. valsartan + captopril (1.2%) vs. captopril (0.9%) decreased dose; valsartan (0.1%) vs. valsartan + captopril (0.2%) vs. captopril (0.1%) discontinued treatment angioedema: valsartan (0.2%) vs. valsartan + captopril (0.5%) vs. captopril (0.5%) decreased dose; valsartan (0.2%) vs. valsartan + captopril (0.2%) vs. captopril (0.3%) discontinued treatment

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
29	valsartan vs.valsartan + captopril vs. captopril: 1001/4885 (20.5%) vs. 1139/4862 (23.4%) vs. 1055/4879 (21.6%) discontinued treatment for any reason (P<0.05 valsartan + captopril vs. captopril); valsartan vs.valsartan + captopril vs. captopril: 282/4885 (5.8%) vs. 438/4862 (9.0%) vs. 375/4879 (7.7%) discontinued treatment due to adverse events (P<0.05 valsartan vs. captopril, valsartan + captopril vs. captopril)	Pre-specified tests for noninferiority for valsartan vs. captopril showed that the upper limit of one-sided 97.5% CI was in the specified margin for noninferiority (P=0.004 intention-to-treat analysis; P=0.002 per-protocol analysis). The effect of valsartan was estimated to be 99.6% of captopril (95% CI 60 to 139). At 1 year, mean dose (mg/day): valsartan 247 ± 105, valsartan 116 ± 53 + captopril 107 ± 53, captopril 117 ± 49; target dose: valsartan 56%, valsartan + captopril 47%, captopril 56% Mean SBP: 2.2 mm Hg lower valsartan + captopril vs. captopril (P<0.001); 0.9 mm Hg lower valsartan vs. captopril (P<0.001)

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
28	Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial (Good)	RCT, multicenter	Men and women $\geq$ 50 years of age with documented AMI and signs or symptoms of HF during the acute phase or new Q-wave anterior infarction or reinfarction	Losartan 12.5mg daily, titrated to 50mg daily vs. captopril 12.5mg three times daily, titrated to 50mg three times daily Mean follow-up 2.7 years

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity	
28	None	Baseline: beta-blockers (79%); aspirin (95%); thrombolytic (54%)	Primary (all-cause mortality), secondary, and tertiary endpoints and fatal or nonfatal stroke were adjudicated by the endpoint committee. Causes for hospital admission were determined by the investigator. Safety and tolerability assessment included discontinuations due to adverse events and prespecified adverse events. Biochemical test were perfomed at a core laboratory and health-related quality-of-life was assessed	Mean age 67 male, 98.5% white	71%

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
28	18% previous MI, 57% Killip class II, 6% HF, 2.5% CABG, 3.4% stroke	31,738 screened/number eligible not reported/5477 enrolled	1082 withdrawn/1 lost to follow-up/5477 analyzed	**Primary endpoint (all-cause mortality):** losartan vs. captopril: RR 1.13 (95% CI 0.99-1.28; P=0.069)

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
28	**Secondary endpoints:** losartan vs. captopril: sudden cardiac death or resuscitated cardiac arrest RR 1.19 (95% CI 0.99-1.43; P=0.072); fatal or nonfatal reinfarction RR 1.03 (95% CI 0.89-1.18; P=0.722)	Monitored	hypotension: losartan (13.3%) vs. captopril (16.3%); cough: losartan (9.3%) vs. captopril (18.7%) (P<0.0001), discontinued treatment (P<0.0001 losartan vs. captopril); angioedema: losartan (0.4%) vs. captopril (0.8%), discontinued treatment (P=0.019 losartan vs. captopril)	skin rash: losartan (3.1%) vs. captopril (4.6%) (P=0.005), discontinued treatment (P=0.0008 losartan vs. captopril); taste disturbance: losartan (0.6%) vs. captopril (2.7%) (P<0.0001), discontinued treatment (P<0.0001 losartan vs. captopril); significant difference losartan vs. captopril in change from baseline for serum uric acid (49.6*u* mol/L vs. 60.8*u* mol/L, respectively P=0.01) and serum potassium (0.19mmol/L vs. 0.22mmol/L, respectively P=0.01)

Evidence table 4. Active-controlled trials of angiotensin II receptor antagonists in patients after recent myocardial infarction (N=2)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
28	losartan vs.captopril: 458/2744 (17%) vs. 624/2733 (23%) discontinued treatment for any reason (P<0.0001); 202/2744 (7%) vs. 387/2733 (14%) discontinued treatment due to adverse events (P<0.0001)	Results did not show superiority or noninferiority for losartan compared to captopril. If losartan had demonstrated noninferiority, this would have also implied that losartan is superior to placebo. This assumption could not be made from the results of the trial. Mean dose at end of trial: losartan 45 $\pm$ 12mg daily, captopril 44 $\pm$ 12mg three times daily; target dose at 1 month: losartan 71%, captopril 70%. Mean SBP/DBP were lower at 1 hour with captopril vs. losartan (P<0.0001), otherwise recorded blood pressures were similar

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2001	Little, 2004 U.S. (Fair)	RCT, crossover	LVEF > 50% by ECHO, no evidence MI on stress ECG, no significant valvular heart disease, resting SBP ≤ 150 mm Hg, mitral valve Doppler flow pattern with peak E wave < peak A wave velocity, peak exercise SBP > 200 mm Hg	Candesartan 16 mg vs. verapamil SR 180 mg (each given daily every evening) for 2 weeks; 2 week washout; patients crossed over to other treatment for 2 weeks
2010	Kasama, 2003 Japan (Fair)	RCT	Men and women with congestive HF	Valsartan 40 to 80 mg daily vs. current drug therapy for 6 months
19	Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	RCT, multicenter	Men and women ≥ 60 years of age (85% > 65 years), NYHA class II-IV HF and LVEF ≤ 40% (by ECHO or radionuclear ventriculography), no previous ACEI or AIIRA use (unless length of therapy ≤ 7 days within 3 months prior to randomization)	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily vs. captopril 12.5mg three times daily, then 25mg, up to 50mg three times daily Mean follow-up 1.5 years

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
2001	2 week washout between treatments	ACEIs (3 patients); beta-blockers (3 patients); diuretics (2 patients)	Endpoints included exercise tolerance, hypertensive response to exercise, QOL (by MLHFQ). Treadmill exercise test (modified Bruce protocol), ECHO, and QOL performed at baseline, end of first 2 weeks treatment, end of second two weeks treatment after cross-over
2010	None	All treated with ACEIs and loop diuretics; no patients treated with beta-blockers	Endpoints included cardiac sympathetic nerve activity, LV function, symptoms. Series of examinations performed prior to treatment and at 6 months
19	Single-blind placebo run-in of 1 to 28 days (matched to losatan or captopril tablets) for patient assessment and clinical stability, and to ensure adherence	All treatments allowed except for open-label ACEIs or AIIRAs Baseline: beta-blockers (22%); ACEIs (23%)	Primary endpoint (all-cause mortality), secondary endpoint (composite sudden cardiac death or resuscitated cardiac arrest); clinical assessment every 4 months, laboratory assessments at 1 month then every 4 months, study outcomes reviewed and classified by independent clinical endpoint committee

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2001	Mean age 64 38% male Ethnicity not reported	48% HTN Baseline BP 140±12/80±5 mm Hg	Number screened not reported/number eligible not reported/22 enrolled	3 withdrawn/number lost to fu not reported/21 analyzed
2010	Valsartan vs. control Mean age (70 vs. 66; NS) Male (62.5% vs. 56.3%; NS) Ethnicity not reported	33% LVEF; 69% NYHA class III, 31% class IV	Number screened not reported/number eligible not reported/32 enrolled	Number withdrawn not reported/number lost to fu not reported/32 analyzed
19	Mean age 71.5 70% male, 82% white, 2% black, 5% Asian, 11% other	31% LVEF, 58% previous MI, 79% ischemia, 52% NYHA class II and 43% class III, 49% HTN	Number screened not reported/number eligible not reported/3152 enrolled	530 died/346 withdrawn/2 lost to fu/3152 analyzed

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
2001	**Endpoint (Increase in exercise duration)** Candesartan (baseline vs. end treatment) 793±182 vs. 845±163 seconds (P<0.05) Verapmil (NS) Candesartan vs. verapamil not reported	**Endpoint (QOL score)** Candesartan (baseline vs. end treatment) 11±14 vs. 5±6 seconds (P<0.05) Verapmil (NS) Candesartan vs. verapamil not reported	Not reported
2010	**Endpoint (NYHA functional class):** Baseline vs. 6 months Valsartan 3.3±0.5 vs. 1.7±0.6 P<0.0005 vs. baseline Control 3.3+0.5 vs. 2.4+0.6 P<0.005 vs. baseline P<0.05 valsartan vs. control		Not reported
19	**Primary endpoint (all-cause mortality):** losartan vs. captopril: 17.7% vs 15.9% HR 1.13 (95.7% CI 0.95-1.35; P=0.16) average annual mortality rate: 11.7% losartan, 10.4% captopril	**Secondary endpoints:** losartan vs. captopril: sudden death or resuscitated cardiac arrest HR 1.25 (95% CI 0.98-1.60; P=0.08); combined total mortality or hospital admission for any reason HR 1.07 (95% CI 0.97-1.19; P=0.18); hospital admissions HR 1.04 (95% CI 0.94-1.16; P=0.45); hospital admissions for HF HR 0.92 (95% CI 0.78-1.08; P=0.32)	Not reported

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2001	Not reported	3 withdrew/withdrawals due to adverse events not reported
2010	Not reported	Not reported
19	Withdrawals due to cough: losartan vs. captopril ~1% vs. ~3% (P<0.001); worsening HF (25% each group)	losartan vs. captopril: 125/1578 (7.9%) vs. 221/1574 (14.0%) discontinued treatment for any reason; ~10% vs. ~15% (P<0.001) discontinued treatment due to any adverse effect; ~3% vs. ~8% (P<0.001) discontinued treatment due to drug-related adverse effect

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(16) Comments
2001	Unable to determine if results statistically significant between treatments
2010	Patients did not receive treatment with a beta-blocker
19	ELITE II was designed as a superiority trial therefore cannot draw any conclusions about equivalence. The superiority of losartan vs. captopril in reducing mortality (not the primary endpoint) seen in ELITE were based on a small number of deaths, ELITE II had 10 times more events and 4 times more patients. For patients on beta-blockers at baseline losartan vs. captopril HR death 1.77 (those without beta-blockers HR 1.05), difference not noted for patients on concomitatnt therapy throughout the study. Patients randomized according to baseline beta-blocker use. No significant difference in heart rate or BP lowering per last measurement of treatment

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
18 (dup 774)	Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	RCT, multicenter	Age > 65 years, NYHA class II-IV HF and LVEF $\leq$ 40%, no previous ACEI use	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily (with placebo for captopril) vs. captopril 6.25mg three times daily, then 25mg, up to 50mg three times daily (with placebo for losartan) Follow-up 48 weeks
455	Houghton, 1999 U.K. ELITE Trial substudy (Fair)	RCT	Age > 65 years, NYHA class II-IV HF and LVEF $\leq$ 40%, no previous ACEI use	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily (with placebo for captopril) vs. captopril 6.25mg three times daily, then 25mg, up to 50mg three times daily (with placebo for losartan) Follow-up 24 weeks

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
18 (dup 774)	2 week placebo run-in	All CV treatments allowed except for open-label ACEIs Baseline: beta-blockers (16%); non-ACEI vasodilators (40%)	Primary endpoint included renal dysfunction (increase sCr by ≥ 26.5umol/L or ≥ 0.3mg/dl from baseline, confirmed by repeat 5-14 days later); secondary endpoints included all-cause mortality and HF hospitalizations (composite all-cause mortality and HF hospitalizations added as protocol amendment); additional prespecified endpoints included worsening HF (NYHA functional class); clinical assessment every 3 months, laboratory assessments at 3, 6, 12 weeks and then every 3 months; study outcomes reviewed and classified by independent clinical endpoint committee
455	2 week placebo run-in	All CV treatments allowed Baseline: diuretics (90%); no patients on beta-blockers	One of the primary endpoints included exercise capacity as measured by a pair of hip-borne pedometers provided to the patient for periods of 2 weeks to assess activity at home; also assessed by 100 m corridor walk test at self-selected slow, normal, and fast speeds. Patients were evaluated at baseline (placebo run-in visit) and at 12 and 24 weeks

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
18 (dup 774)	Mean age 74 67% male, 90% white, 5% black	31% LVEF, 50% previous MI, 68% HF due to IHD, 65% NYHA class II, 34% class III, 2% class IV, 57% HTN	Number screened not reported/number eligible not reported/722 enrolled	176 withdrawn/number lost to fu not reported/722 analyzed
455	Mean age 73 78% male, ethnicity not specified	23% LVEF, 61% HF due to IHD, 94% NYHA class II, 6% class III	Number screened not reported/number eligible not reported/18 enrolled	4 withdrawn/number lost to fu not reported/number analyzed not specified in results for exercise capacity

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
18 (dup 774)	**Primary endpoint (change in baseline sCr):** % increase in serum creatine: Losartan: 10.5% Captopril: 10.5% Additional prespecified endpoints: NYHA functional class (% class I or II): Losartan: baseline=66% end of study=80% Captopril: baseline=64% end of study=81% P<0.001	**Secondary endpoints:** all-cause mortality: Losartan: 4.8% Captopril: 8.7% RR (95% CI) = 0.46 (0.05-0.69) P=0.035 HF hospitalizations: Losartan: 5.7% Captopril: 5.7% RR (95% CI) = 0.04 (-0.74-0.47) P=0.89 composite all-cause mortality and HF hospitalizations: Losartan: 9.4% Captopril: 13.2% RR (95% CI) = 0.32 (-0.04-0.55) P=0.075	Not reported
455	**One of primary endpoints (exercise capacity):** corridor walk time: pedometer scores: mean score (sem) Losartan: baseline=28980 (4862) week 12=27851 (4987) week 24=28073 (6473) Captopril: baseline=28639 (6372) week 12=29474 (6390) week 24=30496 (5777)		Not reported

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
18 (dup 774)	Withdrawals due to cough: losartan 0/352 (0%) vs. captopril 14/370 (3.8%) (P≤0.002); withdrawals due to angioedema: losartan 0/352 (0%) vs. captopril 3/370 (0.8%); withdrawals due to hyperkalemia: losartan 2/352 (0.6%) vs. captopril 6/370 (1.6%); persisting increases in serum potassium ≥ 0.5mmol/L vs. baseline occurred in 18.8% on losartan and 22.7% on captopril (P=0.069)	losartan vs. captopril: 65/352 (18.5%) vs. 111/370 (30.0%) (P≤0.001) discontinued treatment for any reason or died; 43/352 (12.2%) vs. 77/370 (20.8%) discontinued treatment due to any adverse event (excluding death) (P≤0.002)
455	Not reported	4 withdrawals in the captopril group (none in the losartan group)/3 withdrawals following adverse clinical events; 1 patient died

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(16) Comments
18 (dup 774)	85% patients on losartan achieved target dose (mean 42.6mg) compared to 71% on captopril (mean 122.7mg). Authors report the difference in discontinuation rate did not account for 46% difference in total mortality as the difference was seen predominately in patients who continued on treatment (losartan 11/298 or 3.7% vs. captopril 24/282 or 57%)
455	Methods state sample size gave study power of 75% to detect 15% difference in corridor walk time at P=0.05

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
273	Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	RCT, multicenter	Age > 65 years, NYHA class II-IV HF and LVEF ≤ 40%, no previous ACEI use, English speaking with accesss to a phone and able to use the phone to answer questions	Titration at weekly intervals: losartan 12.5mg once daily, then 25mg, up to 50mg once daily (with placebo for captopril) vs. captopril 6.25mg three times daily, then 25mg, up to 50mg three times daily (with placebo for losartan) Follow-up 48 weeks
1032	Willenheimer, 2002 Sweden HEAVEN Study (Fair)	RCT, multicenter	Males and females ≥ 18 years, stable HF, NYHA class II-III and LVEF ≤ 45%, on ACEI for ≥ 3 months, able to perform 6-min-walk test	Valsartan 80mg once daily titrated after 1 week to 160mg once dailys vs. enalapril 5mg twice daily titrated after 1 week to 10mg twice daily Follow-up 12 weeks

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
273	2 week placebo run-in	All CV treatments allowed Baseline medications not specified	Main objective to measure health related QOL using two instruments, the disease specific Minnesota Living with Heart Failure (LIhFE) and a more general Sickness Impact Profile (SIP) administrerd at baseline (within 7 days prior to randomization) and after 12 and 48 weeks of double-blind therapy
1032	2 week placebo run-in	All other medications kept stable if possible Baseline: ACEIs (100%), beta-blockers (77%)	Primary endpoint included exercise capacity (6-min-walk test) assessed at -2, 0, 6, and 12 weeks; secondary endpoints included clinical status (dyspnea-fatigue index DFI) that describes severity of symptoms (0=worst, 12=no symptoms) and QOL (Minnesota Living with Heart Failure Questionnaire MLWHFQ) using 20 of 21 questions (worst score=100), both assessed at 0 and 12 weeks

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(8) Age Gender Ethnicity		(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
273	Mean age 74 male, 88% white, 10% black	76%	30% LVEF, 68% HF due to IHD, 63% NYHA class II, 37% class III/IV	Number screened not reported/300 eligible/278 enrolled	75 discontinued early from trial (30/147 losartan; 45/153 captopril)/29 lost to fu, withdrawn, or protocol violation/203 complete data available
1032	Mean age 68 male, ethnicity not specified	75%	61% HF due to IHD, 71% NYHA class II, 29% class III	Number screened not reported/146 enrolled/141 randomized	14 withdrawn/number lost to fu not reported/134 analyzed for ITT primary endpoint; 118 analyzed for per protocol population

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
273	**Main objective (HRQOL):** LIhFE (mean change from baseline (sem)): Losartan=-9 (2.5) P=0.586 Captopril=-11 (2.5) P=0.414 SIP: (mean change from baseline (sem)): Losartan=-2.7 (0.5) P=0.689 Captopril=-3 (1) P=0.982		Not reported
1032	**Primary endpoint (exercise capacity):** 6-min-walk test: mean (sd) in minutes Valsartan: baseline=418.2(112.9) 6 weeks=419.3(115.9) 12 weeks=423.7(118.7) Enalapril: baseline=424(115.1) 6 weeks=437.6(106.2) 12 weeks=423.7(113.7)	**Secondary endpoint (exercise capacity):** DFI: LSM change (se) Valsartan=0.24 (0.16) Enalapril=0.26 (0.16) MLWHFQ: LSM change (se) Valsartan=0.7 (1.3) Enalapril=0.9 (1.3)	Adverse events recorded at all visits

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
273	Not reported	75 total withdrawals (30/147 losartan; 45/153 captopril)/46 withdrawals (losartan 16/147 or 10.9% vs. captopril 29/153 or 19.0% for unfavorable reasons (death, clinical or laboratory adverse events)
1032	All adverse events: valsartan 35/70 (50%) vs. enalapril 45/71 (63%); headache: valsartan 4/70 (5.7%) vs. enalapril 1/71 (1.4%); diarrhea: valsartan 3/70 (4.3%) vs. enalapril 2/71 (2.8%); dizziness: valsartan 3/70 (4.3%) vs. enalapril 6/71 (8.5%)	14 total withdrawals including death (valsartan 5/70 or 7.1% vs. enalapril 9/71 or 12.7%)/5 withdrawals due to adverse events (2 valsartan; 3 enalapril)

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(16) Comments
273	After unblinding in ELITE, composite statistical approach used for HRQOL to account for differential dropout rates (noted that higher withdrawal rate with captopril due to adverse events or death and lack of QOL data at time of discontinuation may impact analysis)
1032	Patients stabilized on ACEI prior to inclusion

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
324	Dunselman, 2001 Europe REPLACE (Fair)	RCT, multicenter	Age ≥ 21 years, ambulatory, chronic moderate symptomatic HF, NYHA class II-III and LVEF ≤ 40%, in sinus rhythm, stable on enalapril 10mg twice daily and diuretic (± digoxin) for 28 days prior to randomization	Telmisartan 10, 20, 40, or 80mg once daily vs. enalapril 10mg twice daily Follow-up 12 weeks
20	McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Fair)	RCT, multicenter	NYHA class II, III, or IV HF, 6-min-walk distance (6MWD) < 500m, LVEF < 40%	Candesartan 4, 8, or 16mg once daily vs. enalapril 10mg twice daily vs. candesartan 4 or 8mg once daily plus enalapril 10mg twice daily Follow-up 43 weeks

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
324	Screening phase on enalapril 10mg twice daily and diuretic (+ digoxin) for 28 days	Long-acting nitrates, hydralazine, prazosin, beta-blockers, anticoagulants, antiplatelet agents Baseline: digoxin (39%), utilization of other baseline medications not specified	Primary endpoint included bicycle exercise duration (upright sitting position using bicycle exercise test protocol 2hrs after morning medications) assessed at least twice during screening and at 4 and 12 weeks; secondary endpoints included NYHA functional class (assessed at screening and during treatment), QOL (Minnesota Living with Heart Failure Questionnaire MLHF) assessed at screening and after 4 and 12 weeks of treatment
20	Three phases (each 1 week duration): enalapril 2.5mg twice daily plus placebo candesartan; enalapril 2.5mg twice daily plus candesartan 2mg daily; enalapril 2.5mg twice daily plus placebo candesartan	Medications for HF Baseline: diuretics (84%), digoxin (71%), beta-blockers (14% candesartan group, 13% combination group, 23% enalapril group; P<0.05 both vs. enalapril group) At 19 weeks, eligible patients (without contraindications and did not refuse therapy) were randomized to metoprolol or placebo	Endpoints included change from baseline in 6MWD (performed in duplicate), NYHA functional class, and QOL (Minnesota Living with Heart Failure Questionnaire) assessed at weeks 17 or 18 and week 43

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
324	Mean age 65 89% male, ethnicity not specified	26% LVEF, 78% HF due to IHD, 64% NYHA class II, 36% class III	Number screened not reported/number eligible not reported/378 enrolled	11 withdrawn/number lost to fu not reported/367 analyzed for primary endpoint; 378 analyzed for safety
20	Mean age 63 85% male, ethnicity not specified	27% LVEF, 72% HF due to IHD, 63% NYHA class II, 35% class III, 2% class IV	Number screened not reported/899 eligible/768 enrolled	Number withdrawan not reported/number lost to fu not reported/768 analyzed

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
324	**Primary endpoints (exercise capacity):** bicycle exercise duration: mean (sd) exercise duration (s) relative to enalapril: Telmisartan10 mg = 7.2 (16) Telmisartan 20 mg = 6.8 (15) Telmisartan 40 mg = 0.8 (14) Telmisartan 80 mg = 5.7 (16)	**Secondary endpoint (exercise capacity):** MLHF: Replacement of enalapril by any dose of telmisartan studies did not significnatly affect the total MLHF score. NYHA functional class: There were no significant changes detected for any group in NYHA classification.	Monitored vital signs and laboratory tests at 4 and 12 weeks; 12 lead ECG before each exercise test and 24hr Holter ECG at baseline and 12 weeks; type, onset, duration, intensity, treatment required, outcome, relationship to study drug, documented for all adverse events during study; serious adverse events were fatal, life-threatening, disabling, or requiring prolonged hospital stay
20	**Endpoints (exercise capacity):** 6MWD: mean (se) at baseline and follow-up in m Candesartan: baseline=379 (5) follow-up=390 (6) Candesartan/Enalapril: baseline=386 (5) follow-up=385 (6) Enalapril: baseline=374 (8) follow-up=387 (11)	**Endpoints:** NYHA functional class: No significant differences between groups QOL (Minnesota Living with Heart Failure Questionnaire): No significant differences between groups	Not reported

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
324	Cough: telmisartan 9/301 (3%) vs. enalapril 4/71 (5.6%) (P=0.3)	11 withdrawals for protocol violations (4 telmisartan 10mg; 2 telmisartan 40mg; 3 telmisartan 80mg; 2 enalapril 20mg)/9 withdrawals due to adverse events (6 withdrawals due to death: 2 telmisartan 20mg, 1 telmisartan 40mg, 1 telmisartan 80mg, 2 enalapril 20mg; 3 withdrawals due to adverse events with telmisartan)
20	Potassium: candesartan - 0.23±0.03 mmol/L vs. enalapril 0.01±0.05 mmol/L (P<0.05) at 43 weeks; vs. candesartan plus enalapril 0.11+0.03 mmol/L (P<0.05) at 43 weeks	Total withdrawals not reported/withdrawals due to adverse events not reported

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(16) Comments
324	Patients stabilized on ACEI prior to inclusion
20	Pilot trial. Study terminated 6 weeks early due to concern by External Safety and Efficacy Monitoring Committee [increase in HF hospitalizations with candesartan and candesartan plus enalapril compared to enalaparil alone (3 way group comparison P=0.048) and mortality plus HF hospitalization (3 way comparison P=0.058)] although not powered to assess morbidity and mortality

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
545	Lang, 1997 U.S., Canada (Fair)	RCT, multicenter	Symptomatic HF, NYHA class II-IV and LVEF $\leq$ 45%, received stable doses of an ACEI for 6 weeks and a diuretic for 2 weeks	Losartan 12.5mg, titrated as tolerated to 25mg daily vs. losartan 12.5mg, titrated as tolerated to 25mg, then 50mg daily vs.enalapril 2.5mg titrated as tolerated to 5mg, then 10mg twice daily Follow-up 12 weeks
312	Dickstein, 1995 Scandinavia (Fair)	RCT, multicenter	Symptomatic HF, stabilized on an ACEI	Losartan 12.5mg, titrated as tolerated to 25mg or 50mg once daily vs. enalapril 2.5mg titrated as tolerated sequentially to 5 and 10mg twice daily (placebo tablets provided to secure blinding due to different dosage intervals) Follow-up 8 weeks

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
545	After screening visit, placebo in additional to stable ACEI and diuretic for 3 visits (time period not specified) during baseline exercise period; open-label ACEI discontinued prior to randomization	Digoxin (dose stable for previous 2 weeks), non-ACEI vasodilators (dose stable for previous 6 weeks) Baseline: digoxin (85%), beta-blockers (10.5% losartan 25mg group, 2.5% losartan 50mg group, 7.9% enalapril group), other vasodilators (34.2% losartan 25mg group, 55% losartan 50mg group, 60.5% enalapril group; P<0.05 losartan 25mg vs. enalapril)	Endpoints included change from baseline in symptom-limited treadmill exercise duration (patients randomized to "treadmill patient" if completed 2 consecutive baseline treadmill tests where exercise duration did not differ by more than 10% or "non-treadmill patient") assessed at 6, 11, and 12 weeks post-randomization, 6-min walk test assessed at 6, 9, and 12 weeks post-randomization, dyspnea-fatigue index assessed at 6, and 12 weeks post-randomization, and signs and symptoms of HF (dyspnea, PND, orthopnea, jugular venous pressure, peripheral edema, pulmonary rales, and third heart sound), and NYHA functional class
312	Three week placebo run-in while on stable ACEI doses	Diuretic and digoxin doses kept stable if possible Baseline: digoxin (63%), beta-blockers (19% losartan 25mg group, 11% losartan 50mg group, 7% enalapril group; difference not statistically significant)	Primary endpoints included assessment of exercise capacity (change from baseline in 6-min walk test and dyspnea-fatigue index, both assessed at 8 weeks with average of last two baseline tests was used as baseline measurement), and clinical status (dyspnea, PND, orthopnea, jugular venous pressure, peripheral edema, pulmonary rales, and third heart sound), and NYHA functional class assessed at baseline and weeks 1, 2, 3, 4, 6 and 8

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(8) Age Gender Ethnicity		(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
545	Mean age 58 male, 71% white, 22% black, 5% Hispanic, 3% Asian	78%	47% HF due to IHD, 47% NYHA class II, 51% class III, 2% class IV	Number screened not reported/number eligible not reported/116 enrolled	Number withdrawan not reported/number lost to fu not reported/number analyzed not specified
312	Mean age 64 male, ethnicity not specified	77%	23% LVEF, 70% HF due to IHD, 84% NYHA class III, 16% class IV	Number screened not reported/number eligible not reported/166 enrolled	Number withdrawn not reported (stated that 156 completed trial per protocol)/number lost to fu not reported/166 analyzed

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(12) Results	(12) Results	(13) Method of adverse effects assessment?
545	**Endpoints:** symptom-limited treadmill exercise duration: mean change (sd) in seconds Losartan 25 = 37 (135) Losartan 50 = 37 (119) Enalapril = 49 (123) 6-min walk test: mean change (sd) in m Losartan 25 = 9 (48) Losartan 50 = 3 (71) Enalapril = 0 (63) dyspnea-fatigue index: mean change (sd) Losartan 25 = 0.4 (1.5) Losartan 50 = 0.3 (1.7) Enalapril = 0.5 (1.7)	**Endpoints:** signs and symptoms of HF: no statistically significant difference among treatment groups NYHA functional class: # (%) improvement Losartan 25 = 6 (15.7%) Losartan 50 = 6 (15.7%) Enalapril = 7 (18.4%)	Not reported
312	**Primary endpoints (exercise capacity):** 6-min walk test: mean (sd) change at 8 weeks in m Losartan 25 mg = 18 (60) Losartan 50 mg = 12 (50) Enalapril 20 mg = 14 (48) dyspnea-fatigue index: mean (sd) change at 8 weeks Losartan 25 mg = 0.7 (2.0) Losartan 50 mg = 0.4 (1.7) Enalapril 20 mg = 0.7 (1.7)	**Primary endpoints:** clinical status: No statistically significant differences among treatments were observed NYHA functional class: % worsening class: Losartan 25 mg = 1.9% Losartan 50 mg = 5.3% Enalapril 20 mg = 1.7%	Not reported

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
545	Potassium: losartan 25mg -0.16±0.43 mEq/L vs. losartan 50mg 0.12±0.42 mEq/L vs. enalapril -0.05±0.47 mEq/L; sCr: losartan 25mg 0.02±0.14 mg/dl vs. losartan 50mg 0.02±0.28 mg/dl vs. enalapril 0.08±0.15 mg/dl (losartan 50mg vs. enalapril P<0.05)	Total withdrawals not reported/3 withdrawals due to adverse clinical experiences (1 in each group)
312	Dizziness: losartan 25mg (9.6%) vs. losartan 50mg (8.9%) vs. enalapril 20mg (6.9%); hypotension: losartan 25mg (5.8%) vs. losartan 50mg (7.1%) vs. enalapril 20mg (6.9%); cough: losartan 25mg (3.8%) vs. losartan 50mg (7.1%) vs. enalapril 20mg (6.9%)	Total withdrawals not reported/losartan 25mg 1.9% vs. losartan 50mg 3.6% vs. enalapril 20mg 8.6% discontinued treatment due to adverse experience

Evidence table 5. Active-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

ID	(16) Comments
545	5 deaths occurred in the losartan 50mg group compared to 1 in the losartan 25mg group and none in the enalapril group (none of the deaths were considered to be related to study drug)
312	Pilot trial. 89% patients on maintenance ACEI prior to enrollment

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2034	Blanchet, 2005 Canada (Fair)	RCT, single center	Symptomatic HF, NYHA class II or III, LVEF ≤ 40%; chronic treatment with stable and optimal dose ACEI and beta-blocker (patients not on beta-blocker due to intolerance also eligible) 3 months prior to enrollment	Irbesartan 75 mg once daily for 7 to 10 days, doubled to 150 mg (down titration allowed) vs. placebo for 6 months
2020	Matsumori, 2003 Japan (Fair)	RCT, multicenter	Men and women ≥ 20 years, symptomatic HF due to previous MI, HTN heart disease, dilated cardiomyopathy or valvular disease, NYHA class II or III, with LVEF ≤ 45% within 2 months prior to enrollment	Candesartan 4mg once daily for 2 to 4 weeks, doubled to 8 mg for 6 months vs. placebo Mean follow-up 5.2 months

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
2034	Stable and optimal dose of ACEI and beta-blocker for 3 months before enrollment	Baseline (irbesartan vs. placebo) ACEI (100% each group) Beta-blocker (90.9% vs. 81.8%) Diuretic (72.7% vs. 72.7%) Digoxin (77.3% vs. 72.7%) Spironolactone (27.3% vs. 27.2%)	Primary endpoint was total exercise duration during submaximal exercise test. Patient evaluation within 2 weeks of screening and at 6 months by same physician and exercise specialist
2020	Run-in of 2 to 4 weeks with ACEI discontinued to assess stability of symptoms; single candesartan 4mg test dose administered	Baseline (candesartan vs. placebo) Beta-blocker (18.9% vs. 21.5% Diuretic (84.5% vs. 81.9%) Digoxin (51.4% vs. 52.8%) Vasodilators (55.4% vs. 58.3%)	Primary endpoint (confirmed progression to CHF) included patient hospitalization for CHF; addition of, or increase in, any medication for CHF. Secondary endpoint of CV event included progression of HF, cardiac death, life-threatening arrhythmias, MI, CAD, stroke or TIA. Patient evaluation 2 to 4 week intervals

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2034	Irbesartan vs. placebo Mean age 59 vs. 54.4 Male 91% vs. 100% Ethnicity not reported	NYHA II (irbesartan 86% vs. placebo 100%) Etiology CAD (irbesartan 59% vs. placebo 27%; P=0.09) LVEF 26%	Number screened not reported/number eligible not reported/34 enrolled	1 withdrawn/number lost to fu not reported/33 analyzed
2020	Mean age 64 Male 53% Ethnicity not reported	NYHA % II/III (candesartan vs. placebo) 76/24 vs. 72/28 LVEF 35%	Number screened not reported/number eligible not reported/313 enrolled	111 withdrawn/number lost to fu not reported/292 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
2034	**Primary endpoint** Submaximal exercise duration Irbesartan 26% increase (baseline 1069±506 vs. 6 months 1350±727 seconds; P=0.018) Placebo 7% increase (+128±529 seconds)	Submaximal exercise duration Irbesartan vs. placebo 68% vs. 36% increased exercise duration (P=0.08)	
2020	**Primary endpoint** Progression to CHF Candesartan vs. placebo 7.4% vs. 22.2%; ARR 14.8% 95% CI 6.8 to 22.8; P=0.0004) calculated NNT=1.9 (95% CI 1.6, 2.4)	**Secondary endpoint** **CV events** Candesartan vs. placebo 10.8% vs. 22.9%; ARR 12.1% 95% CI 3.6 to 20.6; P<0.01)	**Subgroup analysis** Significant benefit with candesartan in following subgroups: Age (< or ≥ 65 years) NYHA class II HF Previous ACEI With or without previous beta-blocker

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
2034	Monitored	Adverse events leading to discontinuation not reported Reason not to increase/reduce irbesartan Symptomatic hypotension (n=5) Hyperkalemia (n=3) Increase sCr (n=1) Other symptoms (n=3)	Increase sCr Irbesartan vs. placebo (105±25 vs. 97+20 mmol/L; P=0.02) Change potassium (NS)
2020	Monitored by independent monitoring board	Adverse events (18/155 candesartan 11.6% vs. 6/150 placebo 4.0%)	Candesartan n=151; Placebo n=147 Drug-related adverse events Candesartan (31.1%) Placebo (21.1%) P<0.05 Postural light-headedness Candesartan (8.6%) Placebo (2.0%) Nonpostural light-headedness Candesartan (9.3%) Placebo (3.4%) Hypotension Candesartan (6.6%) Placebo (1.4%) Non-CV adverse effects Candesartan (58.9%) Placebo (51.0%)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
2034	1 withdrawal/number withdrawals due to adverse events not reported	No significant difference in ACEI dose at baseline or change in ACEI dose; mean dose irbesartan 113±38 mg/day in the irbesartan group
2020	111 withdrawn/exited study/number withdrawals due to adverse events (18/155 candesartan 11.6% vs. 6/150 placebo 4.0%)	Study terminated after second interim safety analysis (after 2/3 target population enrolled) due to event rate achieving pre-specified P≤ 0.0205

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2030	Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis) (Good)	RCT, multicenter	Inclusion criteria Val-HeFT (see Cohn, 2001 below) with elderly ≥ 65 vs. non-elderly < 65 years	Valsartan 40mg twice daily, doubled every 2 weeks to 160mg twice daily Mean follow-up 1.9 years

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
2030	Single-blind twice daily placebo run-in of 2 to 4 weeks to confirm eligibility, clinical stability, assess adherence (per Val-HeFT Cohn, 2001)	Standard therapy for HF Elderly vs. non-elderly ACEI (90.1% vs. 95%; P<0.001) BB (29.2% vs. 40%; P<0.001) Diuretic (87.9% vs. 83.3%; P<0.001) Digoxin (66.1% vs. 68.4%; P=0.084) CCB (13.8% vs. 10.7%; P=0.001) spironolactone (4.4% vs. 5.5%; P=0.064)	Two primary endpoints: time to death and time to first morbid event (defined as death sudden death with resuscitation, hospitalization for HF, or IV inotropes or vasodilators for > 4 hours without hospitalization); secondary endpoints included NYHA functional class, QOL by MLHFQ (U.S., U.K., Australia, Italy). Patient evaluation at 2, 4, and 6 months and then every 3 months

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2030	Elderly vs. non-elderly Mean age (72 vs. 54.5; P<0.001) Male (78.8% vs. 81.1%; P=0.044) White (94.3% vs. 86.8%; P<0.001)	Elderly vs. non-elderly NYHA class III and IV (43.3% vs. 33.5%; P<0.001) LVEF (26.9% vs. 26.6%; P=0.062)	Number screened not reported/number eligible not reported/5010 enrolled	430 withdrawn due to adverse events/number lost to fu not reported/5010 analyzed (per Val-HeFT Cohn, 2001)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
2030	**Primary endpoints** Valsartan vs. placebo All-cause mortality Elderly (25.1% vs. 24%; RR 1.041; P=0.638) Non-elderly (15.2% vs. 15%; RR 1.001; P=0.871) 1st morbid event Elderly (34.4% vs. 37.6%; RR 0.882; P=0.074) Non-elderly (24.1% vs. 26.9%; RR 0.854; P=0.093)	**Secondary endpoints** Valsartan vs. placebo CV death Elderly (21.3% vs. 20.7%; RR 1.024; P=0.781) Non-elderly (13.4% vs. 13.1%; RR 1.011; P=0.808) HF hospitalizations Elderly (15.9% vs. 21.6%; RR 0.713; P<0.001) Non-elderly (12.2% vs. 15.6%; RR 0.736; P=0.012)	**Other endpoints** Valsartan vs. placebo (change from baseline; placebo subtracted least squares mean difference) MLHFQ score Elderly (n=1409) -2.04; P=0.029) Non-elderly (n=1601) -1.78; P=0.036) Change NYHA functional class not reported

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
2030	Not reported	Adverse events leading to discontinuation not reported	Selected adverse events **E**lderly vs. non-elderly Any adverse event Valsartan (93.3% vs. 90.1%) Placebo (92.7% vs. 86.7%) Dizziness (excluding vertigo) Valsartan (23.7% vs. 26.1%) Placebo (18.2% vs. 18.0%) Hypotension Valsartan (14.3% vs. 13.5%) Placebo (8.6% vs. 7.5%) Aggravated CHF Valsartan (13.0% vs. 9.4%) Placebo (16.9% vs. 14.3%) Hyperkalemia Valsartan (7.6% vs. 5.6%) Placebo (3.7% vs. 2.8%) Renal impairment Valsartan (5.8% vs. 5.1%) Placebo (3.2% vs. 2.9%) Atrial fibrillation Valsartan (6.5% vs. 4.2%) Placebo (9.6% vs. 6.3%)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
2030	Not reported for subgroup analysis	Subgroup analysis reported significant effect on HF hospitalizations in elderly and non-elderly subgroups with no significant effect on mortality in either subgroup. More non-elderly patients received concomitant beta-blockers

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2017	Carson, 2003 U.S., Australia, Europe, South Africa Val-HeFT Trial (Hospitalization subanalysis) (Good)	RCT, multicenter	Men and women ≥ 18 years of age, clinical findings of HF for at least 3 months before screening, NYHA class II, III, or IV and clinically stable, LVEF < 40% and LV dilatation on ECHO, and at least 2 weeks on fixed-dose regimen that could include an ACEI, diuretic, digoxin, and beta-blocker	Valsartan 40mg twice daily, doubled every 2 weeks to 160mg twice daily Mean follow-up 1.9 years
2046	Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials (Good)	RCT, combined results of 2 component trials, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV; if class II, required cardiac hospitalization within previous 6 months), LVEF ≤ 40% measured within the past 6 months	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.3 years

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
2017	Single-blind twice daily placebo run-in of 2 to 4 weeks to confirm eligibility, clinical stability, assess adherence (per Val-HeFT Cohn, 2001)	Standard therapy for HF; Baseline:ACEIs (93%), beta-blocker (35%), diuretic (85%), digoxin (67%) (per Val-HeFT Cohn, 2001)	Two primary endpoints: mortality and combined mortality and morbidity (defined as cardiac arrest with resuscitation, hospitalization for HF, or IV inotropes or vasodilators for > 4 hours without hospitalization); endpoint of hospitalization limited to first hospitalization for worsening HF(per endpoint committee). Subanalysis included all hospitalizations due to worsening HF or other causes (per investigator). Patient evaluation at 2, 4, and 6 months and then every 3 months
2046	None	Standard therapy for HF (including ACEI in CHARM-Added; no ACEI in CHARM-Alternative); Overall baseline: ACEI (55.7%), beta-blocker (55.1%), diuretic (88%), digoxin (52.7%), spironolactone (20.1%), other vasodilators (39.4%), aspirin (54.3%)	Primary endpoint was CV death or hospital admission for worsening CHF. Secondary outcomes included: CV death; CHF admission; CV death, CHF admission, or non-fatal MI; CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; all-cause mortality. Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, then every year.

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2017	Mean age 63 80% male, 90% white, 7% black, 3% other (per Val-HeFT Cohn, 2001)	48% LVEF < 27%, 62% NYHA class I-II and 38% class III-IV	Number screened not reported/number eligible not reported/5010 enrolled	430 withdrawn due to adverse events/number lost to fu not reported/5010 analyzed (per Val-HeFT Cohn, 2001)
2046	Mean age 65 74% male, 90% European, 4% black, 6% other	29% LVEF; 35% NYHA class II, 62% class III, 3% class IV; MI 58%, stroke 9%, HTN 49%, DM 29%	Number screened not reported/number eligible not reported/4576 enrolled	957 discontinued study medication (due to AE or lab)/7 lost to fu/4576 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
2017	**Subanalysis endpoint (all-cause hospitalizations):** valsartan vs. placebo: 2856 vs. 3106 (8% difference; P=0.145)	**Subanalysis endpoint (HF hospitalizations):** valsartan vs. placebo: 923 vs. 1189 (22.4% difference; P=0.002)	HF hospitalizations: valsartan vs. placebo: + ACEI (18.7% difference; P=0.012) - ACEI (56.4% difference; P=0.010) + BB (10.7% difference; P=0.685) - BB (26.3% difference; P<0.001) + ACEI, - BB (23% difference; P=0.003) + ACEI, + BB (5.6% difference; P=0.982) - ACEI, - BB (55.7% difference; P=0.028) - ACEI, + BB (58.6% difference; P=0.171)
2046	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.82 (95% CI 0.74-0.90; P<0.001) NNT=18 (95% CI 12-36)	**Secondary endpoints:** candesartan vs. placebo: CV death HR 0.84 (95% CI 0.75-0.95, P=0.005); HF hospitalization HR 0.76 (95% CI 0.68-0.85, P<0.001); combined CV death, HF hospitalization, nonfatal MI HR 0.82 (95% CI 0.75-0.90, P<0.001); combined CV death, HF hospitalization, nonfatal MI, nonfatal stroke HR 0.84 (95% CI 0.76-0.92, P<0.001); combined CV death, HF hospitalization, nonfatal MI, nonfatal	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
2017	Not reported	Not reported for subanalysis	
2046	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 4.2% vs. placebo 2.1% (P<0.001); increased sCr: candesartan 7.1% vs. placebo 3.5% (P<0.001); hyperkalemia: candesartan 2.8% vs. placebo 0.5% (P<0.0001)	Study drug discontinued in 29/109 (26.6%) on ACEI, beta-blocker, spironolactone, and candesartan vs. 23/128 (18) on ACEI, beta-blocker, spironolactone, and placebo (P=0.110)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
2017	Not reported for subanalysis	Subanalysis of hospitalizations showed no significant difference in total hospitalizations with valsartan vs. placebo, but a significant reduction in HF hospitalizations (P=0.002); a significant reduction in HF hsopitalizations were seen in patients on the following concomitant medications: + ACEI; - ACEI; - BB; + ACEI - BB; - ACEI - BB; no significant difference in subgroups of patients receiving a BB
2046	957 of the survivors discontinued study medication due to adverse events or lab abnormalities (528 or 23.1% on candesartan vs. 429 or 18.8% on placebo; P<0.001)	Overall results of the 2 trials showed a significant reduction in mortality with candesartan in patients with HF and low LVEF compared to placebo. At 6 months, target dose of 32mg achieved in 60% on candesartan vs. 73% on placebo; mean daily dose candesartan 24 mg at 6 months

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2042	O'Meara, 2005 North America CHARM-QOL (Fair)	RCT, multicenter (sites in North America)	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily
2047	O'Meara, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-NYHA class (Good)	RCT, combined results of 3 component trials, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.1 years

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
2042	None	Standard therapy for HF; Baseline: ACEIs, if appropriate per protocol (46%), beta-blocker (56.8%), digoxin (52.7%), spironolactone (14.5%)	Pre-specified secondary outcome was evaluation of the McMaster Overall Treatment Evaluation (OTE) questionnaire. Questionnaire administered at 6, 14, 26 months, and at the final visit. Primary endpoint was all-cause death for CHARM-Overall Trial.
2047	None	Standard therapy for HF; Baseline: ACEIs, if appropriate per protocol (41%), beta-blocker (55%), digoxin (43%), spironolactone (17%)	Outcome evaluation of change in NYHA functional class assessed at baseline, at 2 weekly intervals during titration, then every 4 months. Primary endpoint was all-cause death for CHARM-Overall Trial.

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2042	Mean age 65 67% male	40% LVEF; 37% NYHA class II, 61% class III, 2% class IV; MI 53%, stroke 10%, HTN 67%, DM 36%	Number screened not reported/number eligible not reported/2498 enrolled	Number withdrawn not reported/number lost to fu not reported/2498 analyzed
2047	Mean age 66 68% male	39% LVEF; 45% NYHA class II, 52% class III, 3% class IV; MI 53%, stroke 9%, HTN 55%, DM 28%	Number screened not reported/number eligible not reported/7599 enrolled	Number withdrawn not reported/number lost to fu not reported/7599 analyzed (refer to CHARM-Overall)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
2042	**Main endpoint reported (QOL)** McMaster OTE questionnaire: Last visit carried forward Improvement (Scores +1 to +7) Candesartan: 37.7% Placebo: 33.5% Deterioration (Scores -7 to -1) Candesartan: 10.8% Placebo: 12.0% P=0.017	**Main endpoint reported (QOL)** McMaster OTE questionnaire: Worst rank visit carried forward Improvement (Scores +1 to +7) Candesartan: 32.1% Placebo: 27.5% Deterioration (Scores -7 to -1) Candesartan: 26.4% Placebo: 28.6% P=0.029	Improvement perceived as important, very important, or extremely important (N=890)t: Last visit carried forward Candesartan: 76% Placebo: 73% Worst rank visit carried forward Candesartan: 78% Placebo: 74%
2047	**Reported endpoint:** Change in NYHA functional class Last visit carried forward (N=7599) Candesartan: 35.4% improved, 9.0% deteriorated Placebo: 32.5% improved, 10.3% deteriorated P=0.003	**Reported endpoint:** **C**hange in NYHA functional class Worst rank carried forward (N=7587) Candesartan: 29.7% improved, 28.8% deteriorated Placebo: 26.8% improved, 31.3% deteriorated P=0.003	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
2042	Not reported	Adverse events leading to discontinuation not reported	Not reported
2047	Not reported	Not reported (refer to CHARM-Overall)	Not reported

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
2042	Not reported	No heterogeneity of the effect of candesartan across the subgroups of gender, age ≥ or < 75, NYHA class, treatment with or without beta-blockers.
2047	Not reported (refer to CHARM-Overall)	Test for heterogeneity not statistically significant (interaction between treatment and trial). Candesartan showed similar benefit over placebo in subgroups of gender, age > or < 75, NYHA class, treatment with or without beta-blockers.

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
24	Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	RCT, combined results of 3 component trials, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.1 years
25	McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV; if class II, required cardiac hospitalization within previous 6 months), LVEF ≤ 40% measured within the past 6 months, treatment with the same dose of an ACEI for ≥ 30 days	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.4 years

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
24	None	Standard therapy for HF; Baseline: ACEIs, if appropriate per protocol (41%), beta-blocker (55%), diuretic (83%), digoxin (43%), spironolactone (17%), CCB (20%), other vasodilators (38%), aspirin (55%)	Primary endpoint was all-cause death. All deaths classified as CV unless non-CV cause established. Clinic visits every 4 months; laboratory assessments in North America at baseline, 6 weeks, 14 months, then every year.
25	None	ACEI, standard therapy for HF; Baseline: ACEI (100%), beta-blocker (55%), diuretic (90%), digoxin (58%), spironolactone (17%), other vasodilators (37%), aspirin (51%)	Primary endpoint was CV death or unplanned admission for worsening CHF (signs and symptoms of worsening CHF requiring IV diuretics). Secondary outcomes included: CV death, CHF admission, or non-fatal MI (diagnosis made by cardiac markers and ECG changes or clinical presentation); CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; new-onset DM Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, then every year.

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
24	Mean age 66 68% male, 90% European, 4% black, 6% other	LVEF < 30% (28%), ≥ 30-39% (29%), > 40-49% (18%), ≥ 50% (17%); 45% NYHA class II, 52% class III, 3% class IV; MI 53%, stroke 9%, HTN 55%, DM 28%	Number screened not reported/7601 eligible/7599 enrolled	1189 discontinued study medication/10 lost to fu/7599 analyzed
25	Mean age 64 79% male, 90% European, 5% black, 5% other	28% LVEF; 24% NYHA class II, 73% class III, 3% class IV; 62% IHD as cause of HF; MI 56%, stroke 9%, HTN 48%, DM 30%	Number screened not reported/number eligible not reported/2548 enrolled	375 discontinued study medication/4 lost to fu/2548 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
24	**Primary endpoint (all-cause mortality):** candesartan vs. placebo: unadjusted HR 0.91 (95% CI 0.83-1.00; P=0.055)	**Secondary endpoints:** candesartan vs. placebo: combined CV death or HF hospitalization HR 0.84 (95% CI 0.77-0.91, P<0.0001); CV death HR 0.88 (95% CI 0.79-0.97, P=0.012); HF hospitalizations HR 0.79 (95% CI 0.72-0.87, P<0.0001)	candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.84 (95% CI 0.78-0.91, P<0.0001); combined CV death, HF hospitalization, MI, stroke HR 0.85 (95% CI 0.79 0.92, P<0.0001); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.86 (95% CI 0.80-0.93, P<0.0001)
25	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.85 (95% CI 0.75-0.96; P=0.011) calculated NNT=23 (95% CI 12-156)	**Secondary endpoints:** candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.85 (95% CI 0.76-0.96, P=0.010); combined CV death, HF hospitalization, MI, stroke HR 0.87 (95% CI 0.77-0.98, P=0.020); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.87 (95% CI 0.77-0.97, P=0.015); all-cause mortality HR 0.89 (95% CI 0.77-1.02, P=0.086); CV death HR 0.84 (95% CI 0.72-0.98, P=0.029); HF hospitalizations HR 0.83 (95% CI 0.71-0.96, P=0.014)	Subgroup analyses +ACEI/+BB (n=497), +ACEI/-BB (n=524) candesartan vs. placebo: all-cause mortality +ACEI/+BB HR 0.88 (95% CI 0.72-1.08, P=0.22), +ACEI/-BB RR 0.88 (95% CI 0.73-1.07, P=0.20)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
24	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 3.5% vs. placebo 1.7% (P<0.0001); increased sCr: candesartan 6.2% vs. placebo 3.9% (P<0.0001); hyperkalemia: candesartan 2.2% vs. placebo 0.6% (P<0.0001)	Angioedema: candesartan 5/3803 (0.13%) vs. placebo 3/3796 (0.08%); of 2743 with lab surveillance, sCr doubled in candesartan 82/1263 (6%) vs. placebo 47/1279 (4%) (P=0.002); serum potassium increased 0.14 mmol/L with candesartan (P<0.0001) with no change in the placebo group at 6 weeks; potassium $\geq$ 6.0 mmol/L was seen in 31/1294 (2%) of candesartan vs. 15/1310 (1%) placebo (P=0.017)
25	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 4.5% vs. placebo 3.1% (P=0.79); increased sCr: candesartan 7.8% vs. placebo 4.1% (P=0.0001); hyperkalemia: candesartan 3.4% vs. placebo 0.7% (P<0.0001)	Angioedema: candesartan 2/1276 (0.16%) vs. placebo 3/1272 (0.24%) (all were on ACEIs); in those with lab surveillance, sCr at least doubled with candesartan 32/436 (7%) vs. placebo 27/447 (6%) (P=0.5); potassium $\geq$ 6.0 mmol/L was seen in 12/447 (3%) of candesartan vs. 5/459 (1%) placebo (P=0.089)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
24	1189 of the survivors discontinued study medication/1430 withdrew due to adverse events or lab abnormalities (797/3803 candesartan 21.0% vs. 633/3796 placebo 16.7%; P<0.0001)	Overall results of the 3 trials combined showed a reduction in mortality with candesartan in patients with HF (borderline significance), primarily due to lower rates of CV death with candesartan. The benefit with candesartan was seen regardless of baseline treatment with ACEIs, beta-blockers, or other HF medication classes. Annual mortality rates were 8.1% on candesartan and 8.8% on placebo. At 6 months, target dose achieved in 63% (mean 24mg) on candesartan and 75% on placebo. At 6 months, SBP decreased 5.2 mm Hg and DBP 3.0 mm Hg from baseline on candesartan (P<0.001 vs. placebo).
25	375 of the survivors discontinued study medication/542 withdrew due to adverse events or lab abnormalities (309/1276 candesartan 24.2% vs. 233/1272 placebo 18.3%; P=0.0003)	The addition of an AIIRA to an ACEI reduced CV death and HF hospitalization compared to treatment with an ACEI. Benefit was seen regardless of baseline treatment with beta-blockers, or other HF medication classes. Investigators felt 96% patients on optimal ACEI doses (enalapril 16.8 and 17.2mg/d , lisinopril 17.7 and 17.7mg/d, captopril 82.2 and 82.7mg/d, ramipril 6.8 and 7.3mg/d in the candesartan and placebo groups, respectively). At 6 months, target dose achieved in 61% (mean 24mg) on candesartan and 73% on placebo. At 6 months, SBP decreased 4.6 mm Hg (P=0.007) and DBP 3.0 mm Hg (P=0.004) from baseline on candesartan vs. placebo.

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
26	Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks, LVEF < 40%, ACEI intolerance	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 2.8 years
27	Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, symptomatic HF (NYHA class II-IV) for ≥ 4 weeks, history cardiac hospitalization, LVEF > 40%	Candesartan 4mg or 8mg (decided by study physician), doubled minimum every 2 weeks (as tolerated) to target dose 32mg once daily Median follow-up 3.1 years

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
26	None	Standard therapy for HF (although intolerant of ACEI); Baseline: beta-blocker (55%), diuretic (85%), digoxin (45%), spironolactone (24%), other vasodilators (42%), aspirin (57%)	Primary endpoint was CV death or unplanned admission for worsening CHF (signs and symptoms of worsening CHF requiring IV diuretics). Secondary outcomes included: CV death, CHF admission, or non-fatal MI (diagnosis made by cardiac markers and ECG changes or clinical presentation); CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; new-onset DM Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, and 14, 26, and 38 months.
27	None	Baseline: ACEI (19%), beta-blocker (56%), diuretic (75%), digoxin (28%), spironolactone (11%), CCB (31%), other vasodilators (38%), aspirin (58%)	Primary endpoint was CV death or unplanned admission for worsening CHF (signs and symptoms of worsening CHF requiring IV diuretics). Secondary outcomes included: CV death, CHF admission, or non-fatal MI (diagnosis made by cardiac markers and ECG changes or clinical presentation); CV death, CHF admission, non-fatal MI, or non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, or coronary revascularization; any death or CHF admission; new-onset DM Clinic visit at 2, 4, and 6 weeks, at 6 months, then every 4 months; laboratory assessments in North America at baseline, 6 weeks, then yearly. Adjudicated outcomes by blinded committee for cause of death, first MI, and first CHF admission were basis for formal analysis; investigator reported events were also analyzed.

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
26	Mean age 66 68% male, 88% European, 4% black, 8% other	30% LVEF; 48% NYHA class II, 48% class III, 4% class IV; 69% IHD as cause of HF; MI 61%, stroke 9%, HTN 49%, DM 27%	Number screened not reported/number eligible not reported/2028 enrolled	338 discontinued study medication/3 lost to fu/2028 analyzed
27	Mean age 67 60% male, 92% European, 4% black, 4% other	54% LVEF; 61% NYHA class II, 37% class III, 2% class IV; 56% IHD as cause of HF; MI 45%, stroke 9%, HTN 65%, DM 28%	Number screened not reported/3025 eligible/3023 enrolled	488 discontinued study medication/3 lost to fu/3023 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
26	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.77 (95% CI 0.67-0.89; P=0.0004) calculated NNT=14 (95% CI 9-35)	**Secondary endpoints:** candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.78 (95% CI 0.68-0.90, P=0.0007); combined CV death, HF hospitalization, MI, stroke HR 0.80 (95% CI 0.69-0.91, P=0.001); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.81 (95% CI 0.71-0.92, P=0.002)	candesartan vs. placebo: all-cause mortality HR 0.87 (95% CI 0.74-1.03, P=0.11); CV death HR 0.85 (95% CI 0.71-1.02, P=0.072); HF hospitalizations HR 0.68 (95% CI 0.57-0.816, P<0.0001)
27	**Primary endpoint (CV death or HF hospitalization):** candesartan vs. placebo: HR 0.89 (95% CI 0.77-1.03; P=0.118)	**Secondary endpoints:** candesartan vs. placebo: combined CV death, HF hospitalization, MI HR 0.90 (95% CI 0.78-1.03, P=0.126); combined CV death, HF hospitalization, MI, stroke HR 0.88 (95% CI 0.77-1.01, P=0.078); combined CV death, HF hospitalization, MI, stroke, coronary revascularization procedure HR 0.91 (95% CI 0.80-1.03, P=0.123)	candesartan vs. placebo: CV death HR 0.99 (95% CI 0.80-1.22, P=0.918); HF hospitalizations HR 0.85 (95% CI 0.72-1.01, P=0.072)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
26	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 3.7% vs. placebo 0.9% (P<0.0001); increased sCr: candesartan 6.1% vs. placebo 2.7% (P<0.0001); hyperkalemia: candesartan 1.9% vs. placebo 0.3% (P=0.0005); cough: candesartan 0.2% vs. placebo 0.4% (P=0.69); angioedema: candesartan 0.1% vs. placebo 0.0% (P=0.50)	Angioedema: candesartan 3/1013 (0.30%) vs. placebo 0/1015 (0.0%), all cases of angioedema were in patients with previous ACEI intolerance due to angioedema or anaphylaxis; of patients with lab surveillance, sCr at least doubled in 5.5% of 311on candesartan vs. 1.6% of 307 on placebo (P=0.015); potassium $\geq$ 6.0 mmol/L was seen in 3% of 321 on candesartan (n=321) vs. 1.3% of 315 on placebo (P=0.26)
27	Not reported	Adverse events leading to discontinuation: hypotension: candesartan 2.4% vs. placebo 1.1% (P=0.009); increased sCr: candesartan 4.8% vs. placebo 2.4% (P=0.0005); hyperkalemia: candesartan 1.5% vs. placebo 0.6% (P=0.029)	Of patients with lab surveillance, sCr at least doubled in 6% on candesartan vs. 3% on placebo (P=0.007); potassium $\geq$ 6.0 mmol/L was seen in 2% on candesartan vs. 1% on placebo (P=0.32)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
26	338 of the survivors discontinued study medication/414 withdrew due to adverse events or lab abnormalities (218/1013 candesartan 21.5% vs. 196/1015 placebo 19.3%; P=0.23)	Use of an AIIRA in patients unable to tolerate an ACEI reduced CV death and HF hospitalization compared to placebo. At 6 months, target dose achieved in 59% (mean 23mg) on candesartan and 73% on placebo. At 6 months, SBP decreased 4.4 mm Hg and DBP 3.9 mm Hg from baseline on candesartan vs. placebo (P<0.0001 for both)
27	488 of the survivors discontinued study medication/474 withdrew due to adverse events or lab abnormalities (270/1514 candesartan 17.8% vs. 204/1509 placebo 13.5%; P=0.001)	Use of an AIIRA in patients with HF and preserved LVEF did not differ significantly from that of placebo. At 6 months, target dose achieved in 67% (mean 25mg) on candesartan and 79% on placebo. At 6 months, SBP decreased 6.9 mm Hg and DBP 2.9 mm Hg from baseline on candesartan vs. placebo (P<0.0001)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
16	Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	RCT, multicenter	Men and women ≥ 18 years of age, clinical findings of HF for at least 3 months before screening, NYHA class II, III, or IV and clinically stable, LVEF < 40% and LV dilatation on ECHO, and at least 2 weeks on fixed-dose regimen that could include an ACEI, diuretic, digoxin, and beta-blocker	Valsartan 40mg twice daily, doubled every 2 weeks to 160mg twice daily Mean follow-up 1.9 years
17	Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis (Fair)	RCT, multicenter	Men and women ≥ 18 years of age, clinical findings of HF for at least 3 months before screening, NYHA class II, III, or IV and clinically stable, LVEF < 40% and LV dilatation on ECHO, and at least 2 weeks on fixed-dose regimen that could include an ACEI, diuretic, digoxin, and beta-blocker; subgroup analysis was in patients who were not treated with an ACEI	Valsartan 40mg twice daily, doubled every 2 weeks to 160mg twice daily Mean follow-up 1.9 years

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
16	Single-blind twice daily placebo run-in of 2 to 4 weeks to confirm eligibility, clinical stability, assess adherence	Standard therapy for HF; Baseline:ACEIs (93%), beta-blocker (35%), diuretic (85%), digoxin (67%)	Two primary endpoints: mortality and combined mortality and morbidity (defined as cardiac arrest with resuscitation, hospitalization for HF, or IV inotropes or vasodilators for > 4 hours without hospitalization); secondary endpoints included change from baseline to last available observation of LVEF, NYHA class, QOL, signs and symptoms of HF. Patient evaluation at 2, 4, and 6 months and then every 3 months; 60% of patients received a QOL assessment using the Minnesota Living with HF questionnaire
17	Single-blind twice daily placebo run-in of 2 to 4 weeks to confirm eligibility, clinical stability, assess adherence	Standard therapy for HF except for 7.3% of 5010 in Val-HeFT that did not receive ACEIs Baseline: beta-blocker (38%), diuretic (80%), digoxin (59%), spironolactone (7%)	Two primary endpoints: mortality and combined mortality and morbidity (defined as cardiac arrest with resuscitation, hospitalization for HF, or IV inotropes or vasodilators for > 4 hours without hospitalization); secondary endpoint included QOL (assessed using the Minnesota Living with HF Questionnaire MLWHFQ); subanalysis of exercise capacity after 4 months by 6-min walk test. Patient evaluation at 2, 4, and 6 months and then every 3 months

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
16	Mean age 63 80% male, 90% white, 7% black, 3% other	27% LVEF, 57% CHD as cause of HF, 62% NYHA class II and 36% class III	Number screened not reported/number eligible not reported/5010 enrolled	430 withdrawn due to adverse events/number lost to fu not reported/5010 analyzed
17	Mean age 67 76% male, 82% white, 12% black	28% LVEF, 68% CHD as cause of HF, 47% NYHA class III-IV	Number screened not reported/number eligible not reported/5010 enrolled in Val-HeFT/366 not treated with ACEI in substudy	77 withdrawn/number lost to fu not reported/366 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
16	**Primary endpoints (mortality and combined mortality and morbidity):** valsartan vs. placebo: all-cause mortality RR 1.02 (98% CI 0.88-1.18; P=0.80); combined morbidity and mortality RR 0.87 (97.5% CI 0.77-0.97; P=0.009), calculated NNT=31 (95% CI 17-140)	**Secondary endpoints:** valsartan vs. placebo: HF hospitalizations RR 0.725 (P<0.001); mean change in LVEF (4% vs. 3.2%, P=0.001); improvement in NYHA class (23.1% vs. 20.7%), worsening (10.1% vs. 12.8%) (P<0.001); signs and symptoms of HF improved with valsartan vs. placebo (P<0.01); QOL (little change with valsartan vs. worsening average 1.9 with placebo, P=0.005)	Subgroup analyses: [+ACEI/-BB (n=3034); +ACEI/+BB (n=1610); -ACEI/-BB (n=226); -ACEI/+BB (n=140)] valsartan vs. placebo: mortality +ACEI/+BB RR > 1.0 (P=0.009), -ACEI/-BB RR < 1.0 (P=0.012), -ACEI/+BB RR 0.67 (95% CI 0.42-1.06); combined morbidity and mortality +ACEI/+BB RR > 1.0 (P=0.10), -ACEI/-BB (P=0.003), +ACEI/-BB (P=0.002), -ACEI/+BB (P=0.037), -ACEI/±BB RR 0.56 (95% CI 0.39-0.81); combined morbidity and mortality in black patients (n=344) RR 1.11 (95% CI 0.77-1.61)
17	**Primary endpoints:** mortality: number (%) Valsartan = 32 (17.3%) Placebo = 49 (27.1%) RR = 0.67 95% CI (0.42-1.06) combined mortality and morbidity: number (%) Valsartan = 46 (24.9%) Placebo = 77 (42.5%) RR = 0.56 95% CI (0.39-0.81) NNT = 6 (95% CI 4-12)	**Secondary endpoints:** HF hospitalizations:number (%) Valsartan = 24 (13.0%) Placebo = 48 (26.5%) CV death:number (%) Valsartan = 29 (15.7%) Placebo = 40 (22.1%) QOL:mean change (sem) Valsartan = -0.98 (1.71) Placebo = 3.17 (1.98)	Exercise capacity substudy:for the 35 patients in the substudy mean change in walk distance: Valsartan = 50.3 m Placebo = -34.2 m P = 0.022

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
16	Not reported	Adverse events leading to discontinuation: dizziness: valsartan 1.6% vs. placebo 0.4% (P<0.001); hypotension: valsartan 1.3% vs. placebo 0.8% (P=0.124); renal impairment: valsartan 1.1% vs. placebo 0.2% (P<0.001)	Mean change BUN: valsartan increase 5.9mg/dl vs. placebo increase 3.3mg/dl (P<0.001); mean change sCr: valsartan increase 0.18mg/dl vs. placebo increase 0.10mg/dl (P<0.001); mean change serum potassium: valsartan increase 0.12mmo/l vs. placebo decrease 0.07mmol/l (P<0.001)
17	Not reported	Adverse events leading to discontinuation: hypotension: valsartan 0.5% vs. placebo 0.6% (P=0.988); life-threatening laboratory abnormalities: valsartan 0.5% vs. placebo 0.6% (P=0.988)	Dizziness: valsartan 23.9% vs. placebo 18.9%; hypotension: valsartan 14.7% vs. placebo 5.6%; increase sCr: valsartan 0.18+0.2mg/dl vs. placebo 0.10+0.02mg/dl (P=0.009)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
16	Overall adverse events leading to discontinuation: valsartan 249 (9.9%) vs. placebo 181 (7.2%) (P<0.001)	Results showed that valsartan added to standard therapy for HF did not improve survival but did have a benefit in decreasing the combined morbidity and mortality endpoint. Subgroup analyses showed higher mortality in patients on valsartan in combination with an ACEI and beta-blocker. A decrease in mortality as well as the combined endpoint was seen in patients on valsartan + beta-blocker but -ACEI. Treatment with valsartan + ACEI decreased the combined endpoint compared to an ACEI alone. Patients were randomized according to baseline beta-blocker but not ACEI use. Annual mortality on placebo 9% (12% anticipated). Target dose achieved in 84% (mean 254mg) on valsartan and 93% on placebo. SBP decreased 5.2±16 mm Hg on valsartan vs. 1.3±15.0 mm Hg on placebo at 1 year.
17	77 total withdrawals (17.3% valsartan vs. 24.9% placebo)/41 withdrawals due to adverse events (18/185 valsartan 9.7% vs. 23/181 placebo 12.7%; P=0.367)	Higher percentage of patients in NYHA class III-IV compared to patients on ACEI in Val-HeFT (P<0.05). SBP decreased 8.1±1.2 mm Hg on valsartan vs. 3.2±1.2 mm Hg on placebo at last observation (P=0.004)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
955	Tonkon, 2000 U.S. (Poor)	RCT, multicenter	Men and postmenopausal or surgically sterile women ≥ 18 years of age with stable HF NYHA class II or III, LVEF ≤ 40%, and ≥ 6 weeks on stable doses of an ACEI and ≥ 2 weeks on a diuretic, seated SBP ≥ 90 mm Hg, sCr ≤ 2.2 mg/dl, BUN ≤ 50 mg/dl	Irbesartan starting doses of 12.5mg, 37.5mg, or 75mg, titrated at weekly intervals to target dose 150mg once daily for as maximum of 4 weeks; open-label ACEI determined by investigator and maintained at constant dose Mean follow-up 12 weeks
811	Riegger, 1999 Europe STRETCH Trial (Fair)	RCT, multicenter	Men and women 21 to 80 years of age with mild to moderate symptomatic HF (NYHA class II or III), LVEF 30 to 45%	Candesartan 4mg, 8mg, 16mg or placebo for 12 weeks (titrated to 8mg and 16mg doses at weekly intervals)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
955	AIIRAs, beta-blockers, CCBs, vasodilators, NSAIDs were withdrawn and ACEI and diuretics were stabilized	Digoxin and long-acting nitrates (in addition to ACEI and diuretics)	Main endpoints include exercise tolerance (assessed by symptom-limited maximum exercise treadmill test) and clinical status (NYHA functional class determination) performed at 24±3hrs after administration of baseline study medication and at 6, 8, and 12 weeks
811	4 week placebo run-in, stabilized on diuretics, cardiac glycosides, long-acting nitrates; 2 week washout for patients on ACEI	Diuretics, cardiac glycosides, long-acting nitrates kept constant	Primary endpoint was total exercise time determined by bicycle ergometry ≥ 2 times during run-in and at 6 and 12 weeks during treatment. Secondary endpoints included signs and symptoms of HF and NYHA functional class

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
955	Mean age 64 76% male, 82% white	28% LVEF, 53% IHD as cause of HF, 79% NYHA class II, 21% class III	Number screened not reported/145 enrolled/109 randomized	12 withdrawn/number lost to fu not reported/97 analyzed
811	Mean age 62 68% male, 99.8% white	39% LVEF, 71% CHD as cause of HF, 81% NYHA class II, 19% class III	Number screened not reported/926 enrolled/844 randomized	55 withdrawn/number lost to fu not reported/807 analyzed ITT; 629 per-protocol population

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
955	**Main endpoint (exercise tolerance):** exercise treadmill test: median change from baseline at week 12 irbesartan: +64 seconds (IQR +21 TO +109) placebo: +41 seconds (IQR: -19 to +131)	**Main endpoint (clinical status):** NYHA functional class: of patients who changed classes irbesartan: 14% improved, 7% worsened placebo: 14% improved, 12% worsened	
811	**Primary endpoint (total exercise time):** bicycle ergometry: mean change from baseline for <=12 weeks placebo 30.8 seconds; Candesartan 4mg 39.7 seconds; Candesartan 8 mg 45.8 seconds (approached being significantly different from placebo P=0.069); Candesartan 16 mg 47.2 seconds (significantly different from placebo P=0.046)	**Secondary endpoints:** signs and symptoms of HF: NYHA functional class % of patients with change in NYHA functional class Placebo 13.9% improved, 84.6% no change, 1.5% deteriorated; Candesartan 4mg 19.2% improved, 79.8% no change, 1.0% deteriorated; Candesartan 8 mg 20.3% improved, 79.7% no change, 0% deteriorated; Candesartan 16 mg 16.9% improved, 82.1% no change, 1.0% deteriorated. None of the Candesartan groups were significantly different from placebo	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
955	Spontaneously reported adverse events and adverse events elicited by general questioning were recorded	Adverse events leading to discontinuation: cardiovascular events: irbesartan 4 vs. placebo 2	Dizziness: irbesartan 23% vs. placebo 23%; hypotension: irbesartan 12% vs. placebo 0%; headache: 12% vs. placebo 19%; potassium: irbesartan +0.01 mEq/L vs. placebo -0.08mEq/L; sCr: irbesartan +0.08 mg/dl vs. placebo +0.04 mg/dl
811	All adverse events recorded and intensity rated as mild, moderate, or severe	Serious adverse events: candesartan 4mg (1.4%) vs. candesartan 8mg (5.7%) vs. candesartan 16mg (5.6%) vs. placebo (4.7%)	Adverse events possibly related to symptomatic hypotension: candesartan 4mg (1.5%) vs. candesartan 8mg (2.8%) vs. candesartan 16mg (0.5%) vs. placebo (1.9%); increase in sCr: candesartan 4mg (2.9%) vs. candesartan 8mg (4.2%) vs. candesartan 16mg (0.9%) vs. placebo (1.9%)

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
955	12 total withdrawals (7 irbesartan; 5 placebo)/6 withdrawals due to adverse events (4 irbesartan; 2 placebo)	Not powered to demonstrate statistically significant benefit for any endpoint
811	55 total withdrawals (7 candesartan 4mg; 12-19 per other treatment groups)/35 withdrawals due to adverse events: candesartan 4mg (1.9%) vs. candesartan 8mg (4.7%) vs. candesartan 16mg (5.6%) vs. placebo (4.3%)	Phase 2 trial

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
432	Hamroff, 1999 U.S., France (Fair)	RCT, multicenter	Patients with symptomatic HF consistent with NYHA class III or IV	Losartan 50mg once daily vs. placebo for 6 months
1007	Warner, 1999 U.S. (Fair)	RCT with crossover	Patients evaluated for CAD as cause of dyspnea with LVEF > 50%, SBP ≤ 150 mm Hg, mitral valve Doppler flow pattern with peak E wave less than peak A wave velocity (E/A < 1.0), and hypertensive response to exercise with peak SBP > 200 mm Hg, no previous AIIRA use	Losartan 50mg once daily vs. placebo for 2 weeks, wash-out for 2 weeks, then crossed over to losartan or placebo for 2 weeks

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
432	2 week single-blind tolerability phase	Treatment with maximally tolerated doses of ACEI > 3 months, in addition to digoxin and diuretics; other therapy for HF allowed including beta-blockers	Primary endpoint included NYHA functional class assessed prior to randomization and at 3 and 6 months. Secondary endpoints included laboratory safety parameters and doses of concomitant background medications.
1007	2 week washout in between two, 2 week treatments	All baseline medications continued during study (7/20 beta-blocker, 6/20 diuretic, 5/20 CCB, 6/20 ACEI)	Main endpoints include exercise tolerance (assessed by treadmill exercise test using modified Bruce Protocol) and QOL (Minnesota Living With Heart Failure questionnaire) at baseline and after 2 weeks of treatment, 2 to 4 hrs after study medication; tests were then repeated after 2 weeks of being crossed over to the other treatment

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
432	Mean age 61 49% male, ethnicity not specified	26% LVEF, 30% IHD as cause of HF, NYHA class 3.2	Number screened not reported/number eligible not reported/33 enrolled	7 withdrawn/2 lost to fu/33 analyzed
1007	Mean age 64 20% male, ethnicity not specified	80% HTN, resting BP 143/79±8.8 mm Hg	Number screened not reported/number eligible not reported/21 enrolled	1 withdrawn/none lost to fu/20 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
432	**Primary endpoints:** NYHA functional class % improvemed by at least 1 NYHA class losartan: 56% vs placebo: 6% NNT = 2 (95% CI 1-4) Mean (sem) functional class at baseline, 3 months, 6 months losartan: 3.2(0.4), 2.9 (0.6), 2.5(0.5) placebo: 3.0(0.4), 3.0 (0.5), 3.0(0.5)	**Secondary endpoints:** Doses of concomitant background medications: mean(sem) furosemide dose in mg at baseline, 3 months, 6 months losartan: 11.5(1.1), 10.9(1.1), 10.5(1.2) placebo: 9.9(1.0), 10.0(1.1), 10.8(1.1) Laboratory parameters: Serum electrolytes, creatinine, and blood urea nitrogen were unchanged in both groups Doses of other background medications were unchanged in both treatment groups	
1007	**Main endpoint (exercise tolerance): note: crossover study** treadmill exercise test: mean (sd) exercise time Baseline: 11.3(2.5) min Placebo: 11.0(2.0) min Losartan: 12.3(2.6) min Losartan significantly different from both placebo and baseline (P<0.05)	**Main endpoint (QOL):** Minnesota Living With Heart Failure questionnaire: mean (sd) score Baseline: 25(22) Placebo: 22(26) Losartan: 18(22) Losartan significantly different from placebo (P<0.05)	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
432	Not reported	Adverse events leading to discontinuation: nausea in 1 patient on losartan, nausea in 1 patient on placebo	Treatment reported to be well-tolerated in both groups, without adverse side effects
1007	Not reported	1 patient on losartan withdrew due to increase in sCr from 1.5 to 2.0mg/dl	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
432	7 total withdrawals (3 losartan; 4 placebo)/2 withdrawals due to adverse events (1 in each group)	Mean daily dose of captopril 175mg in the losartan group vs. 117mg in the placebo group, method of adjustment of concomitant medications (secondary endpoint) not described
1007	1 total withdrawal (losartan)/1 withdrawal due to adverse event (losartan)	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
420	Granger, 2000 U.S., Canada, Europe (Fair)	Multicenter	Left ventricular ejection fraction less than 35%; CHF (NYHA class II through IV); intolerance of ACE inhibitors (perceived angioedema, anaphylaxis, neutropenia, cough, symptomatic hypotension or azotemia)	Candesartan 4-16 mg once daily Placebo Titration at 2 weeks (8 mg) and 4 weeks (16 mg) Duration 12 weeks

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment
420	1-week single-blind placebo run-in	Not reported	Evaluations or quality of life (Minnesota Living with Heart Failure questionnaire and SF-36 Health Survey) and adverse events conducted after 2, 4, 6, 8 and 12 weeks

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
420	65.7 68.9% male Ethnicity not reported	NYHA class II=53.7% NYHA class III=40.7% NYHA class IV=5.5% Ischemic cause of heart failure=71.5% Medical history MI=62.2% Stroke=6.3% Hypertension=37.4% Diabetes=18.9% Atrial fibrillation or flutter=24.4% Sustained ventricular tachycardia or fibrillation=12.2% Implated defibrillator=2.9% Medications Digoxin=61.1% Diuretics=74.4% Beta Blockers=21.1% ARBs(> 1 month pre-randomization)=10.4% Aspirin=55.9% Hydralazine=12.6% Lipid-lowering agents=24.8% Amiodarone=15.2%	Number screened not reported/288 eligible/270 enrolled	43(15.9%) withdrawn/0 lost to fu/270 analyzed

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(12) Results	(12) Results	(12) Results
420	Minnesota Living with Heart Failure Questionnaire (% change): Candesartan=0 Placebo=9.5% decline median scores at baseline and final visit Candesartan: 32, 32 SF-36 *Better* Candesartan=45% Placebo=54% *Worse* Candesartan=11% Placebo=9%		

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(14) Adverse Effects Reported
420	Not reported	Cough Placebo=64.8% Candesartan=68.2% Renal Failure Placebo=11.0% Candesartan=11.2% Angioedema Placebo=4.4% Candesartan=4.5% Mortality Placebo=3.3% Candesartan=3.4	

Evidence table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

ID	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
420	43 total withdrawals (31/179 candesartan 17.3% vs. 12/91 placebo 13.2%)/29 withdrawals due to adverse events (21/179 candesartan 11.7% vs. 8/91 placebo 8.8%) Discontinuation because of renal insufficiency Placebo=3% Candesartan=7%	

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
2024	Barnett, 2004 Scandinavia, U.K., the Netherlands (Good)	RCT, Multicenter	Male or female 35 to 80 years, type 2 DM (treated with diet; diet plus oral hypoglycemics ≥ 1 year; or oral agents prior to insulin ≥ 1 year, with diagnosis < 40 years and BMI ≤ 25 at diagnosis), mild to moderate HTN (resting BP < 180/95 mm Hg after ≥ 3 months ACEI), normal renal morphology, urinary albumin excretion rate 11 to 999 µg/min with 2 values > 10, glycosylated hemoglobin < 12%, sCr < 1.6 mg/dl, GFR > 70 ml/min/1.73m2

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/interventions
2024	Telmisartan 40 mg once daily; doubled to 80mg after 4 weeks Enalapril 10 mg once daily; doubled to 20mg after 4 weeks Doses could be reduced after 2 months at investigator's discretion; could not then be increased Duration 5 years	All antihypertensive agents (required inclusion of an ACEI) were continued for 1 month, after which the ACEI was discontinued	Antihypertensive agents (excluding ACEIs and AIIRAs) allowed after 2 months if SBP > 160 or DBP > 100 mm Hg

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled
2024	Primary endpoint included change in GFR (measurement of plasma clearance iohexol) after 5 years; secondary endpoint were annual changes in GFR rate, UAE, sCr, BP, clinical events (ESRD, MI, stroke, CHF), all cause death, adverse event rate, lab abnormalities. Patients examined by nephrologist every month for first 6 months, then every 3 months. BP evaluated at 2 weeks, after 1, 2, 3, 6, 9, and 12 months, and every 6 months over 5 years	Mean age 61 73% male 98% white	BP 152/85 mm Hg HTN duration (telmisartan vs. enalapril) 8 vs. 5.5 years Diabetes duration 8 years GFR (telmisartan vs. enalapril) 91.4±21.5 vs. 94.3±22.1 sCr (telmisartan vs. enalapril) 1.02±0.21 vs. 0.99±0.2	Number screened not reported/number eligible not reported/250 enrolled

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results
2024	82 withdrawn (telmisartan 32%, enalapril 34%)/2 lost to follow-up/216 analyzed	**Primary endpoint (mean change in GFR rate at 5 years):** Telmisartan -17.5 ml/min/1.73m2 Enalapril -15.0 ml/min/1.73m2 Difference -2.6ml/min/1.73m2 (95% CI -7.1 to 2.0) Telmisartan noninferior to enalapril due to lower boundary -7.1 greater than pre-defined value of -10	**Secondary endpoints:** change in sCr from baseline (telmisartan vs. enalapril) 0.10 vs. 0.10, 0 difference (95% CI -0.66 to 0.65); reported similar rates of annual decrease in GFR from baseline

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
2024	Not reported	Total adverse events Telmisartan 115/120 (95.8%) Enalapril 130/130 (100%) Increased sCr (to < 2.3 mg/dl) Telmisartan 2/120 (1.7%) Enalapril 2/130 (1.5%) Stroke Telmisartan 6/120 (5%) Enalapril 6/130 (4.6%) CHF Telmisartan 9/120 (7.5%) Enalapril 7/130 (5.4%) Nonfatal MI Telmisartan 9/120 (7.5%) Enalapril 6/130 (4.6%) Death Telmisartan 6/120 (5%) Enalapril 6/130 (4.6%)	Total withdrawals Telmisartan 38/120 (31.7%) Enalapril 44/130 (33.9%) Adverse event withdrawals Telmisartan 20/120 (16.7%) Enalapril 30/130 (23.1%)

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(16) Comments
2024	High drop-out rate (nearly half of which left within first 2 years); potential confounding with effect of analysis based on last observation carried forward

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
36	Nakao, 2003 Japan COOPERATE (Good)	RCT, AIIRA vs. ACEI vs. combination	Age between 18 and 70 years, chronic nephropathy (defined as sCr 133-398umol/L or GFR 20-70 ml/min/1.73m2), non-diabetic renal disease, persistent proteinuria (urinary protein excretion > 0.3g/24hrs), no history of allergic reaction to medications, including ACEIs
1	Lacourciere, 2000 Canada (Poor)	Multicenter	Male and female outpatients with type 2 diabetes mellitus diagnosed at 30 years of age or later; mild to moderate essential hypertension (sitting diastolic BP (SIDBP) 90 to 115 mm Hg); early nephropathy characterized by a UAE rate 20 to 350 µg/min without evidence of urinary tract infection
587	Luno, 2002 Spain (Fair)	Multicenter, open	Male and female outpatients between 18 and 80 years old with primary proteinuric nephropathies for more than 6 months; patients were included irrespective of their BP if proteinuria measured by the sulfosalicylic acid method was greater than 2 g in at least two 24-hour urine collections and the GFR, estimated by CrCl > 50 mL/min/1.73 m2

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/interventions
36	Losartan titrated every 3-4 weeks until 100mg daily (25mg 8a.m., 25mg 12p.m., 50mg 5p.m.) with placebo; trandolapril 3mg once daily with placebo twice daily; combination of both drugs at the same doses Mean follow-up 2.9 years	All antihypertensive agents including ACEIs were discontinued for 3 weeks; 301 patients received single-blind run-in of trandolapril 0.5mg increased to 6mg for 18 weeks to determine maximum dose for renoprotection (e.g., mean percent change in daily excretion urinary protein reached plateau with 3mg); trandolapril was then discontinued for 3 weeks	Antihypertensive agents (excluding ACEIs and AIIRAs) used to achieve BP < 130/80 mm Hg
1	Losartan 50 mg once daily; doubled at week 8 if SIDBP > 85 mm Hg Enalapril 5 mg once daily; titrated to 10 mg if SIDBP > 95 mm Hg at 4 weeks; doubled at week 8 if SIDBP > 85 mm Hg *Early up-titration was permitted starting at week 4 for patients having SIDBP > 105 mm Hg* Duration 1 year	Antihypertensive medications (other than beta blockers and/or nitrates for stable angina) were discontinued during a 7-day washout period 2-4 week single-blind placebo run-in period	HCTZ 12.5 mg titrated to 25 mg to achieve a goal SIDBP of 85 mm Hg starting at week 12 Additional antihypertensive agents other than ACE inhibitors, AIIRAs, CCBs then added
587	Lisinopril 10-40 mg once daily Candesartan 8-32 mg once daily Lisinopril 5-20 mg + Candesartan 4-16 mg After 2 weeks, dosage doubled every 2 weeks up to maximum dose (above) if SBP > 125 mm Hg or DBP > 75 mm Hg Duration 6 months	2-week washout	Antihypertensive medication, such as beta blockers, CCBs and/or thiazide diuretics along or in combination were subsequently introduced from weeks 6 to 12 in order to achieve goal of BP <125/75 mm Hg

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled
36	Primary endpoint included composite doubling sCr or ESRD (GFR < 7ml/min/1.73m2 or dialysis); secondary endpoint was to assess change in BP, daily urinary protein excretion, and to note any adverse reactions. Patients examined by nephrologist every month for first 6 months, then every 3 months. Patients collected 24hr urine samples, 3 days prior to visits; trained nurses measured supine BP after 15 min rest	Mean age 45 47% male 100% Japanese	65% glomerular renal disease, 18% HTN, GFR 38ml/min, sCr 267umol/l, urinary protein excretion 2.5g/day (22% $\geq$ 3g/d, 40% 1-3g/d, 38% < 1g/d), BP 130/75 mm Hg, median 3 antihypertensive agents	336 screened/306 eligible/263 enrolled
1	Laboratory evaluations performed after 4, 12, 28 and 52 weeks	58.5 80.1% male 96.1% white	SIDBP=160.0 DIDBP=96.3 Weight (kg)=91.9 Diabetes duration (years)=10.9 Age at diabetes diagnosis (years)=47.4 Urinary albumin excretion (geometric means)=68.9	Number screened not reported/number eligible not reported/103 enrolled
587	Study visits at 2 4, 6, 8, 12 and 24 weeks after randomization	45 68.7% male Ethnicity not reported	BMI 26.7 kg/m2 SBP 134 mm Hg DBP 81 mm Hg Albumin 3.6 g/dL Cr_{Cl} 95 mL/min	Number screened not reported/number eligible not reported/46 enrolled

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results
36	Unable to determine number withdrawn/7 lost to follow-up/256 analyzed for primary endpoint	**Primary endpoint (composite doubling sCr or ESRD):** losartan 23% (20 of 86) vs. combination 11% (10 of 85) HR 0.40 (95% CI 0.17-0.69; P=0.016), NNT=9 Cox model (95% CI 4-420); trandolapril 23% (20 of 85) HR 0.38 (95% CI 0.18-0.63; P=0.018) NNT=8 Cox model (95% CI 4-227). Benefit of combination therapy seen regardless of baseline urinary protein excretion rate	**Secondary endpoints:** maximal median change in daily urinary protein excretion: losartan -42.1%, trandolapril -44.3%, combination -75.6% (P=0.01 vs. baseline); mean change BP vs. baseline: losartan -5.1±1.6/-2.9±0.9 mm Hg, trandolapril -5.2±1.3/-2.9±0.8 mm Hg, combination -5.3±1.4/-3.0±0.7 mm Hg (decrease similar for all groups; P=0.109)
1	10(10.7%) withdrawn/number lost to fu not reported/98(95.1%) analyzed	Albuminuria change (%) Losartan=35.2% Enalapril=54.7% NS Glomerular filtration rate (GFR) change (%) Losartan=9% reduction Enalapril=9% reduction NS	
587	1(2.2%) withdrawn/number lost to fu not reported/45 analyzed	CrCl change Candesartan 7.7% decrease Lisinopril 2.4% increase Candesartan+Lisinopril: no change NS	

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
36	Not reported	Total adverse reactions: losartan 12% (11/89), trandolapril 22% (19/86), combination 21% (18/88); dry cough: losartan 1%, trandolapril 5.8%, combination 5.7%; hyperkalemia: losartan 4.5%, trandolapril 9.3%, combination 8.0%; sudden death occurred in 1 patient on losartan (thought to be related to rupture of abdominal aneurysm); non-fatal CV event: losartan 2.3%, trandolapril 3.5%, combination 3.4%	5 patients discontinued treatment/unable to determine withdrawals due to adverse events
1	Not reported	<u>Cough</u> Losartan 0% Enalapril 14%; (P=0.006) <u>Uric acid concentration change</u> Losartan (-22.0) µmol/L Enalapril (+12.0) µmol/L; (P=0.001)	<u>Total withdrawals</u> Losartan 6/49(12.2%) Enalapril 5/49(10.2%) <u>Adverse event withdrawals</u> Losartan 2/49(4.1%) Enalapril 1/49(2%)
587	Adverse events were recorded at each visit in response to open questions or as observed in investigators	Not reported	Not reported

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(16) Comments
36	Trial stopped early (anticipated 5yr follow-up) due to significant benefit with combination therapy. Independent risk factors for combined primary endpoint: combination therapy, age, baseline renal function, change in daily urinary protein excretion rate, antiproteinuric response to trandolapril, use of diuretics
1	
587	Doses used in the combination group were half that of the monotherapy groups

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria
39	Muirhead, 1999 Canada (Fair)	Multicenter	Male and female outpatients ≥ 18 years of age, of any racial background with type 2 DM and incipient diabetic nephropathy (defined as AER between 20 and 300 mg/min with GFR ≥ 60 mL/min per 1.73 m^2); normotensive and treated hypertensive patients with a sitting DBP ≤ 95 mm Hg and a sitting SBP ≤ 160 mm Hg
38	Andersen, 2000 Denmark (Fair)	RCT, cross-over	Male and females age 18 to 70 years with a diagnosis of type 1 DM and nephropathy (diagnosed in pateints with persistent albuminuria $\underline{>}$ 300mg/24h, diabetic retinopathy, DM > 10 years, and absence of clinical or laboratory evidence of other kidney disease), GFR > 60mL/min/1.73m2, BP > 145/85 mm Hg

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/interventions
39	Valsartan 80 mg once daily Valsartan 160 mg once daily Captopril 25 mg three times daily Placebo Duration 1 year	28-day washout of ACE inhibitors and CCBs	Customary medication, diuretics, beta blockers
38	Losartan 50mg, losartan 100mg, enalapril 10mg, enalapril 20mg, or placebo each for 2 months	All antihypertensive agents were discontinued for at least 4 weeks	Five patients received furosemide during all treatment periods for prevention of peripheral edema, no other concomitant medications given

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled
39	Clinic visits at weeks 6, 12, 26, 38, and 52	56 72.9% male 90.2% white	Body weight 94.4 kg SSBP 135.6 mm Hg SDBP 83.1 mm Hg AER 56.1 ųg/min GFR 89.9 mL/min per 1.73 m_2	Number screened not reported/number eligible not reported/122 enrolled
38	Objective to evaluate short-term renoprotective effect of AIIRA and compare renal and hemodynamic effects vs. ACEI; GFR (180, 200, 220, 240 min after IV injection 3.7 MBq Cr-EDTA), 24-hour ambulatory BP (Takeda TM2420, every 15 min 7a.m.-11p.m., every 30min 11p.m.-7a.m.), albuminuria (by ELISA) measured at end of each 2 month treatment	Mean age 42 10 males, 6 females (ethnicity not specified)	Duration of DM 33yrs, albuminuria 1156mg/24hr, GFR 90ml/min/1.73m2, BP 147/82 mm Hg, 24hr MAP 104 mm Hg 104	Number screened not reported/number eligible not reported/16 enrolled

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results
39	19(15.6%) withdrawn/0 lost to fu/114 analyzed for GFR; 120 analyzed for AE	AER (µg/min) Valsartan 80 mg 27.8% decrease (P=0.018 vs.placebo) Valsartan 160 mg 21.2% decrease Captopril 26.4% decrease (P=0.009 vs. placebo) Placebo 18.2% increase Valsartan vs. captopril (NS) GFR change (%) Valsartan 80 mg 7.2% decrease Valsartan 160 mg 10.6% decrease Captopril 0.4% increase Placebo 7.7% decrease NS	
38	none withdrawn/none lost to fu/16 analyzed	Albuminuria: losartan 50mg reduced by 33% (95% CI 12-51) vs. placebo, losartan 100mg reduced by 44% (95% CI 26-57) vs. placebo, enalapril 10mg reduced by 45% (95% CI 23-61) vs. placebo, enalapril 20mg reduced by 59% (95% CI 39-72) vs. placebo (all P<0.05 vs. placebo); GFR remained stable with all treatments: losartan 50mg 91±6 ml/min per 1.73m2, losartan 100mg 89±6 ml/min per 1.73m2, enalapril 10mg 89±6 ml/min per 1.73m2, enalapril 20mg 87±6ml/min per 1.73m2, placebo 90±6 ml/min per 1.73m2	24hr MAP decreased from 104±2 mm Hg with placebo vs. 95±2 mm Hg with losartan 50mg, 96±2 mm Hg with losartan 100mg, 98±3 mm Hg with enalapril 10mg, and 93±3 mm Hg with enalapril 20mg (all P<0.05 vs. placebo); all 24hr SBP/DBP reduced with all treatments vs. placebo (P<0.05)

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events
39	Not reported	Total patients with ≥ 1 AE Valsartan 80 mg 9.7% Valsartan 160 mg 22.6% Captopril 34.5% Placebo 13.8% Dry Cough Valsartan 80 mg 3.2% Valsartan 160 mg 9.7% Captopril 20.7% Placebo 3.4%	Total withdrawals Valsartan 80 mg 22.6% Valsartan 160 mg 3.2% Captopril 13.8% Placebo 22.6% Total withdrawals due to adverse events Valsartan 80 mg 3.2% Valsartan 160 mg 3.2% Captopril 6.9% Placebo 0%
38	Not reported	No reported side effects related to losartan or enalapril; serum potassium increased to 4.31±0.1 mmol/L with enalapril 10mg, 4.29±0.1mmol/L with enalapril 20mg, vs. 4.00±0.1 mmol/L with placebo (P<0.05), difference not significant with losartan 50mg (4.18±0.1mmol/L), losartan 100mg (4.13±0.1mmol/L) vs. placebo; sCr: difference not significant vs. placebo (96±5 umol/L), losartan 50mg (94±5 umol/L), losartan 100mg (92±7 umol/L), enalapril 10mg (96±5 umol/L), enalapril 20mg (89±6 umol/L)	All patients completed the study

Evidence table 7. Active-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

ID	(16) Comments
39	
38	Unable to determine long-term effect with 2 month treatment periods. No significant correlations between BP changes in each patient and albuminuria. Authors report the possibility of a type 2 error comparing the antiproteinuric effect of losartan and enalapril at the higher doses

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
2005	Chan, 2004 U.S., Asia, Australia Asian substudy RENAAL (Good)	RCT, multicenter	Refer to RENAAL (Brenner, 2001) below; Asian ethnicity	Refer to RENAAL (Brenner, 2001) below
2013	Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, Israel IDNT (CV substudy) (Good)	RCT, multicenter	Refer to IDNT (Lewis, 2001) below	Refer to IDNT (Lewis, 2001) below Mean follow-up 2.6 years

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity	
2005	Refer to RENAAL (Brenner, 2001) below	Antihypertensive agents other than ACEIs or AIIRAs to achieve target BP (SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg); 82% on CCBs, 35% on diuretics; standard of care for DM	Refer to RENAAL (Brenner, 2001) below	Mean age 59 male, 100% Asian	68%
2013	Refer to IDNT (Lewis, 2001) below	Antihypertensive agents other than ACEIs, AIIRAs, or CCBs to achieve target BP (SBP ≤ 135 mm Hg or 10 mm Hg lower if screening SBP > 145 mm Hg; DBP ≤ 85 mm Hg); 51% on insulin at baseline	Primary endpoint of CV substudy (for overall study see IDNT Lewis, 2001 below) included pre-specified CV outcomes (CV death, MI, HF, permanent neurologic deficit due to stroke, or unplanned revascularization)	Mean age 59 male, 73% white, 14% black, 5% Hispanic, 5% Asian or Pacific Islander, 4% other	67%

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
2005	92% receiving antihypertensive medications, BP 152/82 vs. 152/83 mm Hg (losartan vs. placebo), sCr 1.9mg/dl, HbA1c 8.3% vs. 8.0% (losartan vs. placebo)	Number screened not reported/number eligible not reported/1513 enrolled (252 Asian ethnicity; 220 Asia, 32 other geographic region)	28% on losartan vs. 43% on placebo discontinued treatment/lost to follow-up not reported/252 analyzed
2013	29% CV disease, sCr 1.67mg/dl, HbA1c 8.2%, BP 159/87 mm Hg	Number screened not reported/number eligible not reported/1715 enrolled	16 never received study drug/11 lost to follow-up/1704 analyzed (events of 1715)

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(12) Results	(12) Results
2005	**Primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) at 3.2 years:** losartan vs. placebo RR reduction 0.35 (95% CI 0.07-0.55; P=0.02) NNT= 8 (95% CI 4, 167); no statistically significant difference when components analyzed separately; renal outcomes (ESRD or doubling sCr) RR reduction 0.36 (P=0.034)	**Secondary endpoints (composite CV death, HF, MI, revascularization, unstable angina, stroke):** No statistically significant difference in composite or components of secondary endpoint with losartan vs. placebo
2013	**Primary endpoint CV substudy (composite CV death, HF, MI, stroke, cardiac revascularization) at 2.6 years:** irbesartan vs. placebo HR 0.90 (95% CI 0.74-1.10; P>0.2); irbesartan vs. amlodipine HR 0.90 (95% CI 0.74-1.10; P>0.2)	**Secondary endpoints:** HF (requiring hospitalization or not): irbesartan vs. placebo HR 0.72 (95% CI 0.52-1.00; P=0.048; irbesartan vs. amlodipine HR 0.65 (95% CI 0.48-0.87; P=0.004); no statistically significant difference irbesartan vs. placebo for components of CV death, MI, stroke, or cardiac revascularization

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
2005	Elicited by investigator at study visit	Cough: losartan 22.2% vs. placebo 20% (see also withdrawals due to adverse events)	Total withdrawals losartan (28%) vs. placebo (43%)/withdrawals due to adverse events (losartan/placebo combined): ESRD (n=9); renal insufficiency (n=8); CHF (n=4); MI (n=3); cerebral infarction (n=2)	Losartan 50mg (27%), losartan 100mg (71%) once daily. BP (baseline vs. end): losartan 152/82 vs. 140/73 mm Hg; placebo 152/83 vs. 144/74 mm Hg (NS)
2013	Refer to IDNT (Lewis, 2001) below	Discontinuation due to hyperkalemia: irbesartan (1.9%), amlodipine (0.5%), placebo (0.4%); one episode of early rise in sCr led to discontinuation of irbesartan	Total withdrawals: irbesartan (23.7%), amlodipine (24.5%), placebo (25.5%)/withdrawals due to adverse events: irbesartan (7.6%), amlodipine (9%), placebo (7.2%)	Not powered to detect difference in all-cause mortality or stroke. Statistically significant difference between groups in use of potassium-sparing and combination diuretics, beta-adrenergic blockers, and central and peripheral adrenergic blockers

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
31	Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	RCT, multicenter	Age between 30 and 70 years, documented diagnosis of type 2 DM, HTN (SBP> 135 mm Hg, DBP > 85 mm Hg, or antihypertensive treatment), proteinuria (urinary protein excretion at least 900mg/24hrs), sCr 1.0-3.0mg/dl (women) or 1.2-3.0mg/dl (men)	Irbesartan 75mg titrated to 300mg daily, amlodipine 2.5mg titrated to 10mg daily, or placebo Mean follow-up 2.6 years
32	Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	RCT, multicenter	Male and females age 31 and 70 years with a diagnosis of type 2 DM and nephropathy (defined as ratio urinary albumin to urinary creatinine $\geq$ 300mg/l and sCr 1.3-3.0mg/dl (lower limit 1.5mg/dl for patients > 60kg)	Losartan 50mg titrated to 100mg daily after 4 weeks if BP $\geq$140/90 mm Hg or placebo Mean follow-up 3.4 years

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
31	All ACEIs, AIIRAs, CCBs were discontinued 10 days prior to randomization (BP was controlled by alternate antihypertensive agents during this time)	Antihypertensive agents other than ACEIs, AIIRAs, or CCBs to achieve target BP (SBP ≤ 135 mm Hg or 10 mm Hg lower if screening SBP > 145 mm Hg; DBP ≤ 85 mm Hg); 58% on insulin at baseline	Primary endpoint included composite doubling sCr, onset of ESRD (initiation of dialysis, renal transplantation, or sCr ≥ 6.0mg/dl), or all-cause mortality; secondary CV endpoint included composite CV death, nonfatal MI, HF hospitalization, a permanent neurologic deficit due to stroke, or above the ankle lower limb amputation. Mortality, ESRD, CV endpoints, sCr and potassium, and 24hour urinary protein excretion were monitored quarterly	Mean age 59 67% male, 73% white, 14% black, 5% Hispanic, 5% Asian or Pacific Islander, 4% other
32	All ACEIs and AIIRAs were discontinued 6 weeks prior to randomization and replaced by alternate antihypertensive agents	Antihypertensive agents other than ACEIs or AIIRAs to achieve target BP (SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg); 78% on CCBs, 84% on diuretics; standard of care for DM	Primary endpoint included time to first event composite doubling sCr (first sCr that was twice baseline, confirmed at least 4 weeks later), ESRD (need for chronic or renal transplantation), or all-cause mortality; secondary endpoint included CV morbidity and mortality (composite MI, stroke, first hospitalization for HF or unstable angina, coronary or peripheral revascularization, or death from CV causes); progression of renal disease and changes in level of proteinuria. Follow-up was scheduled for every 3 months	Mean age 60 63% male, 48% white, 15% black, 18% Hispanic, 16% Asian

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
31	29% CV disease, sCr 1.67mg/dl, HbA1c 8.2%, BP 159/87 mm Hg	Number screened not reported/number eligible not reported/1715 enrolled	16 never received study drug/11 lost to follow-up/1715
32	93.5% receiving antihypertensive medications (additional 3% with HTN not on medications), BP 152/82 mm Hg, sCr 1.9mg/dl, HbA1c 8.5%	Number screened not reported/number eligible not reported/1513 enrolled	46.5% on losartan and 53.5% on placebo discontinued treatment/3 lost to follow-up/1513 analyzed

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(12) Results	(12) Results
31	**Primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) at 2.6 years:** irbesartan vs. placebo RR 0.80 (95% CI 0.66-0.97; P=0.02), calculated NNT=16 (95% CI 8-119); irbesartan vs. amlodipine RR 0.77 (95% CI 0.63-0.93; P=0.006), calculated NNT=12 (95% CI 7-35); When analyzed separately, doubling baseline sCr decreased with irbesartan vs. placebo (P=0.003) and vs. amlodipine (P<0.001), decrease in ESRD and decrease all-cause mortality with irbesartan not statistically significant vs. placebo or vs. amlodipine	**Secondary endpoints:** composite CV endpoint: irbesartan vs. placebo RR 0.91 (95% CI 0.72-1.14; P=0.40); irbesartan vs. amlodipine RR 1.03 (95% CI 0.81-1.31; P=0.79); changes in renal function: sCr increased 24% more slowly with irbesartan vs. placebo (P=0.008), sCr mean absolute rates of change were 0.45±0.04mg/dl/yr with irbesartan vs. 0.59±0.04mg/dl/yr with placebo, mean rate of change in CrCl was -5.5±0.36 ml/min per 1.73m2 with irbesartan vs. -6.5±0.37 ml/min per 1.73m2 in the placebo group
32	**Primary endpoint (composite doubling sCr, onset of ESRD, or all-cause mortality) at 3.4 years:** losartan vs. placebo RR 0.84 (95% CI 0.72-0.98; P=0.02 based on results from Cox regression model) [losartan 327/751 (43.5%) vs. placebo 359/762 (47.1%) calculated NNT=28 (95% CI 12-69) based on crude rates of events]; when analyzed separately, doubling baseline sCr decreased with losartan vs. placebo (P=0.006) calculated NNT=23 (95% CI 11-773) as did ESRD (P=0.002) calculated NNT=17 (95% CI 10-59), slight increase in all-cause mortality with losartan was not statistically significant (P=0.88)	**Secondary endpoints:** losartan vs. placebo: composite CV endpoint RR 0.90 (P=0.26); changes in renal function: losartan reduced the rate of decline (reciprocal of sCr concentration) by 18% vs. placebo (P=0.01), and 15.2% reduction in the estimated decline in GFR (median rate of decline 4.4ml/min per 1.73m2 with losartan vs.5.2ml/min per 1.73m2 in the placebo group, P=0.01)

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
31	Protocol established for management of hyperkalemia and to detect early rises in sCr (to assess for renal artery stenosis)	Discontinuation due to hyperkalemia: irbesartan (1.9%), amlodipine (0.5%), placebo (0.4%) (P=0.01 for both comparisons); one episode of early rise in sCr suggestive of renal artery stenosis led to discontinuation of study drug (medication not specified); irbesartan had a lower rate of adverse events/1000 treatment days vs. amlodipine or placebo (P=0.002)	23.7% of patients discontinued treatment/withdrawals due to adverse events not reported although stated that most common reason for discontinuation was clinical CV event	Not powered to detect difference in all-cause mortality or composite CV endpoint. Average MAP was 3.3 mm Hg lower in the irbesartan and amlodipine groups compared to placebo (P=0.001), MAP was not significantly different between irbesartan and amlodipine
32	Elicited by investigator at study visit	Discontinuation due to increased sCr or hyperkalemia: losartan (1.5%, 1.1%, respectively) vs. placebo (1.2%, 0.5%, respectively)	46.5% of patients on losartan discontinued treatment (53.5% on placebo)/withdrawals due to adverse events occurred in 17.2% on losartan and 21.7% on placebo	At 1 year, MAP was 2.2 mm Hg lower in the losartan group (P<0.001) but was not significantly different at the end of the study; the decrease in risk for the primary endpoint remained significant after adjustment for BP

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
777	Plum, 1998 Country not reported (Fair)	RCT	Arterial HTN, sitting DBP < 105 mm Hg and SBP < 180 mm Hg at visit 4; stable renal insufficiency with a sCr between 200 and 600 mmol/L; stable proteinuria of at least 500 mg/24 h	Valsartan 80 mg once daily Placebo Duration 6 months

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(5) Run-in/Washout Period	(6) Allowed other medications/interventions	(7) Method of Outcome Assessment and Timing of Assessment	(8) Age Gender Ethnicity
777	3-month run-in - intervention not reported	Beta blockers, alpha blockers, CCBs, clonidine, minoxidil, furosemide	Examinations every 4 weeks	59 66.7% male Ethnicity not reported

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled	(11) Number withdrawn/ lost to fu/analyzed
777	Weight 82 kg Height 170.8 cm Mean arterial pressure 114.2 mm Hg sCr 356.5 mmol/L Proteinuria 1346 mg/d	Number screened not reported/number eligible not reported/9 enrolled	1(11.1%) withdrawn/0 lost to fu/9 analyzed

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(12) Results	(12) Results
777	Albuminuria change (%) Valsartan 41% decrease Placebo 9.8% increase P<0.05 after 6 months GFR change (%) Valsartan 10% decrease Placebo 10% increase NS after 6 months	

Evidence table 8. Placebo-controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=3)

ID	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
777	Not assessed	Uric acid concentration change Valsartan increase 24 µmol/L (5.6%) Placebo increase 40 µmol/L (8.3%)	Total withdrawals Valsartan 1/5(20%) Placebo 0	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)		(2) Disease	(3) Interventions (drug, dose, duration)
2031	Faulhaber, 1999 Germany (Fair)		Hypertension	Valsartan 80mg daily
2043	Schrader, 2005 Germany, Austria (Fair)	MOSES	Hypertension	Eprosartan 600mg
944	Tedesco, 1999 Country not stated (Fair)		Hypertension	Losartan 50mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
2031	Placebo	6 months	56
2043	Nitrendipine 10mg	2.5 years	1352
944	HCTZ 25mg	2.2 years	69

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
2031	Placebo (11.5%) Valsartan (13.3%)
2043	Not reported
944	None

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2031	Dizziness Valsartan (13.3%) Placebo (7.7%) Increase sCr Valsartan (10.0%) Placebo (11.5%) Hypotension Valsartan (10.0%) Placebo (3.8%) Hyperkalemia Valsartan (6.7%) Placebo (0.0%) Syncope Valsartan (6.7%) Placebo (0.0%
2043	Dizziness/hypotension Eprosartan (12.9%) Nitrendipine (10.6%) Pneumonia Eprosartan (10.8%) Nitrendipine (11.4%) Metabolic disorder Eprosartan (5.5%) Nitrendipine (5.9%)
944	No complaints of cough or complications in sexual performance; no adverse laboratory events reported

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2031	
2043	
944	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
279	Dahlof, 1997 Sweden, Australia, Finland LOA Study (Fair)	Hypertension	Losartan up to 100mg
941	Tanser, 1998 Australia, Canada, Europe, Mexico (Fair)	Hypertension	Candesartan 8mg
795	Rake, 2001 U.S. (Fair)	Hypertension	Eprosartan 1200mg Enalapril 20 mg once daily Placebo
213	Breeze, 2001 North America, Europe, South Africa (Fair)	Hypertension	Eprosartan 800-1200mg
291	De Rosa, 2002 Italy (Fair)	Hypertension	Losartan 12.5-50mg
15	Lithell, 2003 U.S., Canada, Europe SCOPE trial (Fair)	Hypertension	Candesartan 8-16mg (addition of HCTZ 12.5mg and open-label antihypertensive treatment as needed)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control		(5) Duration	(6) Number enrolled
279	Losartan 50mg + HCTZ 12.5mg Amlodipine up to 10mg		12 weeks	898
941	Enalapril 10mg	Placebo	8 weeks	156
795	Enalapril 20mg	Placebo	6 weeks	136
213	Enalapril 5-20mg	Placebo	26 weeks	529
291	Enalapril 5-20mg	Placebo	3 years	50
15	Placebo (addition of HCTZ 12.5mg and open-label antihypertensive treatment as needed)		3.7 years	4937

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events	
279	Losartan (2%) Amlodipine (8%) Losartan + HCTZ (5%) (losartan vs. amlodipine; P=0.01)	
941	Candesartan (8.1%) Enalapril (4.5%)	Placebo (11.5%)
795	Not reported	
213	Withdrawal due to cough Eprosartan (0.7%) Enalapril (2.6%)	
291	Losartan 0 Enalapril (12.5%) NS	
15	Candesartan (15%) Control (17%)	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
279	Any discomfort Losartan (22.5%) Losartan + HCTZ (23.5%) Amlodipine (33.1%) Dizziness upon standing Losartan (10.1%) Losartan + HCTZ (17.1%) Amlodipine (33.1%)
941	Cough Candesartan (16%) Enalapril (31%) Placebo 11%
795	Self-assessed cough *All coughs* Placebo=2/41(4.9%) Enalapril=9/39(23.1%)(p=0.047 for eprosartan vs enalapril) Eprosartan=2/39(5.1%)
213	Cough incidence *Study endpoint analysis* *Definite/Probable/possible* Eprosartan (3.2%) Enalapril (7.6%)
291	Incidence of bother due to cough Losartan 2% Enalapril 12% (P=0.01)
15	Hypotension Candesartan (24.6%) Control (23.4%) Dizziness/vertigo Candesartan (20.9%) Control (20.0%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
279	
941	
795	Investigator reported cough Placebo=3/41(7.3%) Enalapril=11/39(28.2%)NS Eprosartan=5/39(12.8%)
213	Monotherapy endpoint analysis *Definite/Probable/possible* Eprosartan (2.0%) Enalapril (9.7%) (p=0.001)
291	
15	Increase sCr Candesartan (91.0 to 100.6umol/l) Control (91.0 to 96.3 umol/l)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
30	Parving, 2001 Canada, Europe, South America, South Africa (Fair)	Hypertension	Irbesartan 150mg Irbesartan 300mg
2027	Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial (Good)	High CV risk factors	Valsartan 80-160mg (+ HCTZ, other HTN drugs)
2018	Kondo, 2003 Japan (Poor)	High CV risk factors	Candesartan 4mg
11	Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial (Good)	High CV risk factors	Losartan 50-100mg (+ HCTZ 12.5mg)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
30	Placebo	2 years	611
2027	Amlodipine 5-10mg (± HCTZ, other HTN drugs)	4.2 years	15245
2018	Standard therapy	2 years	406
11	Atenolol 50-100mg (± HCTZ 12.5mg)	4.8 years	9193

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events	
30	Irbesartan 150mg (9.2%) Irbesartan 300mg (4.1%) Placebo 17/201(8.4%)	
2027	Valsartan (11.9%) Amlodipine (12.9%)	
2018	Candesartan (4.4%) Control (none reported)	
11	Losartan (13%) Atenolol (18%)	(P<0.0001)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
30	Serious adverse events Irbesartan150/300 (15.4%) Placebo (22.8%) (P=0.02)
2027	Peripheral edema Valsartan (14.9%) Amlodipine (32.9%) (P<0.0001) Dizziness Valsartan (16.5%) Amlodipine (14.3%) (P<0.0001) Headache Valsartan (14.7%) Amlodipine (12.5%) (P<0.0001) Fatigue Valsartan (9.7%) Amlodipine (8.9%) (P=0.075)
2018	Dizziness/lightheadedness Candesartan (4.4%) Control (none reported)
11	Hypotension Losartan (3%) Atenolol (2%) (P=0.001) Cough Losartan (3%) Atenolol (2%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
30	
2027	Mean potassium Valsartan (4.4+0.4 mmol/L vs. 4.4+0.5 mmol/L) Amlodipine (4.4+0.5 mmol/L vs. 4.2+0.5 mmol/L) *Serious adverse events* Angina Valsartan (4.4%) Amlodipine (3.1%) (P<0.0001) Atrial fibrillation Valsartan (2.4%) Amlodipine (2.0%) (P=0.1197) Syncope Valsartan (1.7%) Amlodipine (1.0%) (P<0.0001)
2018	
11	Angioedema Losartan (0.1%) Atenolol (0.2%) Potassium Losartan (0.0+0.4mmol/L) Atenolol (decreased 0.1+0.5mmol/L)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
14	Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease) (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)
13	Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH) (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)
12	Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM) (Good)	High CV risk factors	Losartan 50-100mg (± HCTZ 12.5mg)
29	Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial (Good)	Recent MI	Valsartan 320mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control		(5) Duration	(6) Number enrolled
14	Atenolol 50-100mg	(± HCTZ 12.5mg)	4.8 years	6886
13	Atenolol 50-100mg	(± HCTZ 12.5mg)	4.7 years	1326
12	Atenolol 50-100mg	(± HCTZ 12.5mg)	4.7 years	1195
29	Captopril 150mg	Valsartan 160mg + Captopril 150mg	2.1 years	14,808

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
14	Not reported
13	Losartan14.6% Atenolol 22.1% (P<0.001)
12	Not reported
29	Valsartan (5.8%) Captopril (7.7%) Valsartan + captopril (9.0%) (Valsartan vs. captopril, valsartan + captopril vs. captopril; P<0.05)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
14	Any adverse event Losartan (12.7%) Atenolol (17.3%) (P<0.001) Drug-related adverse event Losartan (6.0%) Atenolol (10.2%) (P<0.001)
13	Hypotension Losartan (4.4%) Atenolol (2.7%) Cough Losartan (4.1%) Atenolol (2.9%)
12	Hypotension Losartan (2%) Atenolol (1%) Cough Losartan (4%) Atenolol (3%)
29	Hypotension (requiring dose reduction) Valsartan (15.1%) Captopril (11.9%) Valsartan + captopril (18.2%) Cough (requiring dose reduction) Valsartan (1.7%) Captopril (5.0%) Valsartan + captopril (4.6%) Angioedema (requiring dose reduction) Valsartan (0.2%) Captopril (0.5%) Valsartan + captopril (0.5%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
14	Serious adverse event Losartan (3.8%) Atenolol (4.4%) Serious, drug-related adverse event Losartan (0.5%) Atenolol (1.0%) (P=0.018)
13	Angioedema Losartan (0.3%) Atenolol (0.3%) Potassium Losartan (-0.002mEq/L) Atenolol (-0.08mEq/L)
12	Angioedema Losartan (0.2%) Atenolol (0.5%) Potassium Losartan (0.05mmol/L) Atenolol (no change)
29	Renal causes (requiring dose reduction) Valsartan (4.9%) Captopril (3.0%) Valsartan + captopril (4.8%) Hyperkalemia (requiring dose reduction) Valsartan (1.3%) Captopril (0.9%) Valsartan + captopril (1.2%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
28	Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial (Good)	Recent MI	Losartan 50mg
2024	Barnett, 2004 Scandinavia, U.K., the Netherlands (Good)	Nephropathy	Telmisartan 40-80mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
28	Captopril 150mg	2.7 years	5477
2024	Enalapril 10-20mg	5 years	250

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events	
28	Losartan 7% Captopril 14%	(P<0.0001)
2024	Telmisartan (16.7%) Enalapril (23.1%)	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
28	Hypotension Losartan (13.3%) Captopril (16.3%) Cough Losartan (9.3%) Captopril (18.7%) (P<0.0001)
2024	Total adverse events Telmisartan (95.8%) Enalapril (100%) Increased sCr (to < 2.3 mg/dl) Telmisartan (1.7%) Enalapril (1.5%) Stroke Telmisartan (5%) Enalapril (4.6%) CHF Telmisartan (7.5%) Enalapril (5.4%) Nonfatal MI Telmisartan (7.5%) Enalapril (4.6%) Death Telmisartan (5%) Enalapril (4.6%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
28	Angioedema (requiring dose reduction) Losartan (0.4%) Captopril (0.8%) Potassium (change from baseline) Losartan (0.19mmol/L) Captopril (0.22mmol/L) (P=0.01)
2024	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
2005	Chan, 2004 US, Asia, Australia Asian substudy RENAAL (Good)	Nephropathy	Losartan 50-100mg
2013	Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, Israel IDNT (CV substudy) (Good)	Nephropathy	Irbesartan 75-300mg
36	Nakao, 2003 Japan COOPERATE (Good)	Nephropathy	Losartan 100mg
536	Lacourciere, 2000 Canada (Poor)	Nephropathy	Losartan 50-100mg ± HCTZ
587	Luno, 2002 Spain (Fair)	Nephropathy	Candesartan 8-32mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
2005	Placebo	3.2 years	252
2013	Amlodipine 2.5-10mg Placebo	2.6 years	1715
36	Trandolapril 3 mg Losartan 100 mg + Trandolapril 3 mg	2.9 years	263
536	Enalapril 5-10 mg ± HCTZ	1 year	103
587	Candesartan 8-32mg Candesartan 4-16 mg + Lisinopril 5-20mg	6 months	46

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
2005	Losartan/placebo combined ESRD (3.6%) Renal insufficiency (3.2%) CHF (1.6%) MI (1.2%) Cerebral infarction (0.8%)
2013	Irbesartan (7.6%) Amlodipine (9%) Placebo (7.2%)
36	Not reported
536	Losartan (4.1%) Enalapril (2%)
587	Not reported

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2005	Cough Losartan (22.2%) Placebo (20%)
2013	Discontinuation due to hyperkalemia Irbesartan (1.9%) Amlodipine (0.5%) Placebo (0.4%) Discontinuation due to early rise sCr Irbesartan 0.2%
36	Total adverse reactions Losartan (12%) Trandolapril (22%) Combination (21%) Dry cough Losartan (1%) Trandolapril (5.8%) Combination (5.7%)
536	Cough Losartan (0%) Enalapril (14%); (P=0.006) Uric acid concentration change Losartan (-22.0 µmol/L) Enalapril (+12.0 µmol/L); (P=0.001)
587	Not reported

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2005	
2013	
36	Hyperkalemia Losartan (4.5%) Trandolapril (9.3%) Combination (8.0%)
536	
587	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)	
39	Muirhead, 1999 Canada (Fair)	Nephropathy	Valsartan 80mg Valsartan 160mg	
38	Anderson, 2000 Denmark (Fair)	Nephropathy	Losartan 50mg	Losartan 100mg
31	Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT (Good)	Nephropathy	Irbesartan 300mg	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control		(5) Duration	(6) Number enrolled
39	Captopril 75 mg Placebo		1 year	122
38	Enalapril 10mg Placebo	Enalapril 20mg	8 months	16
31	Amlodipine 10mg	Placebo	2.6 years	1715

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
39	Valsartan 80mg 3.2% Valsartan 160mg 3.2% Captopril 6.9% Placebo 0%
38	None
31	Not reported

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
39	Total patients with ≥ 1 AE Valsartan 80 mg (9.7%) Valsartan 160 mg (22.6%) Captopril (34.5%) Placebo (13.8%) Dry Cough Valsartan 80 mg (3.2%) Valsartan 160 mg (9.7%) Captopril (20.7%) Placebo (3.4%)
38	Potassium (level increased to) Losartan 50mg (4.18±0.1mmol/L) Losartan 100mg (4.13±0.1mmol/L) Enalapril 10mg (4.31±0.1 mmol/L) Enalapril 20mg (4.29±0.1mmol/L) Placebo (4.00±0.1 mmol/L) Losartan vs. placebo (NS)
31	Hyperkalemia (discontinued) Irbesartan (1.9%) Amlodipine (0.5%) Placebo (0.4%) (P=0.01 for both comparisons) Irbesartan lower rate of adverse events/1000 treatment days vs. amlodipine or placebo (P=0.002)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
39	
38	
31	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
32	Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL (Good)	Nephropathy	Losartan 50-100mg
777	Plum, 1998 Country not reported (Fair)	Nephropathy	Valsartan 80mg
2034	Blanchet, 2005 Canada (Fair)	Heart Failure	Irbesartan 75-150mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
32	Placebo	3.4 years	1513
777	Placebo	6 months	9
2034	Placebo	6 months	34

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
32	Losartan (17.2%) Placebo (21.7%)
777	Not reported
2034	Not reported

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
32	Discontinuation due to increased sCr Losartan (1.5%) Placebo (1.2%) (P=0.01) Discontinuation due to hyperkalemia Losartan (1.1%) Placebo (0.5%) (P=0.01)
777	Uric acid concentration change Valsartan + 24 µmol/L (5.6%) Placebo + 40 µmol/L (8.3%)
2034	Increase sCr Irbesartan vs. placebo (105±25 vs. 97+20 mmol/L; P=0.02)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
32	
777	
2034	Reason not to increase/reduce irbesartan Symptomatic hypotension (22.7%) Hyperkalemia (13.6%) Increase sCr (45.5 4.5%) Other symptoms (13.6%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)		(2) Disease	(3) Interventions (drug, dose, duration)
2020	Matsumori, 2003		Heart Failure	Candesartan 4-8mg
	Japan	(Fair)		

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
2020	Placebo	5.2 months	313

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
2020	Withdrawals due to adverse events (18/155 candesartan 11.6% vs. 6/150 placebo 4.0%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2020	Drug-related adverse events Candesartan (31.1%) Placebo (21.1%) P<0.05 Postural light-headedness Candesartan (8.6%) Placebo (2.0%) Nonpostural light-headedness Candesartan (9.3%) Placebo (3.4%) Hypotension Candesartan (6.6%) Placebo (1.4%) Non-CV adverse effects Candesartan (58.9%) Placebo (51.0%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2020	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
2030	Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis) (Good)	Heart Failure	Valsartan 40-160mg twice daily
19	Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial (Good)	Heart Failure	Losartan up to 50mg
18	Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial (Fair)	Heart Failure	Losartan up to 50mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
2030	Placebo	1.9 years	5010
19	Captopril up to 150mg	1.5 years	3152
18	Captopril up to 150mg	48 weeks	722

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
2030	Not reported
19	Losartan (~10%) Captopril (~15%) (P<0.001)
18	Losartan (12.2%) Captopril (20.8%) (P≤0.002)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2030	Elderly vs. non-elderly Any adverse event Valsartan (93.3% vs. 90.1%) Placebo (92.7% vs. 86.7%) Dizziness (excluding vertigo) Valsartan (23.7% vs. 26.1%) Placebo (18.2% vs. 18.0%) Hypotension Valsartan (14.3% vs. 13.5%) Placebo (8.6% vs. 7.5%) Aggravated CHF Valsartan (13.0% vs. 9.4%) Placebo (16.9% vs. 14.3%) Atrial fibrillation Valsartan (6.5% vs. 4.2%) Placebo (9.6% vs. 6.3%)
19	Withdrawals due to cough Losartan (~1%) Captopril (~3%) (P<0.001)
18	Withdrawals due to cough Losartan (0%) Captopril (3.8%) (P<0.002) Withdrawals due to angioedema Losartan (0%) Captopril (0.8%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
2030	Elderly vs. non-elderly Hyperkalemia Valsartan (7.6% vs. 5.6%) Placebo (3.7% vs. 2.8%) Renal impairment Valsartan (5.8% vs. 5.1%) Placebo (3.2% vs. 2.9%)
19	
18	Withdrawals due to hyperkalemia Losartan (0.6%) Captopril (1.6%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
455	Houghton, 1999 U.K. ELITE Trial substudy (Fair)	Heart Failure	Losartan up to 50mg
273	Cowley, 2000 U.S. ELITE Trial QOL substudy (Fair)	Heart Failure	Losartan up to 50mg
1032	Willenheimer, 2002 Sweden HEAVEN Study (Fair)	Heart Failure	Valsartan 160mg
324	Dunselman, 2001 Europe REPLACE (Fair)	Heart Failure	Telmisartan 10, 20, 40, or 80mg
20	McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD (Poor)	Heart Failure	Candesartan 4, 8, or 16mg once daily
545	Lang, 1997 U.S., Canada (Fair)	Heart Failure	Losartan 25mg Losartan 50mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
455	Captopril up to 150mg	24 weeks	18
273	Captopril up to 150mg	48 weeks	278
1032	Enalapril 20mg	12 weeks	146
324	Enalapril 20mg	12 weeks	378
20	Enalapril 10mg twice daily Candesartan 4 or 8mg once daily plus enalapril 10mg twice daily	43 weeks	768
545	Enalapril 20mg	12 weeks	116

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
455	Losartan (0) Captopril (37.5%)
273	Losartan (10.9%) Captopril (19.0%)
1032	Valsartan (2.9%) Enalapril (4.2%)
324	Telmisartan (3.1%) Enalapril (2.6%)
20	Not reported
545	Losartan 25mg (2.6%) Losartan 50mg (2.5%) Enalapril 20mg (2.7%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
455	Not reported
273	Not reported
1032	All adverse events Valsartan (50%) Enalapril (63%) Headache Valsartan (5.7%) Enalapril (1.4%)
324	Cough Telmisartan (3%) Enalapril (5.6%) (P=0.3)
20	Potassium Candesartan (-0.23±0.03 mmol/L) Enalapril (-0.01±0.05 mmol/L) (P<0.05) Candesartan + enalapril (0.11±0.03 mmol/L)(P<0.05) vs. candesartan (P<0.05) vs. candesartan
545	Potassium Losartan 25mg (-0.16±0.43 mEq/L) Losartan 50mg (0.12±0.42 mEq/L) Enalapril (-0.05±0.47 mEq/L)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
455	
273	
1032	Dizziness Valsartan (4.3%) Enalapril (8.5%)
324	
20	
545	sCr Losartan 25mg (0.02+0.14 mg/dl) Losartan 50mg (0.02+0.28 mg/dl) Enalapril (0.08+0.15 mg/dl) (P<0.05 losartan 50mg vs. enalapril)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
312	Dickstein, 1995 Scandinavia (Fair)	Heart Failure	Losartan 25mg or 50mg
2046	Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials (Good)	Heart Failure	Candesartan 32mg
24	Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial (Good)	Heart Failure	Candesartan 32mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
312	Enalapril 20mg	8 weeks	166
2046	Placebo	3.3 years	4576
24	Placebo	3.1 years	7599

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
312	Losartan 25mg (1.9%) Losartan 50mg (3.6%) Enalapril 20mg (8.6%)
2046	Candesartan (23.1%) Placebo (18.8%) (P<0.001)
24	Candesartan (21.0%) Placebo (16.7%) (P<0.0001)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
312	Dizziness Losartan 25mg (9.6%) Losartan 50mg (8.9%) Enalapril 20mg (6.9%) Hypotension Losartan 25mg (5.8%) Losartan 50mg (7.1%) Enalapril 20mg (6.9%)
2046	Hypotension (discontinued) Candesartan (4.2%) Placebo (2.1%) (P<0.001) Increased sCr (discontinued) Candesartan (7.1%) Placebo (3.5%) (P<0.001) Hyperkalemia (discontinued) Candesartan (2.8%) Placebo (0.5%) (P<0.001)
24	Hypotension (discontinued) Candesartan (3.5%) Placebo (1.7%) (P<0.0001) Increased sCr (discontinued) Candesartan (6.2%) Placebo (3.9%) (P<0.0001) Hyperkalemia (discontinued) Candesartan (2.2%) Placebo (0.6%) (P<0.0001)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
312	Cough Losartan 25mg (3.8%) Losartan 50mg (7.1%) Enalapril 20mg (6.9%)
2046	
24	Angioedema Candesartan (0.13%) Placebo (0.08%) Doubling sCr Candesartan (6%) Placebo (4%) (P=0.002) Potassium > 6mmol/L Candesartan (2.0%) Placebo (1.0%) (P=0.017) (potassium increased 0.14 mmol/L with candesartan (P<0.0001) with no change in the placebo group at 6 weeks)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
25	McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial (Good)	Heart Failure	Candesartan 32mg
26	Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial (Good)	Heart Failure	Candesartan 32mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
25	Placebo	3.4 years	2548
26	Placebo	2.8 years	2028

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
25	Candesartan (24.2%) Placebo (18.3%) (P=0.0003)
26	Candesartan (21.5%) Placebo (19.3%) (P=0.23)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
25	Hypotension (discontinued) Candesartan (4.5%) Placebo (3.1%) (P=0.79) Increased sCr (discontinued) Candesartan (7.8%) Placebo (4.1%) (P=0.0001) Hyperkalemia (discontinued) Candesartan (3.4%) Placebo (0.7%) (P<0.0001)
26	Hypotension (discontinued) Candesartan (3.7%) Placebo (0.9%) (P<0.0001) Increased sCr (discontinued) Candesartan (6.1%) Placebo (2.7%) (P<0.0001) Hyperkalemia (discontinued) Candesartan (1.9%) Placebo (0.3%) (P=0.0005) Cough (discontinued) Candesartan (0.2%) Placebo (0.4%) (P=0.69)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
25	Angioedema Candesartan (0.16%) Placebo (0.24%) Doubling sCr Candesartan (7.0%) Placebo (6.0%) (P=0.5) Potassium > 6mmol/L Candesartan (3.0%) Placebo (1.0%) (P=0.089)
26	Angioedema (discontinued) Candesartan (0.1%) Placebo (0%) (P=0.05) Angioedema Candesartan (0.3%) Placebo (0%) (all in previous ACEI angioedema/anaphylaxis) Doubling sCr Candesartan (5.5%) Placebo (1.6%) (P=0.015) Potassium > 6mmol/L Candesartan (3.0%) Placebo (1.3%) (P=0.26)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)	(2) Disease	(3) Interventions (drug, dose, duration)
27	Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial (Good)	Heart Failure	Candesartan 32mg
16	Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial (Good)	Heart Failure	Valsartan 320mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
27	Placebo	3.1 years	3023
16	Placebo	1.9 years	5010

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
27	Candesartan (17.8%) Placebo (13.5%) (P=0.001)
16	Valsartan (9.9%) Placebo (7.2%) (P<0.001)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
27	Hypotension (discontinued) Candesartan (2.4%) Placebo (1.1%) (P=0.009) Increased sCr (discontinued) Candesartan (4.8%) Placebo (2.4%) (P=0.0005) Hyperkalemia (discontinued) Candesartan (1.5%) Placebo (0.6%) (P=0.029)
16	Dizziness (discontinued) Valsartan (1.6%) Placebo (0.4%) (P<0.001) Hypotension (discontinued) Valsartan (1.3%) Placebo (0.8%) (P=0.124) Renal impairment (discontinued) Valsartan (1.1%) Placebo (0.2%) (P<0.001)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
27	Doubling sCr Candesartan (6%) Placebo (3%) (P=0.007) Potassium > 6.0 mmol/L Candesartan (2%) Placebo (1%) (P=0.32)
16	Mean change sCr Valsartan (increase 0.18mg/dl) Placebo (increase 0.10mg/dl) (P<0.001) Mean change serum potassium Valsartan (increase 0.12mmo/l) Placebo (decrease 0.07mmol/l) (P<0.001)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)		(2) Disease	(3) Interventions (drug, dose, duration)
17	Maggioni, 2002 Val-HeFT subgroup analysis (Fair)	U.S., Australia, Europe, South Africa	Heart Failure	Valsartan 320mg
955	Tonkon, 2000 (Poor)	U.S.	Heart Failure	Irbesartan 150mg
811	Riegger, 1999 STRETCH Trial	Europe (Fair)	Heart Failure	Candesartan 8mg, 16mg
432	Hamroff, 1999 (Fair)	U.S., France	Heart Failure	Losartan 50mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
17	Placebo	1.9 years	366
955	Placebo	12 weeks	109
811	Placebo	12 weeks	844
432	Placebo	6 months	33

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events
17	Valsartan (9.7%) Placebo (12.7%) (P=0.367)
955	Irbesartan (7.0%) Placebo (3.9%)
811	Candesartan 4mg (1.9%) Candesartan 8mg (4.7%) Candesartan 16mg (5.6%) Placebo (4.3%)
432	Losartan (6.25%) Placebo (5.9%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
17	Hypotension (discontinued) Valsartan (0.5%) Placebo (0.6%) (P=0.988) Dizziness Valsartan (23.9%) Placebo (18.9%) Hypotension Valsartan (14.7%) Placebo (5.6%)
955	CV events (discontinued) Irbesartan (7.0%) Placebo (3.9%) Dizziness Irbesartan (23.0%) Placebo (23.0%) Hypotension Irbesartan (12.0%) Placebo (0%)
811	Serious adverse events Candesartan 4mg (1.4%) Candesartan 8mg (5.7%) Candesartan 16mg (5.6%) Placebo (4.7%) Possibly related to symptomatic hypotension Candesartan 4mg (1.5%) Candesartan 8mg (2.8%) Candesartan 16mg (0.5%) Placebo (1.9%)
432	Treatment reported to be well-tolerated in both groups, without adverse side effects

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
17	Headache Irbesartan (19.0%) Placebo (12.0%) Increase sCr Valsartan (0.18+0.2mg/dl) Placebo (0.10+0.02mg/dl) (P=0.009)
955	Headache Irbesartan (19.0%) Placebo (12.0%) Potassium Irbesartan (0.01 mEq/L) Placebo (-0.08mEq/L) sCr Irbesartan (0.08 mg/dl) Placebo (0.04 mg/dl)
811	Increase in sCr Candesartan 4mg (2.9%) Candesartan 8mg (4.2%) Candesartan 16mg (0.9%) Placebo (1.9%)
432	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(1) Author Year Country Trial Name (Quality Score)		(2) Disease	(3) Interventions (drug, dose, duration)
1007	Warner, 1999 (Fair)	U.S.	Heart Failure	Losartan 50mg
420	Granger, 2000 U.S., Canada, Europe (Fair)		Heart Failure	Candesartan 16 mg

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(4) Control	(5) Duration	(6) Number enrolled
1007	Placebo	6 weeks	21
420	Placebo	12 weeks	270

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(7) Withdrawals due to adverse events	
1007	Losartan (5.0%)	Placebo (0%)
420	Candesartan (11.7%) Placebo (8.8%)	

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
1007	Increase in sCr (discontinued therapy)
	Losartan (5.0%)
420	Cough
	Placebo (64.8%)
	Candesartan (68.2%)
	Renal Failure
	Placebo (11.0%)
	Candesartan (11.2%)

Evidence table 9. Adverse events in randomized controlled trials of angiotensin II receptor antagonists

ID	(8) Adverse Effects Reported
1007	
420	Angioedema Placebo (4.4%) Candesartan (4.5%) Discontinuation due to renal insufficiency Placebo (3%) Candesartan (7%)

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Zanabli et al 2004 U.S. (Fair for adverse events)	open label, crossover	Age > 18 and < 70, chronic renal insufficiency (sCr > 1.2 and < 4.0 mg/dl), potassium $\geq$ 4.4 during treatment with AIIRA or ACEI	Lisinopril 5mg X 2 weeks, 10mg X 2 weeks; wash-out X 2 weeks; then losartan 50mg X 2 weeks, 100mg X 2 weeks
Puchler et al 2001 U.S. and Europe (Fair for adverse events)	Meta-analysis RCTs	Mild to moderate HTN	Olmesartan 2.5-80mg 6-12 weeks (7 trials); 3 trials continued up to 52 weeks

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Zanabli et al 2004 U.S. (Fair for adverse events)	Two 2 week wash-outs before each treatment	Amlodipine as need for elevated BP	Serum potassium checked weekly
Puchler et al 2001 U.S. and Europe (Fair for adverse events)	Placebo run-in after withdrawal of antihypertensive agents	No	Monitoring incidence treatment-emergent and serious adverse events (adverse events classified as mild, moderate, severe), clinical laboratory data, ECG, and physical exam

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Zanabli et al 2004 U.S. (Fair for adverse events)	Age range 39 to 68 43% male Ethnicity not reported	Not reported	Number screened not reported/30 eligible/9 enrolled
Puchler et al 2001 U.S. and Europe (Fair for adverse events)	Mean age 55 54% male 87% white, 5% black, 7% Hispanic, 1% Asian or other	Not reported	Number screened not reported/number eligible not reported/number enrolled not reported

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment?
Zanabli et al 2004 U.S. (Fair for adverse events)	2 withdrawn/number lost to fu not reported/7 analyzed	Potassium Lisinopril 5.0±0.18mEq/L Losartan 4.6±0.17mEq/L (P=0.005) sCr Lisinopril 2.4mg/dl Losartan 2.4mg/dl	Same as method of outcome assessment.
Puchler et al 2001 U.S. and Europe (Fair for adverse events)	Number withdrawn (safety population) 440/number lost to fu not reported/3095 analyzed for safety	Treatment emergent adverse events: Olmesartan 51.5% Placebo 47.2% Drug-related adverse events: Olmesartan 26.9% Placebo 22.0% Serious adverse events: Olmesartan 2.0% Placebo 1.4%	Same as method of outcome assessment.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Zanabli et al 2004 U.S. (Fair for adverse events)	See Results	Total withdrawals: 2 patients failed to comply with regular blood draws No withdrawals due to adverse events reported
Puchler et al 2001 U.S. and Europe (Fair for adverse events)	Headache: Olmesartan 7.8% Placebo 9.4% Cough: Olmesartan 1.4% Placebo 1.1% Hypotension: Olmesartan 0.1% Placebo 0% Hyperkalemia: Olmesartan 0.2% Placebo 0% GI: Olmesartan 8.6% Placebo 5.2% Liver/biliary: Olmesartan 4.0% Placebo 3.6%	Total withdrawals: Olmesartan 9.4% Placebo 14.2% Withdrawals due to adverse events: Olmesartan 2.1% Placebo 1.1%

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Biswas et al 2002 England (Fair for adverse events)	Retrospective cohort	Dispensed National Health Service prescriptions written by GPs in England between December 1996 and November 1998.	Valsartan
Benz et al 1997 (Fair overall, fair for adverse events)	RCT	Male and female outpatients aged 18 to 80 years with uncomplicated essential hypertension and a history of ACE inhibitor-induced cough.	Valsartan 80mg, lisinopril 10mg, or 25 mg hydrochlorothiazide for 6 weeks.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Biswas et al 2002 England (Fair for adverse events)	NA	NA	Questionnaire sent to prescribing GP at least 6 months after the date of the first prescription for each individual patient. Mailed questionnaire to GP and patient. An 'event' was defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, and unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any complaint considered to be of sufficient importance to enter into the patient's notes.
Benz et al 1997 (Fair overall, fair for adverse events)	2 to 4 weeks of single-blind placebo treatment to wash out previous antihypertensive medication and demonstrate the absence of cough and the presence of raised blood pressure, followed by 2 to 4 weeks of lisinopril challenge to confirm he presence of an ACE inhibitor-induced cough. Then a further 2 weeks of single-blind placebo treatment to confirm that the cough had resolved and to wash out the lisinopril before randomization.	No	Presence of a dry, persistent cough determined using a patient questionnaire at each visit after enrollment. Assessments at enrollment, before and after the lisinopril challenge, at randomization, and at 3 and 6 weeks of double-blind treatment.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Biswas et al 2002 England (Fair for adverse events)	Mean age (SD) for males 61.1 (12.1); females 65.4 (12.5); age not recorded for 11.7% of patients. 40.5% male, 59% female, 0.5% not specified Ethnicity not reported	Major indication for prescribing: hypertension 64.3%, cough 1.9%, not specified 29.2%.	14,127 of 25,838 (55%) forms mailed were returned.
Benz et al 1997 (Fair overall, fair for adverse events)	Mean age 53.6 55% male 93% white, 3.1% black, 3.9% other	93% of valsartan group and 100% of lisinopril and hydrochlorothiazide patients had significant medical history and/or concomitant diagnosis. (statistically significant, p-value not reported)	197 screened/141 eligible/129 enrolled

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment?
Biswas et al 2002 England (Fair for adverse events)	1246 forms were void. Reasons: no longer registered with doctor (762), blank forms (246), no record of treatment in notes (166), valsartan prescribed but not taken (22), duplicate form for patient (33), patient's doctor died, moved, or retired (17). 12,881 analyzed.	295 events in 209 patients (1.6% of the cohort) were reported to have been adverse reactions to valsartan. Most frequently reported adverse reaction was unspecified side effects in 57 (0.4%) patients, malaise/lassitude in 37 (0.3%) patients, and dizziness in 19 (0.1%). Two reports of drug interaction: 1 ibuprofen causing indigestion and heartburn, 1 warfarin causing "deranged INR."	Same as method of outcome assessment.
Benz et al 1997 (Fair overall, fair for adverse events)	23 withdrew/1 lost to followup/128 analyzed	Incidence of dry persistent cough after 3 or 6 weeks (combined) treatment: valsartan 19.5% lisinopril 68.9% hydrochlorothiazide 19%. Difference: Valsartan vs lisinopril 49.4%, p<0.001 valsartan vs hydrochlorothiazide 0.5% P<0.969 HCTZ vs lisinopril 49.9%, P<0.004	Details of any adverse experiences, including a worsening of an existing condition, recorded at each visit.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Biswas et al 2002 England (Fair for adverse events)	See Results	19.9% had stopped taking valsartan by 6 months (2562/14,127). Most frequent reasons for stopping treatment were "not effective" (847 reports, 6.5%), malaise/lassitude 265 reports, 2%), and dizziness (146 reports, 1.1%).
Benz et al 1997 (Fair overall, fair for adverse events)	89 patients (69%) reported an adverse experience; majority mild to moderate in severity. Frequency of any dry cough (persistent or not): lisinopril 71.1%, valsartan 21.4%, HCTZ 19%. 4 cases of cough with lisinopril considered severe. Headache: valsartan 16.7%, HCTZ 14.3%, lisinopril 2.2% Headache considered related to trial drugs: valsartan 4.8%, HCTZ 7.1%, lisinopril 0.	Withdrawals due to adverse events: lisinopril 10 patients, valsartan 3 patients, HCTZ 2 patients. Withdrawals due to dry cough: 1 valsartan, 8 lisinopril, 0 HCTZ

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	RCT	Elderly patients with hypertension with a history of cough while taking any ACE inhibitor, free of respiratory disease and major cardiac disorders such as advanced heart failure or unstable angina, and nonsmokers for at least one year.	losartan, lisinopril, or metolazone once daily for a maximum of 10 weeks.
Elliot 1999 US (Poor overall, fair for adverse events)	RCT	At least 18 years old with essential hypertension. Women of childbearing potential required to be using contraception.	Initially, eprosartan 200 mg twice daily or enalapril 5 mg once daily. At 3-week intervals, dose titrated as needed to a maximum dose of 300mg eprosartan twice daily or enalapril 20mg once daily. At the end of week 12, maximum doses were supplemented with hydrochlorothiazide 12.5 mg daily.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Lisinopril 10mg administered in a single-blind fashion for a maximum of 8 weeks to confirm presence of ACE inhibitor-induced cough, then dechallenge with placebo for 4 weeks.	No	Presence of cough recorded by a questionnaire administered by a trained nurse. Visual analog scale marked "I never cough" (score of 0) to "I have intolerable cough." Visits scheduled at 2-week intervals, but visits were permitted at 1-week intervals if the cough was annoying to the patient's daily life.
Elliot 1999 US (Poor overall, fair for adverse events)	3- to 5-week single-blind placebo run-in period, an 18-week double-blind titration period, and an 8-week maintenance period.	No	Pulmonary assessment (physician's examination of the chest by auscultaton and percussion, if abnormal) performed at screening, at randomization, at weeks 6 and 12 of the titration phase, and at the end of the maintenance phase. Presence and character of cough assessed by the investigator regarding type, duration, severity, frequency, and probable cause of cough. Cough categorized as definite, probable, possible, or a "tickle in throat." At each visit, patients completed quality-of-life questionnaire with a five-point tolerability rating scale of frequency (never, seldom, occasional, frequent, or constant) and severity for each of 10 commonly-experienced adverse events (one of which was cough). Cough that occurred at any time during the trial was recorded as an adverse experience.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Mean age 73 (SD 5) 42.9% male Ethnicity not reported	No differences among groups in duration of hypertension, blood pressure, and body mass index. No other information on diagnoses reported.	Number screened/eligible not reported/84 enrolled
Elliot 1999 US (Poor overall, fair for adverse events)	Mean age 56 (SEM 0.7) 56.5% male 86.4% white, 7.6% black, 1.1% Asian, 4.9% other	83% history of prior antihypertensive therapy, 56% prior ACE inhibitor therapy, 0.8% prior ACE inhibitor-associated cough, 13% current smokers.	Number screened/eligible not reported/528 enrolled

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment?
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Not reported	Incidence of cough: 97% lisinopril, 18% losartan, 21% metolazone (P<0.001 lisinopril vs losartan). Median time to development of cough with lisinopril was 15 days. VAS score for frequency of cough: lisinopril 6.0 cm (± 1.2), losartan 0.8 cm (± 0.2) P<0.001 lisinopril vs losartan	Not described for events other than cough.
Elliot 1999 US (Poor overall, fair for adverse events)	Not reported	Incidence of definite cough at 12 weeks: 14 (5.4%) enalapril, 4 (1.5%) eprosartan (RR 3.45, 95% CI 1.26-10.0) Incidence of definite cough at 26 weeks: 6.1% enalapril, 1.5% eprosartan (RR 1.41, 95% CI 1.89)	Not described for events other than cough.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Chan et al 1997 Taiwan and Hong Kong (Poor overall, fair for adverse events)	Other than development of cough, no other major adverse events occurred.	4 patients withdrew in lisinopril group due to intolerable cough, no other withdrawals.
Elliot 1999 US (Poor overall, fair for adverse events)	See Results	7 enalapril, 2 eprosartan patients withdrew due to cough

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	RCT, crossover	Men aged 40-49 years with newly diagnosed hypertension, married, with never-treated essential hypertension (DBP 95 mm HG o greater and less than 110 mm Hg) without sexual dysfunction symptoms.	Carvedilol 50mg once daily or valsartan 80mg once daily for 16 weeks, then after another 4-week placebo period, crossed over to the alternative regimen.
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	RCT	Men aged 40-49 years, married, with newly diagnosed, previously untreated essential hypertension (diastolic blood pressure 95 mmHg or higher and less than 110 mmgHg) and without sexual dysfunction symptoms.	Valsartan 80 mg daily or atenolol 50 mg once daily for 16 weeks. After 8 weeks the dose was doubled in the non-responders (DBP >90mmHg).

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	4-week placebo run-in before each treatment period.	No	At each visit, patients given a questionnaire with instructions for self-completion. Questionnaires completed by the respondent in a private area. Questions dealing with sexual function (Have you noted a decrease of interest in sex? Did you have problems in gaining an erection? Did you have problems in maintaining an erection? How many times did you have sexual intercourse in the last 2 weeks?) were part of a series of questions on various aspects of quality of life. Assessments at the screening visit (baseline) and every 4 weeks thereafter.
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	4-week placebo run-in.	No	At each visit, patients given a questionnaire with instructions for self-completion. Questionnaires completed by the respondent in a private area. Questions dealing with sexual function were part of a series of questions on various aspects of quality of life. Primary measure of treatment effect on sexual function was sexual activity assessed as mean number of sexual intercourse episodes per month. Assessments at the screening visit (baseline), at the end of the placebo period and after 8 weeks and 16 weeks of treatment.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	Mean age 46.6 100% male Ethnicity not reported	Newly diagnosed, previously untreated essential hypertension. Men with erectile dysfunction were excluded from analysis.	Number screened, eligible not reported/160 enrolled
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	Mean age not reported (range 40-49) 100% male Ethnicity not reported	Newly diagnosed, previously untreated essential hypertension. Men with erectile dysfunction were excluded from analysis.	Number screened, eligible not reported/110 enrolled

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment?
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	6 withdrawn/6 lost to followup/number analyzed not clear (those with erectile dysfunction not analyzed, but number not reported)	Decrease from baseline in episodes of sexual intercourse per month after 4 weeks of active treatment: carvedilol from 8.2 to 4.4 (-46%, P<0.01 vs baseline) valsartan from 8.3 to 6.6 (-21%, NS) Episodes of sexual intercourse per month after 16 weeks of treatment: carvedilol 3.7 $\pm$ 1.4 (P<0.01 vs baseline) valsartan 10.2 $\pm$ 4.6 (NS vs baseline) difference between groups P<0.01	Not described for events other than decrease in sexual activity.
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	Not reported.	Change from baseline in episodes of sexual intercourse per month after 8 weeks: atenolol: from 6.0 to 5.0 (P=0.061 vs placebo) valsartan: from 5.8 to 6.5 (P=0.053 vs atenolol) Episodes of sexual intercourse per month after 16 weeks: atenolol: 4.2 (P<0.05 vs placebo) valsartan: 7.3 (P=0.01 vs atenolol)	Not described for events other than decrease in sexual activity.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Fogari et al 2001 Italy (Fair overall, fair for adverse events)	Erectile dysfunction spontaneously reported: carvedilol: 15 patients (13.5%) valsartan: 1 patient (0.9%) p<0.001	6 withdrawals (1 valsartan, 1 carvedilol, 4 placebo) 2 withdrawals due to hypotension (1 valsartan, 1 carvedilol).
Fogari et al 2002 Italy (Poor overall, fair for adverse events)	Erectile dysfunction spontaneously reported: atenolol 10 patients (18.2%) valsartan 0 patients	Not reported

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	RCT	Men and women 21 years or older, with uncomplicated primary hypertension who had previously reported cough with an ACE inhibitor, otherwise generally healthy.	Losartan 50mg, lisinopril 20mg, or hydrochlorothiazide 25mg once daily.
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	RCT	Patients between ages 18 and 80 with uncomplicated mild to moderate essential hypertension and a history of ACE inhibitor-related dry cough.	Telmisartan 80 mg, lisinopril 20 mg for up to 8 weeks.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	Patients with a history of ACE inhibitor-associated cough received lisinopril 20mg once daily in a single-blind manner for up to 6 weeks; those with moderate or more dry cough on two consecutive visits entered single-blind placebo washout period. At least 2 weeks later, patients with no dry cough on two consecutive visits were randomized to 8-week double-blind treatment period.	No	Symptom Assessment Questionnaire and Visual Analogue Scale were independently completed by patients at all clinic visits before being seen by the physician or study nurse. Questionnaire assessed the severity of nine symptoms, including dry cough. Visual Analogue Scale completed to assess patient's perception of frequency of cough. Clinic visits were scheduled every 2 weeks, but patients were permitted to return earlier if indicated (i.e., if a persistent dry cough developed).
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	7-day screening period; challenge period of up to 6 weeks, during which the patients received single-blind, double dummy lisinopril, a 4-week washout period, double-blind treatment period of up to 8 weeks, and a 1-week, post-treatment placebo period.	Permitted paracetamol 2g per day or less and aspirin not exceeding 325 mg per day for prophylaxis of coronary artery disease.	Assessment for presence of cough performed using a Symptom Assessment Questionnaire and a Visual Analogue Scale independently completed by patients at all visits. SAQ evaluated incidence and severity of 9 symptoms: dry cough, dry mouth, leg cramps, racing heart, heartburn, headache, sore throat, nocturnal urination, and facial flushing. Severity of these indicated on 5-point scale ranging from "not at all" to "extremely." Visual Analogue Scale assessed frequency of symptoms appearing on the SAQ, ranging from "I never have the symptom" to " I have the symptom constantly." Frequency of cough measured at the end of the lisinopril challenge period, end of placebo and washout phase. "Time to positive" response for the development of cough during the double-blind period was also analyzed.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	Mean age ~ 56 (SD ~ 10.5) 36% male White: 81% losartan, 98% lisinopril (p<0.05 vs losartan group), 88% hydrochlorothiazide Black: 10% losartan, 0 lisinopril, 7% hydrochlorothiazide Other: 8% losartan, 2% lisinopril, 4% hydrochlorothiazide	No differences among groups in duration of hypertension or blood pressure. All had uncomplicated primary hypertension, otherwise generally healthy.	Number screened, eligible not reported/135 enrolled
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	8% age 31-40, 60.2% age 41-64, 31.8% age 65 or older 38.6% male, 61.4% female 89.8% white (other ethnicities not reported).	Median duration of hypertensive disease 10.6 years for placebo, 9.3 years for telmisartan, and 6.5 years for lisinopril.	216 screened/135 eligible/92 enrolled

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	Number withdrawn, lost to followup not reported/135 analyzed	Number of patients with dry cough during 8 weeks of treatment (includes responses "a little", "moderately", "quite a bit", or "extremely") losartan 29.2% lisinopril 71.7% (P<0.01 vs other groups) HCTZ 34.1% Change in VAS from end of washout to end of treatment period (higher is more frequent cough): lisinopril 3.0 cm losartan 0.9 cm hydrochlorothiazide 1.2 cm (P<0.01 lisinopril vs losartan and HCTZ)	For events other than cough, spontaneous report.
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	4 withdrawn/0 lost to followup/88 analyzed	Occurrence of dry cough during 8 weeks of treatment: telmisartan15.6% (P=0.004 vs lisinopril) lisinopril 60% placebo 9.7% (P=0.001 vs lisinopril) Frequency of dry cough on VAS at 8 weeks of treatment (higher is more frequent cough): telmisartan 0.83 cm (P=0.0016 vs lisinopril) lisinopril: 2.87 cm placebo: 0.92 cm (P=0.0028 vs lisinopril)	Other than cough, monitored by physical examinations, ECG, laboratory tests, and patient adverse events reporting.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe) (Fair overall, fair for adverse events)	At least one adverse event spontaneously reported: losartan 52.1%, lisinopril 63.0%, HCTZ 43.9% Drug-related adverse events: lisinopril 45.7%, losartan 22.9%, HCTZ 17.1% p<0.05 lisinopril vs losartan, <0.01 vs HCTZ	Not reported
Lacourciere 1999 Canada (Fair overall, fair for adverse events)	Adverse events reported: 66.7% placebo patients, 53.1% telmisartan patients, 44.4% lisinopril patients. Except for cough, most were mild to moderate in intensity and not considered treatment-related.	Of those entering double-blind treatment period (n=92): 4 withdrew. 3 discontinued due to adverse events (groups not specified)

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions (drug, dose, duration)
Paster et al 1998 US (Fair overall, fair for adverse events)	RCT	Generally healthy men and women, of legal age, with hypertension and a history of ACE inhibitor-induced cough.	Losartan 50mg once daily, lisinopril 20mg once daily, or placebo for up to 8 weeks.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Paster et al 1998 US (Fair overall, fair for adverse events)	Open-label lisinopril 20mg once daily for a maximum of 6 weeks as a challenge to reproduce the dry cough. Those with dry cough on two consecutive visits proceeded to 4-week, placebo washout, during which total disappearance of cough had to be documented on two consecutive visits. Those who met criteria for first 2 phases were randomly allocated to 8 weeks double-blind therapy.	No	Incidence and severity of dry cough assessed at each visit using the SAQ, which listed nine symptoms (dry mouth, cramps in legs, dry cough, racing heart, heartburn, headache, sore throat, getting up at night to pass urine, and flushing face). Primary efficacy question was dry cough. Patients marked whether they had experienced the symptom in the previous week and, if so, the extent to which it had bothered them (not at all, a little, moderately, quite a bit, or extremely). Patients also used a VAS at each visit to quantify their perception of cough frequency, ranging from "I never cough" to "I am constantly coughing." Clinic visits scheduled every 2 weeks through out all phases of the trial but could be scheduled more frequently if clinically indicated (i.e., if a patient developed persistent dry cough).

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Paster et al 1998 US (Fair overall, fair for adverse events)	Mean age 57.1 (range 31-83) 49% male 90% white, 3% Asian, 5% black, 2% other	Mean duration of hypertension 10 years (range 0.3-40 years)	Number screened, eligible not reported/100 enrolled

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment?
Paster et al 1998 US (Fair overall, fair for adverse events)	8 withdrawn/2 lost to followup/97 analyzed	Incidence of dry cough during 8 weeks of treatment: losartan 36.7% lisinopril 87.5% (P≤ 0.001 compared with losartan and placebo) placebo 31.4%	At each visit, patients were asked a non-leading question concerning how they had felt since the last visit. Physician investigator assessed whether any adverse experiences were related to therapy. Investigators masked to treatment.

Evidence table 10. Studies of adverse events of angiotensin II receptor antagonists

Author Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Paster et al 1998 US (Fair overall, fair for adverse events)	No serious clinical or laboratory adverse events. 11/31 (35.5%) losartan patients, 11/34 (32.4%) lisinopril patients, and 20/35 (57.1%) placebo patients reported at least one clinical adverse event. Adverse events judged to be drug related in 2 losartan (6.5%) vs 5 lisinopril (14.7%) and 9 placebo (25.7%).	Withdrawals due to adverse events1 lisinopril (cough), 0 losartan, 5 placebo.

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Internal Validity: Randomization adequate?	Internal Validity: Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Tedesco, 1999 Country not stated	Method not reported	Method not reported	Yes	Yes	Yes, but method not described
Dahlof, 1997 Sweden, Australia, Finland	Method not reported	Method not reported	Yes	Yes	Not reported
Tanser, 1998 Australia, Canada, Europe, Mexico	Not reported	Not reported	Yes	Yes	Yes, but method not described
Rake, 2001 U.S.	Not reported	Not reported	Yes	Yes	Yes
Breeze, 2001 North America, Europe, South Africa	Not reported	Not reported	Yes	Yes	Yes
De Rosa, 2002 Italy	Not reported	Not reported	Yes	Yes	Yes, but method not described
Schrader, 2005 Germany, Austria MOSES (Fair)	Yes	Yes	Yes	Yes	Yes

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Tedesco, 1999 Country not stated	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Dahlof, 1997 Sweden, Australia, Finland	Yes	Yes, but method not described	Yes/No/No/No	No
Tanser, 1998 Australia, Canada, Europe, Mexico	Yes, but method not described	Yes, but method not described	No/No/No/No	No
Rake, 2001 U.S.	Yes	Yes	No/No/No/No	Not reported
Breeze, 2001 North America, Europe, South Africa	Yes	Yes	Yes/No/No/No	No
De Rosa, 2002 Italy	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Schrader, 2005 Germany, Austria MOSES (Fair)	No	No	No/No/No/Yes	No

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating	External Validity: Number screened/eligible/enrolled
Tedesco, 1999 Country not stated	Yes	Unable to determine	Fair	Number screened not reported/number eligible not reported/69 enrolled
Dahlof, 1997 Sweden, Australia, Finland	Yes	Unable to determine	Fair	Number screened not reported/number eligible not reported/898 enrolled
Tanser, 1998 Australia, Canada, Europe, Mexico	No (2 patients excluded due to not having post-randomization assessments of cough)	Yes (2)	Fair	Number screened not reported/301 eligible/156 enrolled
Rake, 2001 U.S.	No (4 had insufficient information to analyze QOL)	Yes (4)	Fair	231 screened/number eligible not reported/136 enrolled
Breeze, 2001 North America, Europe, South Africa	No, different numbers of patients excluded from cough and QOL assessments	Yes (6 due to lack of baseline and/or endpoint questionnaires)	Fair	Number screened not reported/number eligible not reported/529 enrolled
De Rosa, 2002 Italy	No	No	Fair	Number screened not reported/number eligible not reported/50 enrolled
Schrader, 2005 Germany, Austria MOSES (Fair)	Yes	Yes (53 withdrew consent prior to taking study drug)	Fair	Number screened not reported/1405 eligible/1352 enrolled

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only?
Tedesco, 1999 Country not stated	Recent MI or stroke, renal failure, chronic severe liver disease, congestive HF	Yes	Not reported
Dahlof, 1997 Sweden, Australia, Finland	Women of child-bearing age, significant renal impairment, MI within previous 6 months, angina, congestive HF, beta-blockers and other antihypertensive agents, previous AIIRA or CCB	Yes	Yes
Tanser, 1998 Australia, Canada, Europe, Mexico	Obstructive pulmonary disease; smoking; concomitant medication including NSAIDs; aspirin; codeine; antitussive agents; secondary or malignant hypertension; sitting DBP > 105 mm Hg or 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	Yes	No
Rake, 2001 U.S.	Not reported	Yes	No
Breeze, 2001 North America, Europe, South Africa	Not reported	Yes	No
De Rosa, 2002 Italy	Significant cardiovascular, cerebrovascular, renal or hepatic disease, recent MI and secondary HTN	Yes	No
Schrader, 2005 Germany, Austria MOSES (Fair)	Internal carotid artery occlusion or stenosis > 70%, HF NYHA class III-IV, > 85 years at time of cerebrovascular event, treatment with anticoagulants for cardiac arrhythmia, high grade aortic or mitral valve stenosis, unstable angina pectoris	No	No

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Control group standard of care?	Funding	Relevance?
Tedesco, 1999 Country not stated	Yes	Not reported	Yes
Dahlof, 1997 Sweden, Australia, Finland	Yes	Financial support by Merck & Co., Inc. (coordination efforts of sponsor employee acknowledged)	Yes
Tanser, 1998 Australia, Canada, Europe, Mexico	Yes	Supported by a grant from Astra Hassle	Yes
Rake, 2001 U.S.	Yes	Funded by SmithKline Beecham Pharmaceutical Inc	Yes
Breeze, 2001 North America, Europe, South Africa	Yes	Funded by SmithKline Beecham Pharmaceutical Inc	Yes
De Rosa, 2002 Italy	Yes	Not reported	Yes
Schrader, 2005 Germany, Austria MOSES (Fair)	Yes	Supported by Solvay Pharmaceuticals GmbH and Aventis Pharma Germany (Solvay Pharmaceuticals provided study medication)	Yes

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

	Internal Validity				
Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Yamamoto, 2003 Japan	Not randomized	Not randomized	Yes	Yes, but inadequate details	No

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Yamamoto, 2003 Japan	No	No	Yes/Yes/No/No	No

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating	External Validity Number screened/eligible/enrolled
Yamamoto, 2003 Japan	Yes	No	Poor	Number screened not reported/number eligible not reported/100 enrolled

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only?
Yamamoto, 2003 Japan	Severe organ failure of brain, heart, or kidney; severe DM or hepatic disease; dementia or psychiatric disease preventing QOL assessment	No	Not reported

Quality table 1. Active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=6)

Author, Year Country	Control group standard of care?	Funding	Relevance?
Yamamoto, 2003 Japan	Yes	Not reported	Yes

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Internal Validity Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes	Yes	Yes	Yes	Yes
Parving, 2001 Canada, Europe, South America, South Africa	Not reported	Not reported	Yes	Yes	Yes, but method not described
Trenkwalder, 2005 U.S., Canada, Europe SCOPE trial substudy (demographics, risk factors, comorbidities)	Yes	Yes	Yes	Yes	Yes

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes	Yes	Yes/No/No/Yes	No
Parving, 2001 Canada, Europe, South America, South Africa	Yes, but method not described	Yes, but method not described	Yes/No/Yes/No	No
Trenkwalder, 2005 U.S., Canada, Europe SCOPE trial substudy (demographics, risk factors, comorbidities)	Yes	Yes	Yes/No/No/Yes	No

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes (although 13 excluded post-randomization for data quality concerns)	Yes (27 total: 13 data quality concerns; 14 no study drug dispensed)	Fair
Parving, 2001 Canada, Europe, South America, South Africa	Yes	No	Fair
Trenkwalder, 2005 U.S., Canada, Europe SCOPE trial substudy (demographics, risk factors, comorbidities)	Yes (see SCOPE trial below)	Yes (see SCOPE trial below)	Fair

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Number screened not reported/4964 randomized/4937 enrolled	Secondary HTN, SBP ≥ 180 mm Hg, orthostatic hypotension, need for treatment with other than HCTZ during run-in, MI or stroke within previous 6 months, decompensated HF, AST or ALT > 3 times upper limit normal, sCr > 180umol/l (men) and > 140 umol/l (women), contraindications to study drug or HCTZ, serious concomitant diseases affecting survival, alcohol or drug abuse; dementia, treatment with drugs for dementia, conditions that preclude MMSE, vitamin B12 deficiency or hypothyroidism treated < 12 months, neurosyphilis or AIDS, severe brain disorder, certain mental disorders, psychopharmacologic therapy started with previous 6 months
Parving, 2001 Canada, Europe, South America, South Africa	Number screened not reported/1469 eligible/611 enrolled	Nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within two years, and an indication for angiotension-converting-enzyme (ACE) inhibitors or angiotensin II receptor antagonists
Trenkwalder, 2005 U.S., Canada, Europe SCOPE trial substudy (demographics, risk factors, comorbidities)	Number screened not reported/4964 randomized/4937 enrolled	See SCOPE (Lithell, 2003) below

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Lithell, 2003 U.S., Canada, Europe SCOPE trial	Yes	Not reported	Yes	Financially supported by AstraZeneca (data entered into sponsor's database, employees of sponsor were non-voting members of the Executive and Steering Committees)	Yes
Parving, 2001 Canada, Europe, South America, South Africa	Yes	No	Yes	Supported by a grant from Sanofi-Synthlabo and Bristol-Myers Squibb	Yes
Trenkwalder, 2005 U.S., Canada, Europe SCOPE trial substudy (demographics, risk factors, comorbidities)	Yes	Not reported	Yes	Unrestricted support by AstraZeneca; two authors employees of manufacturer povoding funding	Yes

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Papademetriou, 2004 U.S., Canada, Europe SCOPE trial substudy (ISH)	Yes	Yes	Yes (except for higher CV risk in candesartan group; 38.9% vs. 32.5% control)	Yes	Yes
Degl'Innocenti, 2004 U.S., Europe SCOPE trial substudy (QOL)	Yes	Yes	Yes	Yes	Yes
Faulhaber, 1999 Germany	Method not reported	Method not reported	Yes	Yes	Not Reported

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Papademetriou, 2004 U.S., Canada, Europe SCOPE trial substudy (ISH)	Yes	Yes	Yes/No/No/Yes	No
Degl'Innocenti, 2004 U.S., Europe SCOPE trial substudy (QOL)	Yes	Yes	Yes/No/No/Yes	No
Faulhaber, 1999 Germany	Yes	Yes	Yes/No/Yes/No	No

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Papademetriou, 2004 U.S., Canada, Europe SCOPE trial substudy (ISH)	Yes (and last value carried forward)	Yes (1 lost to fu)	Fair
Degl'Innocenti, 2004 U.S., Europe SCOPE trial substudy (QOL)	No	Yes (196 total; reason not reported)	Fair
Faulhaber, 1999 Germany	No (modified intent-to-treat; 6 excluded for completing < 12 weeks)	Yes (6 total for completing < 12 weeks trial)	Fair

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	External Validity: Number screened/eligible/enrolled	External Validity: Exclusion criteria
Papademetriou, 2004 U.S., Canada, Europe SCOPE trial substudy (ISH)	Number screened not reported/1518 randomized with ISH/1518 enrolled	Secondary HTN, SBP > 180 mm Hg, orthostatic hypotension, need for treatment with other than HCTZ during run-in, MI or stroke within previous 6 months, decompensated HF, AST or ALT > 3 times upper limit normal, sCr > 180umol/l (men) and > 140 umol/l (women), contraindications to study drug or HCTZ, serious concomitant diseases affecting survival, alcohol or drug abuse; dementia, treatment with drugs for dementia, conditions that preclude MMSE, vitamin B12 deficiency or hypothyroidism treated < 12 months, neurosyphilis or AIDS, severe brain disorder, certain mental disorders, psychopharmacologic therapy started with previous 6 months; DBP > 90 mm Hg after run-in
Degl'Innocenti, 2004 U.S., Europe SCOPE trial substudy (QOL)	Number screened not reported/number eligible not reported/2850 enrolled	Secondary HTN, SBP > 180 mm Hg, orthostatic hypotension, need for treatment with other than HCTZ during run-in, MI or stroke within previous 6 months, decompensated HF, AST or ALT > 3 times upper limit normal, sCr > 180umol/l (men) and > 140 umol/l (women), contraindications to study drug or HCTZ, serious concomitant diseases affecting survival, alcohol or drug abuse; dementia, treatment with drugs for dementia, conditions that preclude MMSE, vitamin B12 deficiency or hypothyroidism treated < 12 months, neurosyphilis or AIDS, severe brain disorder, certain mental disorders, psychopharmacologic therapy started with previous 6 months; not enrolled at participating site
Faulhaber, 1999 Germany	Number screened not reported/number eligible not reported/56 enrolled	None reported; criteria for study discontinuation included intolerable adverse events (mean sitting DBP > 120 mm Hg, sCr > 600 µmol/L), major protocol compliance violations, withdrawal of consent

Quality table 2. Placebo/active controlled trials of angiotensin II receptor antagonists in patients with hypertension (N=2)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Papademetriou, 2004 U.S., Canada, Europe SCOPE trial substudy (ISH)	Yes	Not reported	Yes	Unrestricted support by AstraZeneca	Yes
Degl'Innocenti, 2004 U.S., Europe SCOPE trial substudy (QOL)	Yes	Not reported	Yes	Sponsored by AstraZeneca (also provided monitoring and coordinating staff)	Yes
Faulhaber, 1999 Germany	Yes	Not reported	Yes	Supported by Novartis	Yes

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Method not reported	Method not reported	Yes	Yes	Yes
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Method not reported	Method not reported	Yes	Yes	Yes
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Method not reported	Method not reported	Yes	Yes	Yes
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Method not reported	Method not reported	Yes	Yes	Yes

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Yes, but method not described	Yes, but method not described	Yes/No/No/No	No
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Yes, but method not described	Yes, but method not described	Yes/No/No/Yes	No

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating	External Validity Number screened/eligible/enrolled
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Yes	No	Good	10,780 screened/9222 eligible/9193 enrolled
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Yes	Unable to determine	Good	10,780 screened/9222 eligible/6886 of 9193 enrolled in substudy
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Yes	No	Good	10,780 screened/9222 eligible/1326 of 9193 enrolled in substudy
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Yes	No	Good	10,780 screened/9222 eligible/1195 of 9193 enrolled in substudy

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Clinical evidence of vascular disease, secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Clinical evidence of vascular disease, secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF ≤ 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Control group standard of care?	Funding	Relevance?
Dahlof, 2002 U.S., U.K., Scandinavia LIFE trial	Yes	Supported by an unrestricted grant from Merck (steering committee had free access to study data in sponsor's database to interpret data and write the manuscript)	Yes
Devereux, 2003 U.S., U.K., Scandinavia LIFE trial substudy (w/o vascular disease)	Yes	Supported by a grant from Merck & Co. (helped refine study, provided data management assistance and data collection, and performed statistical analyses)	Yes
Kjeldsen, 2002 U.S., U.K., Scandinavia LIFE trial substudy (ISH)	Yes	Supported by an unrestricted grant from Merck & Co. (reviewed manuscript)	Yes
Lindholm, 2002 U.S., U.K., Scandinavia LIFE trial substudy (DM)	Yes	Supported by an unrestricted grant from Merck (study data in sponsors database, free access by steering committee; reviewed manuscript)	Yes

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?
Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial	Yes	Yes	Yes	Yes	Yes
Kondo, 2003 Japan	Method not reported	Method not reported	Yes	Yes	No
Julius, 2004 U.S., U.K., Scandinavia LIFE trial substudy (Black patients)	Method not reported	Method not reported	No	Yes	Yes

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?
Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial	Yes, but HCTZ unblinded	Yes	Yes/No/No/No	No
Kondo, 2003 Japan	No	No	Yes/No/No/No	No
Julius, 2004 U.S., U.K., Scandinavia LIFE trial substudy (Black patients)	Yes	Yes	Yes/No/No/No	No

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating	External Validity Number screened/eligible/enrolled
Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial	Yes	No	Good	18,124 screened/15,313 eligible/15,245 enrolled
Kondo, 2003 Japan	Yes	Unable to determine	Poor	Number screened not reported/number eligible not reported/406 enrolled
Julius, 2004 U.S., U.K., Scandinavia LIFE trial substudy (Black patients)	Yes	Unable to determine	Good	10,780 screened/9222 eligible/9193 enrolled (533 Black patients)

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only?
Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial	Renal artery stenosis, pregnancy, acute MI, PTCA or CABG within previous 3 months, clinically relevant valvular disease, stroke within previous 3 months, severe hepatic disease, severe chronic renal failure, congestive HF requiring ACEI therapy, monotherapy with beta-blockers for both CAD and HTN	No	No
Kondo, 2003 Japan	CHF (LVEF < 40%), malignancy, receiving dialysis	No	Not reported
Julius, 2004 U.S., U.K., Scandinavia LIFE trial substudy (Black patients)	Secondary HTN, MI or stroke within previous 6 months, angina requiring beta-blockers or CCBs, HF or LVEF < 40%, any disorder requiring treatment with an AIIRA, beta-blocker, HCTZ, or ACEI	Yes	Not reported

Quality table 3. Active controlled trials of angiotensin II receptor antagonists in patients at high cardiovascular risk (N=4)

Author, Year Country	Control group standard of care?	Funding	Relevance?
Julius, 2004 N. America, S. America, Europe, Africa, Asia, Australia VALUE trial	Yes	Supported by an unrestricted grant from Novartis Pharma AG (executive committee had full access to study data, was responsible for data analysis and had statistician independently analyze and validate analysis done by sponsor statistician, and had control over the right to publish)	Yes
Kondo, 2003 Japan	No	None reported	Yes
Julius, 2004 U.S., U.K., Scandinavia LIFE trial substudy (Black patients)	Yes	Investigator-initiated study supported by Merck & Co., Inc.	Yes

Quality table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

	Internal Validity			
Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Pfeffer, 2003 U.S., Canada, South America, Australia, Africa, Europe, Russia VALIANT trial	Yes	Yes	Yes (note:data missing on similar number of patients for LVEF, Killip class, and site and type of MI)	Yes
Dickstein, 2002 Denmark, Finland, Germany, Ireland, Norway, Sweden, U.K. OPTIMAAL trial	Yes	Yes	Yes	Yes

Quality table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat analysis?
Yes	Yes	Yes	Yes/No/Yes/Yes	No	Yes
Yes	Yes	Yes	Yes/No/Yes/No	No	Yes

Quality table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

		External Validity
Post-randomization exclusions?	**Quality Rating**	**Number screened/eligible/enrolled**
Yes (105 at one site due to potential inadequate informed consent process)	Good	Number screened not reported/number eligible not reported/14,808 enrolled (14,703 analyzed as 105 from one site were censored prior to unblinding)
No	Good	31,738 screened/number eligible not reported/5477 enrolled

Quality table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

Exclusion criteria	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Previous intolerance or contraindication to ACEI or AIIRA, clinically significant valvular disease, any disease known to severely limit life expectancy, written informed consent not available	None	No	Yes
Supine SBP < 100 mm Hg, current treatment with ACEI or AIIRA, unstable angina, hemodynamically significant stenotic valvular disease or dysrhythmia, and planned coronary revascularization	None	Yes (at time of enrollment)	Yes

Quality table 4. Head-to-head trials of angiotensin II receptor antagonists in patients after recent myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both (N=2)

Funding	Relevance?
Supported by a grant from Novartis Pharmaceuticals (sponsor verified all analyses and reviewed manuscript)	Yes
Supported by an unconditional grant from Merck, Sharp and Dohme Research Laboratories (sponsor provided assistance in data management and included 2 non-voting members on the steering committee)	Yes

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Yes	Yes	Yes	Yes
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Method not reported	Method not reported	Yes	Yes
Houghton, 1999 U.K. ELITE Trial substudy	Method not reported	Method not reported	Yes	Yes

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Yes	Yes	Yes	Yes/No/No/Yes
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Yes	Yes	Yes	Yes/No/No/No
Houghton, 1999 U.K. ELITE Trial substudy	Yes	Yes	Yes	Yes/No/No/No

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	No	Yes	No	Good
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Not reported	Yes	No	Fair
Houghton, 1999 U.K. ELITE Trial substudy	No	Yes	Unable to determine	Fair

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Number screened not reported/number eligible not reported/3152 enrolled	Previous intolerance to ACEIs or AIIRAs, SBP < 90 mm Hg, DBP > 95 mm Hg, hemodynamically important stenotic valvular heart disease, acute myocarditis or pericarditis, automatic implanted cardioverter defibrillators, coronary angioplasty within 1 week of enrollment, CABG, AMI or unstable angina within 2 weeks of enrollment, CVA or TIA within 6 weeks of enrollment, documented or significant renal artery stenosis, hematuria, sCr > 220 umol/L
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Number screened not reported/number eligible not reported/722 enrolled	SBP < 90 mm Hg or uncontrolled HTN (DBP > 95 mm Hg), significant obstructive valvular disease or symptomatic ventricular or supraventricular arrhythmia, constrictive pericarditis or acute myocarditis, cardiac surgery likely during study period or angioplasty within previous 72hrs, CABG or ICD within 2 weeks, AMI in previous 72hrs, unstable angina within 3 months, or angina (requiring 5 NTG tabs/wk) within 6 weeks, stroke or TIA in previous 3 months, digitalis toxicity, uncontrolled DM, chronic cough or angioedema of any etiology, untreated thyrotoxicosis or hypothyroidism, renal artery stenosis, contraindication to a vasodilator, unlikely survival for length of study or risk to patient, previous treatment with an AIIRA, sCr $\geq$ 221 umol/L (2.5mg/dl), potassium < 3.5 or > 5.5 mmol/L, potential for noncompliance
Houghton, 1999 U.K. ELITE Trial substudy	Number screened not reported/number eligible not reported/18 enrolled	same exclusion criteria as in ELITE (see above)

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Pitt, 2000 U.S., Canada, Europe, South Africa, South America ELITE II Trial	Yes	Yes (unless length of therapy < 7 days within 3 months prior to randomization)	No (only 22% treated with beta-blockers)	Funded by Merck Research Laboratories (sponsor involved in study design, conduct of the study, statistical analyses, and writing the paper)	No
Pitt, 1997 U.S., Canada, Europe, South Africa, South America ELITE Trial	Yes	Yes	No (only 16% treated with beta-blockers)	Funded by Merck Research Laboratories (sponsor involved in directing and coordinating study, statistical analyses and data coordination, and writing the paper)	No
Houghton, 1999 U.K. ELITE Trial substudy	Yes	Yes	No (none treated with beta-blockers)	Funded by Merck Sharp and Dohme Ltd (role of sponsor not specified)	No

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Cowley, 2000 U.S. ELITE Trial QOL substudy	Method not reported	Yes	Yes	Yes
Willenheimer, 2002 Sweden HEAVEN Study	Method not reported	Method not reported	Yes	Yes
Dunselman, 2001 Europe REPLACE	Method not reported	Method not reported	Yes	Yes
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Method not reported	Method not reported	No	Yes

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Cowley, 2000 U.S. ELITE Trial QOL substudy	Yes	Yes	Yes	Yes/No/No/No
Willenheimer, 2002 Sweden HEAVEN Study	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Dunselman, 2001 Europe REPLACE	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Not reported	Yes	Yes	No/No/Yes/No

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Cowley, 2000 U.S. ELITE Trial QOL substudy	No	No	Yes (QOL data unavailable:10 losartan; 12 captopril)	Fair
Willenheimer, 2002 Sweden HEAVEN Study	No	ITT for primary endpoint; per protocol population	Yes (7 patients; reason not listed)	Fair
Dunselman, 2001 Europe REPLACE	No	No	No	Fair
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Not reported	No	Yes (1 for protocol violation)	Fair

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Cowley, 2000 U.S. ELITE Trial QOL substudy	Number screened not reported/300 eligible/278 enrolled	same exclusion criteria as in ELITE (see above)
Willenheimer, 2002 Sweden HEAVEN Study	Number screened not reported/146 enrolled/141 randomized	Hemodynamically significant primary valvular disease, HF due to pulmonary disease, infective cardiomyopathy, MI or coronary intervention with 3 months, unstable coronary disease, severe arrhythmia, recent stroke, sCr $\geq$ 200 umol/L or other significant laboratory abnormality, AIIRA treatment within previous 3 months, persistent standing SBP < 90 mm Hg, and at investigators discretion
Dunselman, 2001 Europe REPLACE	Number screened not reported/number eligible not reported/378 enrolled	Any life-threatening disease (e.g., cancer, hemodynamically significant pulmonary embolism, AIDS), clinically significant stenotic valvular disease, aortic or mitral regurgitation, or hypertrophic or restrictive cardiomyopathy, history of MI, unstable angina, syncopal episodes, or surgery within previous 6 months, fever, primary renal, hepatic, or metabolic disease, treatment with PDE5 inhibitors, dopamine or beta-agonists, class I antiarrhythmic agents, chronic administration of high doses of NSAIDs or acetaminophen, women of child-bearing potential, treatment with telmisartan or other investigational drug within previous 4 weeks
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Number screened not reported/899 eligible/768 enrolled	Acutely ill, renal impairment, contraindications to study medications

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Cowley, 2000 U.S. ELITE Trial QOL substudy	Yes	Yes	No (based on ELITE)	Funded by Merck Research Laboratories (sponsor includes 4 of first 7 authors on the paper)	No (based on ELITE)
Willenheimer, 2002 Sweden HEAVEN Study	Yes	No	Yes	Funded by a grant from Novartis Pharma (role of sponsor not specified)	Yes
Dunselman, 2001 Europe REPLACE	Yes	No	Yes	Funded by Boehringer-Ingelheim Limited (role of sponsor not specified)	Yes
McKelvie, 1999 U.S., Canada, Europe, South America RESOLVD	Yes	No	No (only 15% treated with beta-blockers during initial 19 weeks of study)	Supported by a grant from Astra (role of sponsor not specified)	No

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Lang, 1997 U.S., Canada	Method not reported	Method not reported	No	Yes
Dickstein, 1995 Scandinavia	Method not reported	Method not reported	Yes	Yes
Little, 2004 U.S.	Method not reported	Method not reported	Not reported	Yes
Kasama, 2003 Japan	Method not reported	Method not reported	Yes	Yes

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Lang, 1997 U.S., Canada	Not reported	Yes, but method not described	Yes, but method not described	No/No/No/No
Dickstein, 1995 Scandinavia	Not reported	Yes	Yes	Yes/No/No/No
Little, 2004 U.S.	Not Reported	Yes	Yes	Yes/No/No/No
Kasama, 2003 Japan	Yes	Not reported	Not reported	No/No/No/No

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Lang, 1997 U.S., Canada	Not reported	No	Unable to determine	Fair
Dickstein, 1995 Scandinavia	Not reported	No	No	Fair
Little, 2004 U.S.	Not reported	No	Yes (1 patient; did not receive study drug)	Fair
Kasama, 2003 Japan	Not reported	Yes	Unable to determine	Fair

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Lang, 1997 U.S., Canada	Number screened not reported/number eligible not reported/116 enrolled	Not reported
Dickstein, 1995 Scandinavia	Number screened not reported/number eligible not reported/166 enrolled	Not reported
Little, 2004 U.S.	Number screened not reported/number eligible not reported/22 enrolled	Current AIIRA or CCB; diseases limiting exercise tolerance
Kasama, 2003 Japan	Number screened not reported/number eligible not reported/32 enrolled	Primary operable valvular heart disease, congenital heart disease, unstable angina, recent AMI, primary hepatic failure, active cancer

Quality table 5. Active controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=9)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Lang, 1997 U.S., Canada	Yes	No	No (only 7% treated with beta-blockers)	Supported by a grant from Merck Research Laboratories (role of sponsor not specified; sponsor included as 3 of primary authors on paper)	No
Dickstein, 1995 Scandinavia	Yes	No	No (only 12% treated with beta-blockers)	Supported by a grant from Merck, Sharp and Dohme Research Laboratories (role of sponsor not specified; sponsor included as 1 of primary authors on paper)	No
Little, 2004 U.S.	Yes	Yes	Yes	None reported Government, private, non-industry	Yes
Kasama, 2003 Japan	No	Not reported	No (patients not treated with beta-blockers)	None reported	No

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	Yes	Yes	Not reported	Yes
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	Yes	Yes	Not reported	Yes
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	Yes	Yes	Not reported	Yes
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	Yes	Yes	Yes	Yes
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Yes	Yes	Yes	Yes
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Yes	Yes	Yes (except greater percent with NYHA class III-IV in placebo vs. valsartan, P<0.05)	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	Yes	Yes	Yes	Yes/No/No/No
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	Yes	Yes	Yes	Yes/No/No/Yes
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	Yes	Yes	Yes	Yes/No/No/Yes
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	Yes	Yes	Yes	Yes/No/No/Yes
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Yes	Yes	Yes	No/No/No/No
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Yes	Yes	Yes	Yes/No/No/No

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	No	Yes	Yes (2 patients without data)	Good
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	No	Yes	No	Good
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	No	Yes	No	Good
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	No	Yes	Yes (2 patients without data - see Overall study)	Good
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Not reported	Yes	No	Good
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Not reported	Yes	Unable to determine	Fair

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	Number screened not reported/7601 eligible/7599 enrolled	Bilateral renal artery stenosis, symptomatic hypotension, MI, stroke, or open-heart surgery in previous 4 weeks, critical aortic or mitral stenosis, non-cardiac disease that may limit 2-year survival, sCr > 265 *u* mol/L, serum potassium > 5.5mmol/L, women of child-bearing potential not on adequate contraception, use of an AIIRA in previous 2 weeks, unwilling to consent
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	Number screened not reported/number eligible not reported/2548 enrolled	Not reported
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	Number screened not reported/number eligible not reported/2028 enrolled	Not reported
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	Number screened not reported/3025 eligible/3023 enrolled	Not reported
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Number screened not reported/number eligible not reported/5010 enrolled	Currently on AIIRA
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Number screened not reported/number eligible not reported/5010 enrolled in Val-HeFT/366 not treated with ACEI in substudy	Not treated with ACEI

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Pfeffer, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Overall Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
McMurray, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Added Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
Granger, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Alternative Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
Yusuf, 2003 U.S., Canada, Australia, Europe, South Africa CHARM-Preserved Trial	No	No	Yes	Supported by AstraZeneca (sponsor managed data, involved in statistical analysis, data interpretation)	Yes
Cohn, 2001 U.S., Australia, Europe, South Africa Val-HeFT Trial	Yes	No	Yes	Supported by a grant from Novartis Pharmaceuticals (sponsor involved in site monitoring, data collection, data analysis)	Yes
Maggioni, 2002 U.S., Australia, Europe, South Africa Val-HeFT subgroup analysis	Yes	No	Yes	Funding provided by Novartis Pharma (role of sponsor in substudy not specified)	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Tonkon, 2000 U.S.	Method not reported	Method not reported	No (open-label ACEI doses inconsistent)	Yes
Riegger, 1999 Europe STRETCH Trial	Yes	Yes	Yes	Yes
Hamroff, 1999 U.S., France	Method not reported	Method not reported	No (higher percent of males in placebo group; mean daily dose captopril higher in losartan group)	Yes
Warner, 1999 U.S.	Method not reported	Method not reported	Not reported	Yes
Granger, 2000 U.S., Canada, Europe	Not reported	Not reported	No NYHA Class II Placebo=47.3% Candesartan=57% NYHA Class III Placebo=49.5% Candesartan=36.3%	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Tonkon, 2000 U.S.	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Riegger, 1999 Europe STRETCH Trial	Not reported	Yes	Yes	Yes/No/No/Yes
Hamroff, 1999 U.S., France	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Warner, 1999 U.S.	Not reported	Yes	Yes	Yes/No/No/No
Granger, 2000 U.S., Canada, Europe	Yes, but method not described	Yes, but method not described	Yes, but method not described	Yes/No/No/No

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Tonkon, 2000 U.S.	Not reported	No	Yes (5 required concomitant medications that were not allowed or patients failed to meet protocol requirements; 6 due to adverse events; 1 voluntarily withdrew)	Poor
Riegger, 1999 Europe STRETCH Trial	No	Yes	Yes (55 total: 29 adverse events; 11 patient's request; 8 exclusion critera; 1 noncompliance; 6 unspecified)	Fair
Hamroff, 1999 U.S., France	No	No	Unable to determine	Fair
Warner, 1999 U.S.	No	No	Yes (1 had increase sCr 1.5 to 2.0mg/dl)	Fair
Granger, 2000 U.S., Canada, Europe	No	Yes	No	Fair

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Tonkon, 2000 U.S.	Number screened not reported/145 enrolled/109 randomized	Concomitant medication or disease causing risk to patient or interfere with study goals
Riegger, 1999 Europe STRETCH Trial	Number screened not reported/926 enrolled/844 randomized	Severe or malignant HTN, symptomatic hypotension, MI within 3 months, hemodynamically relevant arrhythmias, pacemakers or implanted cardioverters, hemodynamically relevant valvular defect or insufficiency, angina, clinically significant disease, autoimmune or wasting disease, psychological illness, drug or alcohol addiction, type 1 DM, uncontrolled DM or requiring insulin, limitation of exercise capacity for reason other than HF, pregnant or lactating wormen, patients unwilling to comply with study protocol or in another clinical trial within 1 month, treatment with concomitant beta-blockers, antihypertensives, other agents causing systemic vasodilation or vasoconstriction, NSAIDs, antiarrhythmics, immunosuppressive or cytotoxic agents, insulin, or any drug altering GI absorption
Hamroff, 1999 U.S., France	Number screened not reported/number eligible not reported/33 enrolled	Not reported
Warner, 1999 U.S.	Number screened not reported/number eligible not reported/21 enrolled	MI on stress echocardiogram, valvular heart disease, other disease that could limit exercise tolerance, previous AIIRA use
Granger, 2000 U.S., Canada, Europe	Number screened not reported/288 eligible/270 enrolled	ACE inhibitor use; creatinine level of 220 umol/L or more; potassium level more than 5.5 mmol/L; history of serious hyperkalemia induced by use of an ACE inhibitor; use of potassium-sparing diuretics; known renal arterial stenosis; renal transplantation; use of angiotensin receptor blocker or any investigational drug within 30 days; pregnancy; poor compliance; uncontrolled hypertension; unstable angina; acute myocardial infarction; percutaneous coronary angioplasty or coronary artery bypass operation within 30 days; stroke or transient ischemic attack within 3 months; obstructive valvular heart disease; constrictive pericarditis; or any noncardiac illness that limited expected survival to less than 2 years

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Tonkon, 2000 U.S.	Yes	No	No (beta-blockers withdrawn)	Funding source not listed (2 primary authors, one of which is the corresponding author, from Bristol-Myers Squibb Pharmaceutical Research Institute)	No
Riegger, 1999 Europe STRETCH Trial	Yes	Not reported	No (beta-blockers not allowed)	Funding source not listed (2 primary authors from Takeda Europe R&D)	No
Hamroff, 1999 U.S., France	Yes	Not reported	No (only 6% on beta-blockers)	No funding source listed	No
Warner, 1999 U.S.	Yes	Yes	Yes	Supported in part by a research grant from NIH and Merck Research Laboratories	Yes
Granger, 2000 U.S., Canada, Europe	Yes	No	Yes	Supported by a grant from Astra Hassle (included as authors of paper)	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials	Yes	Yes	Not reported	Yes
O'Meara, 2005 North America CHARM-QOL	Yes	Yes	Not reported	Yes
O'Meara, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-NYHA class	Yes	Yes	Not reported	Yes
Blanchet, 2005 Canada	Method not reported	Method not reported	Yes	Yes
Matsumori, 2003 Japan	Method not reported	Method not reported	Yes	Yes
Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis)	Yes	Yes	No Elderly significantly > diuretic use, NYHA III-IV, white; significantly less ACEI, BB use, less % male	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials	Yes	Yes	Yes	Yes/No/No/Yes
O'Meara, 2005 North America CHARM-QOL	Yes	Yes	Yes	Yes/No/No/No
O'Meara, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-NYHA class	Yes	Yes	Yes	Yes/No/No/Yes
Blanchet, 2005 Canada	Yes, but method not described	Yes	Yes	Yes/No/No/No
Matsumori, 2003 Japan	Yes	Yes	Yes	Yes/No/Yes/No
Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis)	Yes	Yes	Yes	No/No/No/No

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials	No	Yes	No	Good
O'Meara, 2005 North America CHARM-QOL	Not reported	Yes	No	Fair
O'Meara, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-NYHA class	Not reported	Yes	No	Good
Blanchet, 2005 Canada	Not reported	No	Yes (1 refractory HF leading to cardiac transplantation)	Fair
Matsumori, 2003 Japan	Not reported	Yes	Yes (7 candesartan; 6 placebo: violation good clinical practice, asymptomatic HF, medication not administered, unstable angina)	Fair
Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis)	Not reported	Yes	No	Good

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials	Number screened not reported/number eligible not reported/4576 enrolled	Not reported
O'Meara, 2005 North America CHARM-QOL	Number screened not reported/number eligible not reported/2498 enrolled	Not reported
O'Meara, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-NYHA class	Number screened not reported/number eligible not reported/7599 enrolled	Not reported
Blanchet, 2005 Canada	Number screened not reported/number eligible not reported/34 enrolled	Unable to provide informed consent or perform exercise test limited by dyspnea
Matsumori, 2003 Japan	Number screened not reported/number eligible not reported/313 enrolled	Unstable angina, life-threatening ventricular arrhythmias, severe valvular stenosis, hypertrophic obstructive cardiomyopathy, advanced respiratory disease, MI within 1 month of enrollment, cardiogenic shock or severe hypotension, symptomatic cerebrovascular disease within 3 months, sCr > 2.0 mg/dl, hyperkalemia, advanced hepatic dysfunction or history drug allergy or hypersensitivity, pregnant or nursing women or those of child-bearing potential, treatment with another investigational drug, or considered inelligble by investigators
Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis)	Number screened not reported/number eligible not reported/5010 enrolled	Currently on AIIRA

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Young, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-Low LVEF Trials	No	No	Yes	Supported by AstraZeneca (representatives involved in protocol design, data analysis, data interpretation, and manuscript preparation)	Yes
O'Meara, 2005 North America CHARM-QOL	No	No	Yes	Not reported; authors include manufacturer representatives	Yes
O'Meara, 2004 U.S., Canada, Australia, Europe, South Africa CHARM-NYHA class	No	No	Yes	Not reported; authors include manufacturer representatives	Yes
Blanchet, 2005 Canada	Yes	Not reported	Yes	None reported	Yes
Matsumori, 2003 Japan	Yes	Not reported	Yes (note low BB use: 18.9% candesartan and 21.5% placebo)	Coordinated by, and supported by a grant from, Takeda Chemical Industries, Ltd.	Yes
Baruch, 2004 U.S., Australia, Europe, South Africa Val-HeFT Trial (Elderly subanalysis)	Yes	No	Yes	Funded by Novartis Pharma AG	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	Internal Validity			
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**
Carson, 2003 U.S., Australia, Europe, South Africa Val-HeFT Trial (Hospitalization subanalysis)	Yes	Yes	Yes	Yes

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Carson, 2003 U.S., Australia, Europe, South Africa Val-HeFT Trial (Hospitalization subanalysis)	Yes	Yes	Yes	No/No/No/No

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Carson, 2003 U.S., Australia, Europe, South Africa Val-HeFT Trial (Hospitalization subanalysis)	Not reported	Yes	No	Good

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

	External Validity	
Author, Year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**
Carson, 2003 U.S., Australia, Europe, South Africa Val-HeFT Trial (Hospitalization subanalysis)	Number screened not reported/number eligible not reported/5010 enrolled	Currently on AIIRA

Quality table 6. Placebo-controlled trials of angiotensin II receptor antagonists in patients with heart failure (N=11)

Author, Year Country		Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Carson, 2003 U.S., Australia, Europe, South Africa Val-HeFT Trial (Hospitalization subanalysis)	Yes		No	Yes	Funded by Novartis Pharma AG	Yes

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Internal Validity: Randomization adequate?	Internal Validity: Allocation concealment adequate?	Internal Validity: Groups similar at baseline?	Internal Validity: Eligibility criteria specified?
Nakao, 2003 Japan COOPERATE	Yes	Yes	Yes	Yes
Lacourciere, 2000 Canada	Not reported	Not reported	No SIDBP Losartan 97.2 mm Hg Enalapril 95.3 mm Hg (P=0.025) Mean diabetes duration (years) Losartan 9.2 Enalapril 12.6 (P=0.039)	Yes
Luno, 2002 Spain	Yes	Not reported	Yes	Yes
Muirhead, 1999 Canada	Not reported	Not reported	Yes	Yes

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

		Internal Validity		
Author, Year Country	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination?**
Nakao, 2003 Japan COOPERATE	Yes	Yes	Yes	Yes/No/No/No
Lacourciere, 2000 Canada	Yes, but method not described	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Luno, 2002 Spain	Open	Open	Open	Yes/No/No/No
Muirhead, 1999 Canada	Yes	Yes	Yes	Yes/No/No/No

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Nakao, 2003 Japan COOPERATE	No	Yes	No	Good
Lacourciere, 2000 Canada	No	No	No	Poor
Luno, 2002 Spain	No	Yes	No	Fair
Muirhead, 1999 Canada	No	No	No	Fair

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	External Validity Number screened/eligible/enrolled	External Validity Exclusion criteria
Nakao, 2003 Japan COOPERATE	336 screened/306 eligible/263 enrolled	Need for immediate renal replacement therapy; resistant edema; treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; proteinuria > 10g/d and hypoalbuminemia < 28g/L; renovascular HTN; malignant HTN; MI, or stroke in previous year; severe PVD; severe CHF (NYHA class III-IV); chronic hepatic disease; connective tissue disease; obstructive uropathy; cancer; COPD; drug or alcohol misuse; pregnancy; breastfeeding
Lacourciere, 2000 Canada	Number screened not reported/number eligible not reported/103 enrolled	Evidence or suspicion of renovascular disease; history of malignant HTN; SBP > 210 mm Hg; CVA in the previous 12 months or current transient ischemic attacks; MI within the previous 12 months; clinically significant arteriovenous (AV) conduction disturbances and/or arrhythmias; unstable angina; history of HF; sCr ≥ 200 mmol/L; serum potassium ≥ 5.5 mmol/L or ≤ 3.5 mmol/L; treatment with oral corticosteroids; concomitant use of agents that may affect BP except beta blockers and nitrates used in the treatment of stable angina; drug or alcohol abuse; pregnancy; breast feeding; ineffective contraception
Luno, 2002 Spain	Number screened not reported/number eligible not reported/46 enrolled	Nephrotic patients with serum albumin <3.0 g/dL as well as those with hypertension stage 3 (SBP≥180 mm Hg and/or DBP ≥110 mm Hg), hyperkalemia (>5.0 mmol/L), secondary glomerular diseases, systemic diseases (diabetes mellitus, amyloidosis, systemic lupus erythematosus), or those with any severe cardiovascular even in the last 3 months before randomization; severe cardiac, pulmonary or hepatic disease, HIV infection and neoplasia; corticosteroid and/or immunosuppressive therapy use within six months
Muirhead, 1999 Canada	Number screened not reported/number eligible not reported/122 enrolled	Ineffective birth conrol method; ACEI, CCB use within 28 days prior to randomization; "brittle" diabetes; history of noncompliance with medical regimens

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Nakao, 2003 Japan COOPERATE	Yes	No	Yes
Lacourciere, 2000 Canada	Yes	No	Yes
Luno, 2002 Spain	Yes	No	Yes
Muirhead, 1999 Canada	Yes	No	Yes

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Funding	Relevance?
Nakao, 2003 Japan COOPERATE	Partly funded by a grant from the Progressive Renal Disease Research Projects from the Ministry of Health, Labor, and Welfare in Japan. No other funding source noted	Yes
Lacourciere, 2000 Canada	Supported by a grant from Merck	Yes
Luno, 2002 Spain	Supported by a grant from Astra Zeneca	Yes
Muirhead, 1999 Canada	Supported by a research grant from Novartis	Yes

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Internal Validity: Randomization adequate?	Internal Validity: Allocation concealment adequate?	Internal Validity: Groups similar at baseline?	Eligibility criteria specified?
Andersen, 2000 Denmark	Method not reported	Method not reported	Cross-over trial	Yes
Campbell, 2003 Italy	Method not reported	Not reported	Cross-over trial	Yes
Barnett, 2004 Scandinavia, U.K., Netherlands	Yes	Yes	Yes	Yes

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

		Internal Validity		
Author, Year Country	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination?**
Andersen, 2000 Denmark	Not reported	Yes, but method not described	Yes, but method not described	Yes/No/No/No
Campbell, 2003 Italy	Open	Open	Open	Yes/No/No/No
Barnett, 2004 Scandinavia, U.K., Netherlands	Yes	Yes	Yes	Yes/No/No/No

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Andersen, 2000 Denmark	No	Yes	Unable to determine	Fair
Campbell, 2003 Italy	No	Yes	No	Fair
Barnett, 2004 Scandinavia, U.K., Netherlands	Yes	No	Unable to determine	Fair

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	External Validity Number screened/eligible/enrolled	External Validity Exclusion criteria
Andersen, 2000 Denmark	Number screened not reported/number eligible not reported/16 enrolled	History of malignant HTN, CHF, MI, or stroke within previous 3 months
Campbell, 2003 Italy	Number screened not reported/number eligible not reported/24 enrolled	Contraindication to withdrawal or treatment with ACEIs or AIIRAs; treatment with steroids, NSAIDs, immunomodulators, cytostatic agents within past 6 months; renovascular disease; obstructive uropathy; unstable angina; AMI or CVA within past 6 months; NYHA class II-IV HF; serum potassium > 6 mEq/L, despite control of metabolic acidosis; clinically significant hepatic disease (SGOT or SGPT > 3 times upper limit normal or bilirubin > 1.5 mg/dL); white blood cell count < 3000/mm3; clinical suspicion of renal vein thrombosis; known hypersensitivity to ACEIs or AIIRAs; cancer; collagen vascular disease; treatment with other investigational drugs; pregnancy, breast feeding, or ineffective contraception
Barnett, 2004 Scandinavia, U.K., Netherlands	Number screened not reported/number eligible not reported/250 enrolled	Condition (other than CV disease) restricting long-term survival; known allergy to study drugs or iohexol

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Andersen, 2000 Denmark	Yes	No	Yes
Campbell, 2003 Italy	Yes	No	Yes
Barnett, 2004 Scandinavia, U.K., Netherlands	Yes	Not reported	Yes

Quality table 7. Active controlled trials of angiotensin II receptor antagonists in patients with nephropathy (N=5)

Author, Year Country	Funding		Relevance?
Andersen, 2000 Denmark	Supported by a medical school grant from Merck, Sharp & Dohme	Yes	
Campbell, 2003 Italy	Co-author from Novartis Farma. No funding source noted	Yes	
Barnett, 2004 Scandinavia, U.K., Netherlands	Supported by Boehringer Ingelheim (data handling and trial management suuported by manufacturer)	Yes	

Quality table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Internal Validity: Randomization adequate?	Internal Validity: Allocation concealment adequate?	Groups similar at baseline?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Method not reported	Yes	Yes except for a lower percent of female patients in the placebo group (29% vs. 35% on irbesartan and 31% on amlodipine; P=0.02) Also lower percent of non-Hispanic black patients on irbesartan (11% vs. 15% on amlodipine, 14% on placebo)
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Method not reported	Method not reported	Yes
Plum, 1998 Country not reported	Not reported	Not reported	Yes
Chan, 2004 Asian substudy RENAAL	Method not reported	Method not reported	Yes
Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, (Israel) IDNT CV substudy	Method not reported	Yes	Yes except for differences stated below in IDNT (Lewis, 2001)

Quality table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Yes	Yes	Yes	Yes
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Yes	Yes	Yes	Yes
Plum, 1998 Country not reported	Yes	Yes, but method not described	Yes, but method not described	Yes, but method not described
Chan, 2004 Asian substudy RENAAL	Yes	Yes	Yes	Yes
Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, (Israel) IDNT CV substudy	Yes	Yes	Yes	Yes

Quality table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Yes/No/No/No	No	Yes	Unable to determine
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Yes/No/No/No	No	Yes	Unable to determine
Plum, 1998 Country not reported	Yes/No/No/No	No	Yes	No
Chan, 2004 Asian substudy RENAAL	Yes/No/Yes/No	No	Yes	Unable to determine
Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, (Israel) IDNT CV substudy	Yes/No/No/No	No	Yes	Unable to determine

Quality table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

		External Validity	
Author, Year Country	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Good	Number screened not reported/number eligible not reported/1715 enrolled	Onset of type 2 DM < 20yrs of age, type 1 DM, treatment requiring ACEI, AIIRA, or CCB, CVD (including unstable angina, MI, CABG or PTCA within previous 3 months, NYHA class III or IV HF, TIA within previous 6 months, stroke within previous 3 months), abnormal serum potassium
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Good	Number screened not reported/number eligible not reported/1513 enrolled	Type 1 DM or nondiabetic renal disease (including renal artery stenosis), MI or CABG within previous month, stroke or PTCA within previous 6 months, TIA within previous year, history HF
Plum, 1998 Country not reported	Fair	Number screened not reported/number eligible not reported/9 enrolled	Increase of serum creatinine over 30% within 6 months before the trial; history of heart failure, malignancy, or any disorders requiring immunosuppressive therapy
Chan, 2004 Asian substudy RENAAL	Good	Number screened not reported/number eligible not reported/1513 enrolled (252 Asian ethnicity; 220 Asia, 32 other geographic region)	Refer to RENAAL (Brenner, 2001) below
Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, (Israel) IDNT CV substudy	Good	Number screened not reported/number eligible not reported/1715 enrolled	Refer to IDNT (Lewis, 2001) below

Quality table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Yes	No	Yes
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Yes	No	Yes
Plum, 1998 Country not reported	3-month run-in period	No	Yes
Chan, 2004 Asian substudy RENAAL	Yes	No	Yes
Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, (Israel) IDNT CV substudy	Yes	No	Yes

Quality table 8. Placebo controlled trials of angiotensin II receptor antagonists in patients with nephropathy

Author, Year Country	Funding		Relevance?
Lewis, 2001 U.S., Canada, Central and South America, Asia, Australia, Europe IDNT	Supported by the Bristol-Myers Squibb Institute for Medical Research and Sanofi Synthelabo (biostatistics and data management department of sponsor was responsible for handling the data including data entry, data base review, and audit)		Yes
Brenner, 2001 U.S., Canada, Central and South America, Asia, Europe RENAAL	Supported by Merck and company (one employee of sponsor was a non-voting member of both the steering and safety committees; the steering committee supervised the study design, conduct of the trial, and management and analysis of the data and a subcommittee of which prepared the report)		Yes
Plum, 1998 Country not reported	Supported by Novartis		Yes
Chan, 2004 Asian substudy RENAAL	Supported by Merck	Yes	
Berl, 2003 U.S., Canada, Central and South America, Asia, Australia, Europe, (Israel) IDNT CV substudy	Supported by the Bristol-Myers Squibb Institute for Medical Research and Sanofi Synthelabo (sponsor involved in data collection)	Yes	

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Benz et al 1997	Method not reported	Not reported	93% of valsartan and 100% of lisinopril and HCTZ groups had significant medical history and/or concomitant diagnoses; otherwise similar.	Yes
Chan et al 1997 Taiwan and Hong Kong	Method not reported	Not reported	Yes	Yes
Elliot 1999 US	Method not reported	Not reported	Yes	Yes
Fogari et al 2001 Italy	Method not reported	Not reported	Yes	Yes
Fogari et al 2002 Italy	Method not reported	Not reported	Not reported	Yes

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Benz et al 1997	Yes	Not reported	Yes	Yes/No/No/No
Chan et al 1997 Taiwan and Hong Kong	Yes	Not reported	Yes	No
Elliot 1999 US	Yes	Not reported	Yes	No
Fogari et al 2001 Italy	Yes	Not reported	Yes	Yes/No/No/No
Fogari et al 2002 Italy	Yes	Not reported	Yes	No

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Benz et al 1997	No	1/129 not analyzed	No	Fair
Chan et al 1997 Taiwan and Hong Kong	Not reported	Unable to assess- number analyzed not reported	Not reported	Poor
Elliot 1999 US	Not reported	Unable to assess- number analyzed not reported	Not reported	Poor
Fogari et al 2001 Italy	No	No	No	Fair
Fogari et al 2002 Italy	Not reported	Unable to assess- number analyzed not reported	Not reported	Poor

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Number screened/eligible/enrolled	Exclusion criteria
Benz et al 1997	197 screened/141 eligible/129 enrolled	Clinical heart failure, second or third degree heart block, angina, significant dysrhythmias, valvular heart disease, evidence of hepatic or renal impairment, insulin-dependent diabetes mellitus, pregnancy, history in past 6 months of MI, hypertensive encephalopathy, or cerebrovascular accident, any respiratory condition associated witha cough, and history of smoking within past 2 years.
Chan et al 1997 Taiwan and Hong Kong	Number screened/eligible not reported/84 enrolled	Known intolerance to trial drugs, diabetes, clinically significant laboratory abnormalities, and use of aspirin, NSAIDs, or antitussive agents.
Elliot 1999 US	Not reported	Secondary forms of hypertension, advanced hypertensive retinopathy, average sitting systolic blood pressure >200 mmHg, advanced atrioventricular conduction defects, ventricular tachyarrhythmias requiring therapy, bradycardia, prior myocardial infarction or cerebrovascular accident within past 90 days, congestive heartfailure being treated with nitrates, beta-blockers or calcium channel blockers, unstable diabetes mellitus, or presence of clinically significant renal or hepatic disease or another concurrent severe disease, conditions which could interfere with the assessment of cough: emphysema, asthma or chronic bronchitis, or upper respiratory infectino within 2 weeks of screening; use of anticoagulants or another investigational drug within 30 days of enrollment, chronic sympathomimetic amine or NSAIDs (other than low-dose aspirin) within 7 days of enrollment, and concomitant use of antidepressants or medications known to affect blood pressure or cough.
Fogari et al 2001 Italy	Number screened, eligible not reported/160 enrolled	Diabetes mellitus, obesity, smoking habits, major cardiovascular and noncardiovascular diseases, or conditions requiring any other concomitant medication.
Fogari et al 2002 Italy	Number screened, eligible not reported/110 enrolled	Diabetes mellitus, obesity, smoking habits, major cardiovascular and noncardiovascular diseases, or conditions requiring any other concomitant medication.

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Benz et al 1997	2-4 weeks placebo washout, then 2-4 weeks lisinopril run-in, then 2 more weeks placebo washout.	No	Yes	Not reported	All had hisory of ACE-inhibitor associated cough.
Chan et al 1997 Taiwan and Hong Kong	Up to 8 weeks lisinopril run-in, 4 weeks placebo washout.	No	Yes	Not reported	All had hisory of ACE-inhibitor associated cough.
Elliot 1999 US	3-5 weeks placebo run-in	No	Yes	Supported by grants and contracts from SmithKline Beecham Pharmaceuticals Inc.	Releva nt
Fogari et al 2001 Italy	4 weeks placebo run-in	Yes- all newly-diagnosed, previously untreated hypertension	Yes	Not reported	Men with newly-diagnosed hypertension, excluded if experienced erectile dysfunction
Fogari et al 2002 Italy	4 weeks placebo run-in	Yes- all newly-diagnosed, previously untreated hypertension	Yes	Not reported	Men with newly-diagnosed hypertension, excluded if experienced erectile dysfunction

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Method not reported	Not reported	More white patients in lisinopril group (98%) than losartan (81%), p<0.05; otherwise similar.	Yes
Lacourciere 1999 Canada	Method not reported	Not reported	Yes	Yes
Paster et al 1998 US	Method not reported	Not reported	Yes	Yes

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Yes	Not reported	Yes	No
Lacourciere 1999 Canada	Yes	Not reported	Yes	Yes/No/No/No (1 protocol violation, but type not specified)
Paster et al 1998 US	Yes	Not reported	Yes	Yes/No/No/No (1 protocol violation, but type not specified)

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Loss to follow-up: differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Quality Rating
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Not reported	Yes	No	Fair
Lacourciere 1999 Canada	No	No, 88/92 (96%) analyzed	Yes- 4/92: 3 due to adverse events and 1 due to protocol violations.	Fair
Paster et al 1998 US	No	No, 97/100 (97%) analyzed	Yes, but 97/100 analyzed	Fair

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Number screened/eligible/enrolled	Exclusion criteria
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Number screened, eligible not reported/135 enrolled	Clinically significant laboratory abnormalities, concomitant medications that could alter blood pressure, diabetes mellitus, pregnant or lactating women.
Lacourciere 1999 Canada	216 screened/135 eligible/92 enrolled	Women of childbearing capacity who were not using an effective method of contraception, known or suspected secondary hypertension, clinically significant pulmonary conditions, upper respiratory infections or allergic rhinitis associated with cough, smokers or those who had quit within one year of this study, cardiovascular, metabolic, hepatic, or renal dysfunction.
Paster et al 1998 US	Number screened, eligible not reported/100 enrolled	Other concurrent diseases or medical conditions or taking a medication that could pose a risk to the patient if he or she participated in the study, preclude study completion, or confound interpretation of the study results; clinically significant cardiovascular disease other than uncomplicated essential hypertension, pulmonary disease, clinically significant laboatory abnormalities, and known sensitivity to ACE inhibitors; current smokers or smokers within the preceding year, using concurrent medications that could alter blood pressure, or pregnant or lactating.

Quality Table 9. Quality assessment of randomized controlled trials of adverse events with angiotensin II receptor antagonists

Author Year Country	Run-in/Washout	Class naïve patients only?	Control group standard of care?	Funding	Relevance?
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	6 weeks lisinopril run-in, at least 2 weeks placebo washout	No	Yes	Supported in part by a grant from Merck Research Laboratories	All had hisory of ACE-inhibitor associated cough.
Lacourciere 1999 Canada	6 weeks lisinopril run-in, 4 weeks placebo washout	No	Yes	Not reported	All had hisory of ACE-inhibitor associated cough.
Paster et al 1998 US	Up to 6 weeks lisinopril run-in, 4 weeks placebo washout.	No	Yes	Funding not specified; 6 of 7 authors, including corresponding author, from Merck Research Laboratories	All had hisory of ACE-inhibitor associated cough.

Quality table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?
Biswas et al 2002 England	Yes	NA- not prospective	Yes	Yes
Benz et al 1997	Yes	Yes	Yes	Yes
Chan et al 1997 Taiwan and Hong Kong	Yes	Not reported	Yes	Yes
Elliot 1999 US	Yes	Not reported	Yes	Yes
Fogari et al 2001 Italy	Yes	Yes	Yes	Yes
Fogari et al 2002 Italy	Yes	Not reported	Yes	Yes
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Yes	Not reported	Yes	Yes
Lacourciere 1999 Canada	Yes	Yes	Yes	Yes

Quality table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Biswas et al 2002 England	No- only patients whose doctor returned a form were assessed; low response rate (55%)	No	Yes for some events- covered events taking place 6 months or less after initiation of treatment.	Fair
Benz et al 1997	Yes	No	Yes for cough	Fair
Chan et al 1997 Taiwan and Hong Kong	Yes	No	Yes for cough	Fair
Elliot 1999 US	Yes	Adjusted for center, regimen, and center by regimen interaction	Yes for cough	Fair
Fogari et al 2001 Italy	Yes	No	Yes for decrease in sexual activity	Fair
Fogari et al 2002 Italy	Yes	No	Yes for decrease in sexual activity	Fair
Lacourciere et al 1994 11 countries (Canada, US, and Western Europe)	Yes	No	Yes for cough	Fair
Lacourciere 1999 Canada	Yes	Subgroup analyses by sex, age, and race.	Yes for cough	Fair

Quality table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?
Paster et al 1998 US	Yes	Yes	Yes	Yes
Zanabli et al 2004 U.S.	Not clear	Yes	Yes	Yes
Puchler et al 2001 U.S. and Europe	Not clear	Not reported	Yes	Yes

Quality table 10. Quality assessment of adverse events trials with angiotensin II receptor antagonists

Author, year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Paster et al 1998 US	Yes	No	Yes for cough	Fair
Zanabli et al 2004 U.S.	No	No	Yes	Fair
Puchler et al 2001 U.S. and Europe	Yes	No	Yes	Fair