APPENDIXES

Appendix A: Exact Search Strings

MEDLINE® **Search 1:** Used to identify studies of (a) ACEIs vs. ARBs and (b) ARBs vs. other (non-ACEI) comparators. ACEIs vs. ARBs portion of strategy also used to search the Cochrane Central Register of Controlled Trials.

Database: Ovid MEDLINE® <1966 to May Week 3 2006>
Search Strategy:
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1   (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (7801)
2   losartan/ (3821)
3   angiotensin II type 1 receptor blockers/ (1417)
4   (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (89)
5   or/1-4 (8186)
6   (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril).mp. (20419)
7   angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ (29181)
8   6 or 7 (31620)
9   5 and 8 (2561)
10   limit 9 to yr="1989 - 2006" (2561)
11   limit 10 to humans (1570)
12   limit 11 to english language (1302)
13   exp hypertension/dt (43028)
14   12 and 13 (501)
15   randomized controlled trial.pt. (225487)
16   controlled clinical trial.pt. (73200)
17   Randomized Controlled Trials/ (45397)
18   Random Allocation/ (57318)
19   Double-Blind Method/ (88071)
20   Single-Blind Method/ (10138)
21   or/15-20 (382640)
22   Animal/ not Human/ (3011569)
23   21 not 22 (360978)
24   clinical trial.pt. (447512)
25   exp Clinical Trials/ (188054)
26   (clinic$ adj25 trial$).tw. (122637)
27   ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (84242)
28   Placebos/ (25150)
29   placebo$.tw. (97000)
30   random$.tw. (351176)
31   Research Design/ (44423)
32   (latin adj square).tw. (2271)

33   or/24-32 (817761)
34   33 not 22 (760307)
35   34 not 23 (412905)
36   Comparative Study/ (1296809)
37   exp Evaluation Studies/ (574715)
38   Follow-Up Studies/ (327165)
39   Prospective Studies/ (209742)
40   (control$ or prospectiv$ or volunteer$).tw. (1678468)
41   Cross-Over Studies/ (18169)
42   or/36-41 (3339392)
43   42 not 22 (2575440)
44   43 not (23 or 35) (2038591)
45   23 or 35 or 44 (2812474)
46   14 and 45 (421)
47   limit 46 to abstracts (383)
48   46 not 47 (38)
49   5 and 13 and 23 (812)
50   5 and 13 and 15 (577)
51   limit 50 to humans (576)
52   limit 51 to english language (547)
53   limit 52 to abstracts (526)
54   53 not 47 (355)
55   47 or 54 (738)
56   from 55 keep 1-738 (738)

MEDLINE[®] **Search 2:** Used to identify studies of ACEIs vs. atenolol or amlodipine.

Database: Ovid MEDLINE[®] <1966 to June Week 2 2006>
Search Strategy:
----
1   (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (7907)
2   losartan/ (3866)
3   angiotensin II type 1 receptor blockers/ (1495)
4   (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (89)
5   or/1-4 (8317)
6   (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril).mp. (20515)
7   angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ (29405)
8   6 or 7 (31862)
9   5 and 8 (2616)
10   limit 9 to yr="1989 - 2006" (2616)
11   limit 10 to humans (1616)

12   limit 11 to english language (1344)
13   exp hypertension/dt (43234)
14   12 and 13 (513)
15   randomized controlled trial.pt. (227233)
16   controlled clinical trial.pt. (73582)
17   Randomized Controlled Trials/ (46059)
18   Random Allocation/ (57572)
19   Double-Blind Method/ (88623)
20   Single-Blind Method/ (10243)
21   or/15-20 (385737)
22   Animal/ not Human/ (3039204)
23   21 not 22 (363780)
24   clinical trial.pt. (449329)
25   exp Clinical Trials/ (189510)
26   (clinic$ adj25 trial$).tw. (124237)
27   ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (84782)
28   Placebos/ (25242)
29   placebo$.tw. (97782)
30   random$.tw. (355789)
31   Research Design/ (44740)
32   (latin adj square).tw. (2283)
33   or/24-32 (825939)
34   33 not 22 (767683)
35   34 not 23 (417884)
36   Comparative Study/ (1313583)
37   exp Evaluation Studies/ (581443)
38   Follow-Up Studies/ (330247)
39   Prospective Studies/ (211855)
40   (control$ or prospectiv$ or volunteer$).tw. (1701806)
41   Cross-Over Studies/ (18356)
42   or/36-41 (3382854)
43   42 not 22 (2610193)
44   43 not (23 or 35) (2068318)
45   23 or 35 or 44 (2849982)
46   14 and 45 (430)
47   limit 46 to abstracts (392)
48   46 not 47 (38)
49   5 and 13 and 23 (826)
50   5 and 13 and 15 (589)
51   limit 50 to humans (588)
52   limit 51 to english language (559)
53   limit 52 to abstracts (538)
54   53 not 47 (363)
55   47 or 54 (755)
56   8 and 13 and 45 (5143)

57   amlodipine.mp. or Amlodipine/ (2102)
58   atenolol.mp. or Atenolol/ (5762)
59   57 or 58 (7736)
60   8 and 59 (1120)
61   60 and 13 (767)
62   61 and 45 (678)
63   61 and 23 (501)
64   61 and 15 (388)
65   limit 64 to humans (388)
66   limit 65 to english language (369)
67   limit 66 to abstracts (354)
68   from 67 keep 1-354 (354)

MEDLINE[®] **Search 3:** Used to identify studies of ACEIs vs. placebo published after the June 2005 Drug Class Review on Angiotensin Converting Enzyme Inhibitors.[*]

Database: Ovid MEDLINE[®] <1966 to June Week 4 2006>
Search Strategy:
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1   (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (7931)
2   losartan/ (3878)
3   angiotensin II type 1 receptor blockers/ (1523)
4   (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (90)
5   or/1-4 (8352)
6   (quinapril or perindopril or ramipril or captopril or enalapril or benazepril or trandolapril or fosinopril or moexipril or enalaprilat or cilazapril).mp. (20553)
7   angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ (29480)
8   6 or 7 (31944)
9   5 and 8 (2631)
10   limit 9 to yr="1989 - 2006" (2631)
11   limit 10 to humans (1629)
12   limit 11 to english language (1356)
13   exp hypertension/dt (43305)
14   12 and 13 (516)
15   randomized controlled trial.pt. (227810)
16   controlled clinical trial.pt. (73653)
17   Randomized Controlled Trials/ (46324)
18   Random Allocation/ (57680)
19   Double-Blind Method/ (88793)

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[*] Chou R, Helfand M, Carson S. Drug Class Review on Angiotensin Converting Enzyme Inhibitors. Final Report. June 2005. Available at: www.ohsu.edu/drugeffectiveness/reports/final.cfm. Accessed 17 August 2006.

20   Single-Blind Method/ (10281)
21   or/15-20 (386780)
22   Animal/ not Human/ (3043394)
23   21 not 22 (364697)
24   clinical trial.pt. (449647)
25   exp Clinical Trials/ (190053)
26   (clinic$ adj25 trial$).tw. (124749)
27   ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (84961)
28   Placebos/ (25278)
29   placebo$.tw. (98008)
30   random$.tw. (356966)
31   Research Design/ (44861)
32   (latin adj square).tw. (2289)
33   or/24-32 (828165)
34   33 not 22 (769721)
35   34 not 23 (419156)
36   Comparative Study/ (1316751)
37   exp Evaluation Studies/ (582995)
38   Follow-Up Studies/ (331073)
39   Prospective Studies/ (212521)
40   (control$ or prospectiv$ or volunteer$).tw. (1706292)
41   Cross-Over Studies/ (18430)
42   or/36-41 (3391311)
43   42 not 22 (2617037)
44   43 not (23 or 35) (2073600)
45   23 or 35 or 44 (2857453)
46   14 and 45 (432)
47   limit 46 to abstracts (393)
48   46 not 47 (39)
49   5 and 13 and 23 (829)
50   5 and 13 and 15 (590)
51   limit 50 to humans (589)
52   limit 51 to english language (560)
53   limit 52 to abstracts (539)
54   53 not 47 (364)
55   47 or 54 (757)
56   8 and 13 and 45 (5155)
57   amlodipine.mp. or Amlodipine/ (2108)
58   atenolol.mp. or Atenolol/ (5772)
59   57 or 58 (7752)
60   8 and 59 (1123)
61   60 and 13 (768)
62   61 and 45 (679)
63   61 and 23 (502)
64   61 and 15 (389)

65   limit 64 to humans (389)
66   limit 65 to english language (370)
67   limit 66 to abstracts (355)
68   from 67 keep 1-354 (354)
69   56 and (28 or 29) (1286)
70   limit 69 to humans (1286)
71   limit 70 to english language (1154)
72   limit 71 to abstracts (1150)
73   (2005$ or 2006$).ed. (974282)
74   72 and 73 (52)
75   from 74 keep 1-52 (52)

Appendix B: Methods for Reviewing Indirect Comparison Studies

Introduction

Our review of the literature on the comparative long-term benefits and harms of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin II receptor antagonists (ARBs) for treating hypertension focused, in the first instance, on direct head-to-head comparisons of drugs in the two classes. Because we were uncertain that these direct comparisons would adequately address all aspects of the key questions, we also sought to identify and screen potentially relevant indirect comparison studies – that is, studies in which ACEIs and ARBs were compared, in distinct trials, with a common comparator. This Appendix describes the methods we used to identify and review indirect comparison studies.

Search and Abstract Screening

We began by searching MEDLINE® for studies of ARBs versus other (non-ACEI) comparators, including placebo (see MEDLINE® Search 1 in Appendix A). We screened these abstracts along with the head-to-head trials (see the abstract screening criteria in Appendix C). Note that, for indirect comparisons, we considered only randomized controlled trials (RCTs). We coded each included abstract for treatment duration/length of followup ("12 weeks", "1 year", etc.).

Because a primary objective for evaluating non-head-to-head studies was to expand the pool of evidence regarding long-term results, we restricted the pool of abstracts for further evaluation to those with a treatment duration/length of followup of ≥ 24 weeks. Further, since the credibility of any meta-analysis – particularly for non-head-to-head trials – depends on consistency among studies, we considered only comparators for which there were ≥ 3 trials. The comparators thus identified were atenolol, amlodipine, and placebo.

Next, we searched MEDLINE® for studies of ACEIs versus atenolol or amlodipine (see MEDLINE® Search 2 in Appendix A). To identify potentially relevant ACEI-versus-placebo trials, we began by searching the references of the June 2005 Drug Class Review on Angiotensin Converting Enzyme Inhibitors[*] and supplemented this with a search of MEDLINE® for articles published after that review (see MEDLINE® Search 3 in Appendix A). Finally, the abstracts for all ACEI-versus-other studies were screened for inclusion and evaluated further to identify trials

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[*] Chou R, Helfand M, Carson S. Drug Class Review on Angiotensin Converting Enzyme Inhibitors. Final Report. June 2005. Available at: www.ohsu.edu/drugeffectiveness/reports/final.cfm. Accessed 17 August 2006.

with the right treatment duration/length of followup (≥ 24 weeks) and the right comparators (atenolol, amlodipine, or placebo).

The result of this process was that we identified 76 RCT publications comparing ARBs with atenolol, amlodipine, or placebo over a period of ≥ 24 weeks, and 136 RCT publications comparing ACEIs with the same group of comparators over the same period of time. We were unable to obtain copies of four articles (two each for ACEIs and ARBs), so the final counts were 74 potentially relevant ARB articles and 134 potentially relevant ACEI articles.

Identifying Publications Reporting Outcomes of Interest

Once data from the direct comparator trials had been abstracted, we identified three categories of outcomes that we thought were under-reported in these trials:

- Mortality and major events (myocardial infarction [MI], stroke);
- Measures of carbohydrate metabolism/diabetes control (progression to type 2 diabetes, glycated hemoglobin [HgbA1c], insulin or other diabetes medication dosage, fasting plasma glucose, or aggregated measures of serial glucose measurements);
- Measures of kidney disease (creatinine/glomerular filtration rate [GFR] and proteinuria).

We then screened the indirect comparison literature identified through the process described above in full-text form to identify publications that reported on one or more of these outcomes. Thirty-two (32) ARB-versus-other publications and 42 ACEI-versus-other publications reported one or more of the outcomes of interest and were evaluated further. A list of these 74 publications is provided at the end of this Appendix.

Analysis of Comparability of Trials

In consideration of the special challenges of using indirect (non-head-to-head) comparison studies to infer relative efficacy regarding any particular health outcome, we established minimal criteria before considering any indirect comparison. Our goal was to achieve a reasonable degree of clinical homogeneity without being excessively restrictive at this stage.

We defined three criteria for considering performing an indirect comparison. The first criterion was that the studies must have a common comparator (amlodipine, atenolol, or placebo). The rationale is that comparators cannot be considered equivalent with regard to any particular health outcome. The second criterion was that study populations must be generally comparable, at least with regard to key characteristics relevant to the outcome being assessed. For studies examining event rates (mortality, stroke, or MI), the key characteristic was the mean age of the population. For studies of laboratory measures (HgbA1c, glucose, creatinine, GFR, or proteinuria), the key

characteristic was the mean of the corresponding laboratory measure at baseline. The value for the key characteristic could be different by as much as 10 percent and still be considered to be comparable (e.g., for mortality rates in which the study with the highest mean age for subjects was 70 years, comparable studies could have mean subject ages as low as 63 years). The third criterion was that among studies satisfying the preceding criteria, there must be more than one study of an ACEI versus the comparator and more than one study of an ARB versus the comparator. That is, indirect comparisons for a particular outcome would be considered only if there were at least four comparable studies to evaluate, two for an ACEI and two for an ARB. Notably, we did not restrict studies to the same ACEI or ARB, or any other protocol characteristics.

Despite these relatively liberal criteria for considering indirect comparisons between ACEIs and ARBs, we did not identify any appropriate candidate studies related to an outcome of special interest, and thus we did not attempt to use indirect evidence to infer relative impact of ACEIs versus ARBs.

List of Indirect Comparator Articles Reaching the Final Stage of Evaluation

The following is a list of the 74 indirect comparator publications that met our basic screening criteria (RCT, followup $\geq$ 24 weeks, comparator with $\geq$ 3 trials on ACEI and ARB sides) *and* reported one or more of the outcomes of interest specified above (mortality, MI, stroke, diabetes outcomes, kidney disease outcomes).

Aberg H, Morlin C, Lithell H. Different long-term metabolic effects of enalapril and atenolol in patients with mild hypertension. EGTA Group. J Hum Hypertens 1995;9(2):149-53.

Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001;285(21):2719-28.

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[erratum appears in JAMA 2003 Jan 8;289(2):178]. JAMA 2002;288(23):2981-97.

Anonymous. The treatment of mild hypertension study. A randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. The Treatment of Mild Hypertension Research Group. Arch Intern Med 1991;151(7):1413-23.

Anonymous. Hypertension in Diabetes Study. III. Prospective study of therapy of hypertension in type 2 diabetic patients: efficacy of ACE inhibition and beta-blockade. Diabet Med 1994;11(8):773-82.

Anonymous. Hypertension in Diabetes Study IV. Therapeutic requirements to maintain tight blood pressure control.[erratum appears in Diabetologia 1997 Mar;40(3):366]. Diabetologia 1996;39(12):1554-61.

Anonymous. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317(7160):713-20.

Anonymous. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group[erratum appears in BMJ 1999 Jan 2;318(7175):29]. BMJ 1998;317(7160):703-13.

Arima H, Hart RG, Colman S, et al. Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke 2005;36(10):2164-9.

Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 2003;163(13):1555-65.

Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy[summary for patients in Ann Intern Med. 2003 Apr 1;138(7):I43; PMID: 12667050]. Ann Intern Med 2003;138(7):542-9.

Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345(12):861-9.

Carr AA, Kowey PR, Devereux RB, et al. Hospitalizations for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies. Am J Cardiol 2005;96(11):1530-6.

Chapman N, Huxley R, Anderson C, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke 2004;35(1):116-21.

Cocco G, Ettlin T, Baumeler HR. The effect of amlodipine and enalapril on blood pressure and neurohumoral activation in hypertensive patients with Ribbing's disease (multiple epiphysal dystrophy). Clin Cardiol 2000;23(2):109-14.

Contreras G, Greene T, Agodoa LY, et al. Blood pressure control, drug therapy, and kidney disease. Hypertension 2005;46(1):44-50.

Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359(9311):995-1003.

Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation 2006;113(18):2201-10.

De Cesaris R, Ranieri G, Filitti V, et al. Effects of atenolol and enalapril on kidney function in hypertensive diabetic patients. J Cardiovasc Pharmacol 1993;22(2):208-14.

Derosa G, Ragonesi PD, Mugellini A, et al. Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertens Res 2004;27(7):457-64.

Devereux RB, Dahlof B, Kjeldsen SE, et al. Effects of losartan or atenolol in hypertensive patients without clinically evident vascular disease: a substudy of the LIFE randomized trial. Ann Intern Med 2003;139(3):169-77.

Douglas JG, Agodoa L. ACE inhibition is effective and renoprotective in hypertensive nephrosclerosis: the African American Study of Kidney Disease and Hypertension (AASK) trial. Kidney Int Suppl 2003;(83):S74-6.

Ecder T, Chapman AB, Brosnahan GM, et al. Effect of antihypertensive therapy on renal function and urinary albumin excretion in hypertensive patients with autosomal dominant polycystic kidney disease. Am J Kidney Dis 2000;35(3):427-32.

Fogari R, Preti P, Zoppi A, et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. Am J Hypertens 2002;15(12):1042-9.

Fossum E, Moan A, Kjeldsen SE, et al. The effect of losartan versus atenolol on cardiovascular morbidity and mortality in patients with hypertension taking aspirin: the Losartan Intervention for Endpoint Reduction in hypertension (LIFE) study. J Am Coll Cardiol 2005;46(5):770-5.

Gray A, Clarke P, Raikou M, et al. An economic evaluation of atenolol vs. captopril in patients with Type 2 diabetes (UKPDS 54). Diabet Med 2001;18(6):438-44.

Hansson L. Effects of angiotensin-converting enzyme inhibition versus conventional antihypertensive therapy on the glomerular filtration rate. Cardiology 1995;86 Suppl 1:30-3.

Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354(9192):1751-6.

Himmelmann A, Hansson L, Hansson BG, et al. ACE inhibition preserves renal function better than beta-blockade in the treatment of essential hypertension. Blood Press 1995;4(2):85-90.

Himmelmann A, Hansson L, Hansson BG, et al. Long-term renal preservation in essential hypertension. Angiotensin converting enzyme inhibition is superior to beta-blockade. Am J Hypertens 1996;9(9):850-3.

Hoieggen A, Alderman MH, Kjeldsen SE, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;65(3):1041-9.

Ibsen H, Wachtell K, Olsen MH, et al. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens 2004;22(9):1805-11.

Iino Y, Hayashi M, Kawamura T, et al. Interim evidence of the renoprotective effect of the angiotensin II receptor antagonist losartan versus the calcium channel blocker amlodipine in patients with chronic kidney disease and hypertension: a report of the Japanese Losartan Therapy Intended for Global Renal Protection in Hypertensive Patients (JLIGHT) Study. Clin Exp Nephrol 2003;7(3):221-30.

Iino Y, Hayashi M, Kawamura T, et al. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. Hypertens Res 2004;27(1):21-30.

Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J Am Coll Cardiol 2004;43(6):1047-55.

Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363(9426):2022-31.

Kizer JR, Dahlof B, Kjeldsen SE, et al. Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention For Endpoint reduction in hypertension study. Hypertension 2005;45(1):46-52.

Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA 2002;288(12):1491-8.

Kumagai H, Hayashi K, Kumamaru H, et al. Amlodipine is comparable to angiotensin-converting enzyme inhibitor for long-term renoprotection in hypertensive patients with renal dysfunction: a one-year, prospective, randomized study. Am J Hypertens 2000;13(9):980-5.

Kuperstein R, Sasson Z. Effects of antihypertensive therapy on glucose and insulin metabolism and on left ventricular mass: A randomized, double-blind, controlled study of 21 obese hypertensives. Circulation 2000;102(15):1802-6.

Lakshman MR, Reda DJ, Materson BJ, et al. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Arch Intern Med 1999;159(6):551-8.

Lea J, Greene T, Hebert L, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. Arch Intern Med 2005;165(8):947-53.

Lewis CE, Grandits A, Flack J, et al. Efficacy and tolerance of antihypertensive treatment in men and women with stage 1 diastolic hypertension. Results of the Treatment of Mild Hypertension Study. Arch Intern Med 1996;156(4):377-85.

Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345(12):851-60.

Lindholm LH, Ibsen H, Borch-Johnsen K, et al. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. J Hypertens 2002;20(9):1879-86.

Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359(9311):1004-10.

Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21(5):875-86.

Lithell H, Hansson L, Skoog I, et al. The Study on COgnition and Prognosis in the Elderly (SCOPE); outcomes in patients not receiving add-on therapy after randomization. J Hypertens 2004;22(8):1605-12.

Malmqvist K, Ohman KP, Lind L, et al. Long-term effects of irbesartan and atenolol on the renin-angiotensin-aldosterone system in human primary hypertension: the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA). J Cardiovasc Pharmacol 2003;42(6):719-26.

Massie BM. What is the meaning of LIFE? Implications of the Losartan Intervention for Endpoint reduction in hypertension trial for heart failure physicians. J Card Fail 2002;8(4):197-201.

Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA 1993;270(6):713-24.

Nielsen FS, Rossing P, Gall MA, et al. Impact of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. Diabetes 1994;43(9):1108-13.

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Appendix C: Abstract and Full-Text Screening Criteria

Abstract Screening Instructions

An abstract will be **<u>included</u>** if any of the following criteria apply:

- The study is a <u>direct comparison</u> (any study design) of an ACEI versus an ARB (see list below; additional antihypertensive therapy OK if the same in both groups);
- The study is an <u>indirect comparison</u> (RCT only) of either an ACEI or an ARB (see list below) versus another antihypertensive or placebo (additional antihypertensive therapy OK if the same in all groups);
- The study is an <u>indirect comparison</u> (RCT only) of a combination of an ACEI or an ARB (see list below) plus another antihypertensive versus another antihypertensive or placebo;
- Original data.

An abstract will be **<u>excluded</u>** if any of the following criteria apply**:**

- No patients have hypertension OR some patients have hypertension, but results not reported separately for this subgroup;
- All subjects aged < 18 years OR some subjects aged < 18 years, but results not broken down by age;
- Dose comparison studies with no placebo arm;
- Only comparison is an ACEI + an ARB versus placebo.

An abstract will be identified as a **<u>review</u>** if it is a relevant review article, meta-analysis, methods article, or cost-effectiveness analysis.

For each abstract, please mark either **"EX"** for **<u>Exclude,</u> "IN"** for **<u>Include</u>** or **"R"** for **<u>Review.</u>**

For included studies, please mark:
- "AVA" if the study is a **<u>direct comparison</u>** of an ACEI versus an ARB;
- "AVO" if the study is an **<u>indirect comparison</u>** of either (1) an ACEI or an ARB versus some other antihypertensive or placebo OR (2) a combination of an ACEI or an ARB plus another antihypertensive versus an antihypertensive or placebo.

For all included studies, please also indicate the <u>longest length (weeks or months) of followup</u>.

Thus, coding for each abstract should be either:

- **EX**
- **R**

- **IN AVA** (specify # weeks or # months follow-up, or write "NS" if length of follow-up not specified)
- **IN AVO** (specify # weeks or # months follow-up, or write "NS")

Included ACEIs
benazepril (Lotensin)
captopril (Capoten)
enalapril (Vasotec; Enalaprilat IV)
fosinopril (Monopril)
lisinopril (Prinivil, Zestril)
moexipril (Univasc)
perindopril (Aceon)
quinapril (Accupril)
ramipril (Altace)
trandolapril (Mavik)

Included ARBs
candesartan cilexetil (Atacand)
eprosartan (Teveten)
irbesartan (Avapro)
losartan (Cozaar)
olmesartan medoxomil (Benicar)
telmisartan (Micardis)
valsartan (Diovan)

Direct ACEIs vs. ARBs Comparisons – Full-Text Screening Criteria

Note: Articles coded at the abstract screening stage as included, but having a treatment duration/followup lasting < 12 weeks (n = 88), were excluded at this stage without further review. The remaining 103 included abstracts with treatment duration/followup ≥ 12 weeks were reviewed in full-text form. Screeners were instructed to work from top to bottom of the following list, choosing the first (if any) exclusion reason that applied.

1) **Condition of interest = essential hypertension**

- *Exclude* if no patients have essential hypertension *or* if results not reported separately for subgroup with essential hypertension

2) **Population of interest = adults (≥ 18 years)**

- *Exclude* if all subjects < 18 *or* if results not reported separately for ≥ 18 subgroup

3) Interventions & comparators of interest:

> ACEIS
> benazepril (Lotensin)
> captopril (Capoten)
> enalapril (Vasotec; Enalaprilat IV)
> fosinopril (Monopril)
> lisinopril (Prinivil, Zestril)
> moexipril (Univasc)
> perindopril (Aceon)
> quinapril (Accupril)
> ramipril (Altace)
> trandolapril (Mavik)
>
> ARBS
> candesartan cilexetil (Atacand)
> eprosartan (Teveten)
> irbesartan (Avapro),
> losartan (Cozaar)
> olmesartan medoxomil (Benicar)
> telmisartan (Micardis)
> valsartan (Diovan)

- *Include* "grouped" comparisons, e.g., specific ARB vs. "ACE inhibitors" or unspecified "ARBs" vs. unspecified "ACEIs"
- *Include* ACEI + drug X vs. ARB + drug X (e.g., losartan + HCTZ vs. enalapril + HCTZ)
- *Exclude* ACEI + drug X vs. ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ)
- *Exclude* if ACEI or ARB not on above list

4) Study designs:

- *Include* all clinical study designs (RCTs, non-RCTs, cohorts, etc.); cross-sectional studies OK if time on treatment reported and ≥ 12 weeks
- *Exclude* if not clinical study (review, etc. – please specify)

5) Outcomes of interest:

For Key Question 1:
- Intermediate outcomes:
    - o Blood pressure control
    - o Rate of use of a single antihypertensive agent for blood pressure control
    - o Lipid levels
    - o Progression to type 2 diabetes

- o Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, aggregated measures of serial glucose measurements)
  - o LV mass/function
  - o Creatinine/GFR
  - o Proteinuria
- Health outcomes:
  - o Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific)
  - o Morbidity (cardiac events [MI], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, PVD [as clinically manifest, not markers of], quality of life)

For Key Question 2:
- Safety (overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, switch rates)
- Specific adverse events (including, but not limited to: weight gain, impaired renal function, angioedema, cough)
- Tolerability
- Persistence
- Adherence

6) Sample size:

- *Exclude* if total number of patients randomized to ACEI and ARB treatment arms < 20

7) Treatment duration/length of followup:

- *Exclude* if treatment duration or longest followup < 12 weeks

Appendix D: Data Abstraction Form

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
StudyID	**Geographical location:** [city & state (U.S.) or city & country (foreign)] **Study dates:** [month & year] **Funding source:** **Interventions:** [For each treatment arm, describe drug, dose (incl. titration protocol), and number of patients randomized] **Study design:** [Delete all but one] RCT, parallel-group RCT, crossover Other [specify] **Blinding:** [For each item, Yes/No/NR = not reported] - Patients: - Providers: - Assessors of outcomes: **Was allocation concealment adequate?** [e.g., computer-generated list or central randomization] Yes/No/NR **Baseline/run-in period:** [length & intervention, or NA = not applicable] **Washout period(s):** [crossover trials only; length]	**Number of patients:** - Screened for inclusion: - Eligible for inclusion: - Randomized: - Began treatment: - Completed treatment: - Withdrawals/losses to followup: **Age:** Mean (SD): Median: Range: **Sex (n [%]):** Female: Male: **Race/ethnicity (n [%]):** **Baseline blood pressure:** [by treatment group, if given; indicate how assessed] **Concurrent medications (n [%]):** **Comorbidities (n [%]):** **Recruitment setting:** [Inclusion/exclusion criteria: describe these as reported in article. If tolerability was assessed during run-in or used as an incl/excl criterion, please note this.]	[Where necessary, specify how outcomes were defined and assessed. Report quantitative data and p-values, where available; give N's for specific outcomes if these differ from N's randomized; give time point(s) for abstracted data and note other time points available in the article. Include any results reported separately for subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities.] **1) Blood pressure:** [Prefer seated trough BP, if reported; if BP outcomes other than the one(s) you abstract are reported, list these] **2) Rate of use of a single antihypertensive agent for BP control:** **3) Mortality:** [all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific] **4) Morbidity:** [cardiac events (MI), heart failure, cerebral vascular disease or events (incl. stroke), symptomatic coronary artery disease, end-stage renal disease, PVD, quality of life] **5) Safety:** [overall adverse events (AEs), withdrawals due to AEs, serious AEs reported, switch rates]	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] **General comments:** [Comment here on biases, etc., affecting clinical interpretation] **Quality assessment:** [Assign an overall quality rating of "Good," "Fair," or "Poor" based on the definitions provided in the guidance sheet. If study is rated as "Fair" or "Poor," note important limitations in internal validity (see guidance sheet assessing quality) under "Comments", below.] Overall rating: Comments: **Applicability:** [List the most important (up to 3) limitations affecting applicability, if any, based on the list given in the guidance sheet on assessing applicability.]

Appendix D: Data Abstraction Form

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: [post-baseline/run-in; days, weeks, months] **Duration of post-treatment followup:** [days, weeks, months, or NA = not applicable]	**Inclusion criteria:** **Exclusion criteria:**	**6) Specific adverse events:** [including, but not limited to: weight gain, impaired renal function, angioedema, cough]: **7) Persistence/adherence:** **8) Lipid levels:** **9) Progression to type 2 diabetes:** **10) Markers of carbohydrate metabolism/diabetes control:** [HbA1c, insulin or other diabetes med dosage, fasting plasma glucose, aggregated measures of serial glucose measurements] **11) LV mass/function:** **12) Creatinine/GFR:** **13) Proteinuria:**	

Appendix E: Evidence Table

Evidence Table. Direct comparator studies of ACEIs vs. ARBs

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Amerena, Pappas, Ouellet, et al., 2002
 	
#3620
	Geographical location: Multi-national, multicenter: Canada (14 sites), Australia (12), Germany (11), Italy (9), Greece (7), Russia (6), Spain (5), Hungary (5), Czech Republic (4), Lithuania (2)
	
	Study dates: NR
	
	Funding source: NR (one author affiliated with GSK)
	
	Interventions:
	- Telmisartan (40-80 mg) (n = 264)
	- Enalapril (10-20 mg) (n = 258)
	
	Titrated to higher dose if mean DBP > 90 at wk 6
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: Yes for most outcomes except mean seated trough DBP
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 4 wk placebo
	
	Duration of treatment: 12 wk
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: 882
		- Randomized: 522
		- Began treatment: 522
		- Completed treatment: 482
		- Withdrawals/losses to followup: 40 patients prematurely discontinued treatment (12 due to AEs, reasons for others NR) and 6 more were excluded from ITT analysis (no on-therapy efficacy data)
		- ITT population: 516 (522-6 patients with no efficacy data)
		
		Age:
		Mean (SD): 52 ± 9.6
		Median: NR
		Range: 23 - 77
		
		Sex (n [%]):
		Female: 184 (36%)
		Male: 332 (64%)
		
		Race/ethnicity (n [%]):
		White: 503 (97%)
		Asian + other: 13 (3%)
		
		Baseline blood pressure:
		Seated unblinded trough (24 hr post-dose) SBP and DBP measured using an automated ABPM SpaceLabs 90207 device; mean of 3 measurements used
		
		Baseline values:
		    Telmisartan Enalapril
		SBP: 159.9 ± 12.4 157.7 ± 13.2
		DBP: 103.0 ± 6.3 101.6 ± 6.1
			1) Blood pressure:
			Change from baseline in mean seated trough BP values at 12 wk (mean values NR):
			
			        Telmisartan Enalapril
			        (n = 250) (n = 247) p
			SBP: -11.90 -10.42 p = ns
			DBP: -9.69 -7.67 p < 0.02
			
			DBP response at 12 wk (seated trough DBP < 90 mm Hg and/or a ≥ 10 mm Hg reduction from baseline):
			Telmisartan: 59%
			Enalapril: 50%
			p < 0.05
			
			Also reported 18-24 hr and 24 hr ABPM, daytime, and nighttime BP
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			Any AE:
			Telmisartan: 76/265 (28.7%)
			Enalapril: 82/257 (31.9%)
			
			AE considered to be drug-related:
			Telmisartan: 20 (7.5%)
			Enalapril: 34 (13.2%)
			
			6 serious AEs (treatment group NR), none considered to be drug-related
				General comments:
				- Patients were withdrawn from the study if DBP > 114 or their seated SBP > 200 mmHg at any time
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Statistically significant endpoint not blinded
				
				Applicability:
				- No comorbidities discussed
				- No clear idea of recruitment strategy
				- Run in period on placebo may be selective to patients that got in
				- No real baseline information on the patients' other medical issues

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Concurrent medications (n [%]): No other antihypertensives **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age > 18 - Mild to moderate essential HTN, 95 ≤ DBP ≤ 114 (or 104 in German and Czech sites) **Exclusion criteria:** - Mean SBP ≥ 180 - Secondary HTN - Uncorrected volume or sodium depletion - Severe renal impairment, renal artery stenosis, hepatic impairment, biliary obstructive disorders, electrolyte disturbances, primary aldosteronism, or hereditary fructose intolerance - Known sensitivity to any component of the placebo, telmisartan, or enalapril tablets - Pregnant women, breast-feeding, or women of childbearing potential not using a approved form of birth control	Discontinuation due to AEs: Telmisartan: 4 (1.5%) Enalapril: 8 (3.1%) **6) Specific adverse events:** |	Telmisartan (n = 265)	Enalapril (n = 257)
---	---	---
HA	22 (8.3%)	18 (7.0%)
Cough	2 (0.8)	23 (8.9)
Musculoskel pain	12 (4.5)	8 (3.1)
Malaise/fatigue	6 (2.3)	9 (3.5)
Hypotension	3 (1.1)	10 (3.9)
Viral ENT infect	8 (3)	7 (2.7)	 **7) Persistence/adherence:** Compliance assessed by pill count at clinic visit; similar in both groups **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Avanza, El Aouar, and Mill, 2000 **#5600**	**Geographical location:** Vitoria, Brazil **Study dates:** Unknown **Funding source:** Merck Sharp & Dhome – supplied meds **Interventions:** - Enalapril 20 mg qam + 15 mg qpm (n = 22)	**Number of patients:** - Screened for inclusion: 90 - Eligible for inclusion: 61 - Allocated: 61 - Began treatment: 61 - Completed treatment: 46 - Withdrawals/losses to followup: 15 (4 due to cough, 4 stopped taking study med, 2 noncompliant, 2 altered medication schedule, 2 treatment failures, 1 acute MI)	**1) Blood pressure:** Mean office SBP values reported in text for 7 mo. Posttreatment office DBP for all timepoints and office SBP for all other timepoints reported only graphically in Figure 1. Mean office SBP at 7 mo: Enalapril (n = 15): 146 ± 1.9 Losartan (n = 15): 146 ± 2.1 Enalapril + losartan (n = 16): 143 ± 1.9 p > 0.05 for between-group comparison of	**General comments:** None **Quality assessment:** Overall rating: Poor Comments: - Poor study design - Non-randomized, non-blinded - Small sample size - Non-responders and non-compliant

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	- Losartan 100 mg qam + 75 mg qpm (n = 17)
	- Enalapril 15 mg qam + losartan 100 mg qpm (n = 23)
	
	No dose titration; no co-interventions permitted
	
	Study design:
	Non-randomized controlled clinical trial (CCT)
	Groups assigned sequentially as patients were recruited: Enalapril → enalapril/losartan → losartan
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: Yes (echocardiographers were blinded)
	
	Was allocation concealment adequate?: No
	
	Baseline/run-in period: 12-day washout of prior meds
	
	Duration of treatment: 10 months
	
	Duration of post-treatment followup: NA
		Age:
		Mean (SD): 54 ± 4
		
		Sex (n [%]):
		Female: 19 (41%)
		Male: 27 (59%)
		
		Race/ethnicity (n [%]):
		"All were white or mulatto" (no numbers given)
		
		Baseline blood pressure:
		Office BP measured using a mercury sphygmomanometer after a 10-min rest in a seated position:
		
		Mean baseline values for n = 46 study completers:
		
		          SBP DBP
		Enalapril 173 ± 2.9 104 ± 1.8
		Losartan 170 ± 1.9 103 ± 1.7
		Enalapril + losartan 173 ± 2.8 104 ± 1.5
		
		24-hr ABPM also performed using a SpaceLabs 90207 device, with readings every 20 min
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: University clinics
		
		Inclusion criteria:
		- Both sexes
		- Age 40-60
		- Resting BP indicating moderate hypertension (by JNC-5) after run-in
		- Ambulatory BP confirming moderate hypertension
		- Echo criteria for LVH
			reductions from baseline
			
			At 10 mo, SBP values significantly ($p < 0.05$) higher in the losartan group than in the other 2 groups (shown only graphically in Figure 1)
			
			At the end of month 10 "almost all the patients" had BPs in the normal range (SBP < 140 mm Hg, DBP < 90 mm Hg)
			
			2) Rate of use of a single antihypertensive agent for BP control: NA (no other antihypertensives permitted)
			
			3) Mortality: NR
			
			4) Morbidity:
			1 patient in the enalapril group had an acute MI
			
			5) Safety:
			4/22 patients (18%) in the enalapril group withdrew due to cough
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence:
			2/61 patients were noncompliant (both enalapril)
			4/61 stopped taking study medication (2 losartan, 2 combination group)
			2/61 altered medication schedule (both combination group)
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control:
			Plasma glucose levels (mg%) were in the normal range for all patients and did not change significantly during treatment. There were no significant between-group differences.
			
			                Baseline 10 mo
			Enalapril (n = 15) 90 ± 4 90 ± 4
			Losartan (n = 15) 93 ± 4 94 ± 4
				patients excluded from analysis
				- Reported levels of SBP reduction are far greater than that typically reported in most studies
				- Missing data, including BP values at 10 months
				
				Applicability:
				- Minimal patient characteristics reported
				- Black patients excluded
				- Analyzed very selected population who completed study, complied with treatment, and responded to treatment (not ITT)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

		Exclusion criteria:
		- Black race
		- Obesity (BMI >30)
		- Diabetes
		- Valvular heart disease
		- Secondary hypertension
		- History of complications of hypertension (MI or CHF)
		- Long-term use of corticosteroids, neuroleptics or antidepressants
			Enalapril + losartan (n = 16) 91 ± 4 91 ± 4
			
			11) LV mass/function:
			Mean LVMI (g/m^2)
			
			            Baseline 10 mo
			Enalapril (n = 15) 141 ± 3.9 123 ± 3.6
			Losartan (n = 15) 147 ± 3.8 133 ± 2.8
			Enalapril + losartan (n = 16) 146 ± 3.0 116 ± 4.0*
			*p = 0.011, combination vs. enalapril and vs. losartan at 10 mo; p-values for all other between-group comparisons NS
			
			Percent reduction in LVMI from baseline to 10 mo (see Figure 3):
			Enalapril: 12.4 ± 3.2%*
			Losartan: 9.1 + 2.1%
			Enalapril + losartan: 20.5 ± 5.0%**
			*p < 0.05, enalapril vs. losartan
			**p < 0.01, combination vs. single treatments
			
			12) Creatinine/GFR:
			Creatinine levels (mg%) were in the normal range for all patients and did not change significantly during treatment. There were no significant between-group differences.
			
			            Baseline 10 mo
			Enalapril (n = 15) 1.2 ± 0.2 1.2 ± 0.3
			Losartan (n = 15) 1.1 ± 0.3 1.2 ± 0.3
			Enalapril + losartan (n = 16) 1.2 ± 0.3 1.3 ± 0.3
			
			13) Proteinuria: NR	

Barnett, Bain, Bouter, et al., 2004
 	
#11010
	Geographical location: 39 centers in northern Europe (Denmark, Finland, The Netherlands, Norway, Sweden, and the UK)
	
	Study dates: NR
	
	Funding source: Boehringer Ingelheim
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 250
		- Began treatment: 250
		- Completed treatment: 168
		- Withdrawals/losses to followup: 38 telmisartan group (20 due to AEs, 18 for other causes), 44 enalapril group
			1) Blood pressure:
			Adjusted mean reduction in SBP over 5 yr (last observation carried forward):
			    Telmisartan Enalapril
			    6.9 mm Hg 2.9 mm Hg
			    95% CI: -8.5 to 0.5 mm Hg
			
			Figure 2 demonstrates changes graphically.
				General comments:
				- Primary outcome of study was change in GFR
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Many dropouts; GFR data based on

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Interventions:
	- Telmisartan 40 mg daily for 4 weeks, then forced titration to 80 mg daily (n = 120)
	- Enalapril 10 mg daily for 4 weeks, then forced titration to 20 mg daily (n = 130)
	
	Additional antihypertensives (not ACEIs or ARBs) allowed after 2 mo if SBP > 160 or DBP > 100
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: Yes
	
	Baseline/run-in period:
	1 month – received regular antihypertensive meds including an ACEI (which was then stopped at randomization)
	
	Duration of treatment: 5 years
	
	Duration of post-treatment followup: NA
		(30 due to AEs, 14 for other causes)
		
		Age:
		Mean (SD): 60.6 (8.8)
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 68 (27%)
		Male: 182 (73%)
		
		Race/ethnicity (n [%]):
		White: 246 (98.4%)
		Other: 4 (1.6%)
		
		Baseline blood pressure:
		Measured at trough; method of assessment not further described
		
		Mean baseline values:
		
		    Telmisartan Enalapril
		SBP 152.6 ± 16.6 151.6 ± 15.8
		DBP 85.4 ± 8.8 85.9 ± 7.8
		
		Concurrent medications (n [%]):
		Diuretics: 130 (52%)
		Beta-blockers: 98 (39.2%)
		Calcium channel blockers: 115 (46%)
		Other antihypertensive agents: 88 (35.2%)
		Aspirin: 98 (39.2%)
		Statins: 105 (42%)
		
		Comorbidities (n [%]):
		Duration of diabetes (median [range]):
		Telmisartan: 8.0 yr (0-25)
		Enalapril: 8.0 yr (0-37)
		
		History of cardiovascular disease:
		Telmisartan: 59 (49.2%)
		Enalapril: 63 (48.5%)
		
		Recruitment setting:
		Academic centers in northern Europe
			% of patients with:
			SBP < 160: 75%
			SBP < 140: 42%
			No significant difference between groups.
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Table 2 gives some information, but is imprecise. Based on figures reported, percentages of patients on monotherapy for hypertension during the study were in the following ranges:
			Telmisartan: 15-65%
			Enalapril: 18.5-64.6%
			
			3) Mortality:
			Deaths:
			Telmisartan: 6 (3 due to CV events [stroke, MI, or cardiac insufficiency])
			Enalapril: 6 (2 due to stroke)
			
			4) Morbidity:
			
			          Telmisartan Enalapril
			Stroke 6 6
			CHF 9 7
			Non-fatal MI 9 6
			Incr Cr < 2.3 2 2
			
			5) Safety:
			
			          Telmisartan Enalapril
			Any AE: 115 (95.8%) 130 (100%)
			AE leading to study discontinuation:
			      20 (17%) 30 (23%)
			
			6) Specific adverse events:
			See 4) above.
			Note that patients with know history of angioedema related to ACEIs were excluded.
			
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			Pre-study levels recorded, post-study not given although stated "there were no changes in routine hematologic or blood chemical values in either group."
				data available in only 216 subjects (103 telmisartan, 113 enalapril)
				
				Applicability:
				- Patients all with diabetic nephropathy (~80% microalbuminuria, ~20% macroalbuminuria)
				- Minimal focus on HTN, details of BP assessment not described, and overall targets quite high compared to current recommendations

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

		Inclusion criteria:
		- White or Asian race/ethnicity
		- Age 35-80
		- Type 2 diabetes treated by diet, diet + oral hypoglycemic drugs (for ≥ 1 year), or insulin preceded by treatment with oral agents (for ≥ 1 year)
		- For patients treated with insulin, onset of diabetes > age 40 and BMI > 25 at time of diagnosis
		- History of mild-to-moderate hypertension (mean seated SBP ≤ 180 mm Hg)
		- Current resting BP < 180/95 mm Hg after ≥ 3 months of treatment with ACEI prior to study entry
		- Normal gross renal morphology for ≥ 12 months
		- Urinary albumin excretion rate (mean of 3 consecutive overnight values) of 11-999 μg/min, with 2 values > 10 μg/min
		- HbA1c < 12%
		- Serum creatinine ≤ 1.6 mg/dL (140 μmol/L)
		- GFR ≥ 70 mL/min/1.73 m^2
		- Women who were < 60 had to be either surgically sterile or have negative pregnancy test at enrollment
		
		Exclusion criteria [note – some of these are from a separate article describing methods]:
		- Renal dysfunction not due to diabetic nephropathy
		- Single kidney or known renal artery stenosis
		- New York Heart Association functional class II-IV CHF
		- Known allergy to study drugs or iohexol
		- History of angioedema related to ACEIs
			9) Progression to type 2 diabetes: NA (all had type 2 diabetes with micro/macroalbuminuria)
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR:
			See Fig 1 & Table 3 for details.
			Mean change from baseline (last observation carried forward):
			
			          Telmisartan Enalapril Change
			          (n = 103) (n = 113) (95% CI)
			GFR -17.5 -15.0 -2.6 (-7.1, 2.0)
			
			          Telmisartan Enalapril Change
			          (n = 116) (n = 128) (95% CI)
			Creat 0.10 0.10 0 (-0.66, 0.65)
			
			13) Proteinuria:
			Mean change from baseline (last observation carried forward):
			
			          Telmisartan Enalapril Change
			          (n = 115) (n = 125) (95% CI)
			UAE* 1.03 0.99 1.04
			                                   (0.71, 1.51)
			*UAE = urinary albumin excretion (ratio)	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Black, Graff, Shute, et al., 1997 **#6850**	**Geographical location:** NR, but likely U.S. in Illinois, Florida, Texas, or Oregon **Study dates:** NR **Funding source:** NR, but one author each affiliated with GFI Pharmaceutical Services and Ciba-Geigy Corporation **Interventions:** - Valsartan 80 mg with titration to 160 mg once daily (n = 177) - Valsartan 80 mg with titration to 80 mg twice daily (n = 187) - Lisinopril 10 mg with titration to 20 mg once daily (n = 187) - Placebo (n = 183) Dose titration and co-interventions: Titration allowed after 4 wk for patients with mean seated DBP ≥ 90 and no symptoms of orthostatic hypotension; no co-interventions allowed **Study design:** RCT, parallel-group Stratified by age **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2- to 4-wk placebo run-in **Duration of treatment:** 12 wk **Duration of post-treatment**	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 734 - Began treatment: 734 - Completed treatment: 644 - Withdrawals/losses to followup: 90 ("most" due to AEs or unsatisfactory therapeutic response) **Age:** Mean (SD): 53.5 Median: NR Range: NR **Sex (n [%]):** Female: 39% Male: 61% **Race/ethnicity (n [%]):** White: 81% Black: 14% Other: 4% **Baseline blood pressure:** Trough seated BP measured 3 times each visit after 5-min rest using mercury sphygmomanometer Mean baseline values (± SD): SBP DBP Valsartan 153.64 100.81 80/160 ± 11.07 ± 4.41 Valsartan 154.27 101.66 80/80x2 ± 14.95 ± 4.83 Lisinopril 153.93 100.99 10/20 ± 14.94 ± 4.45 **Concurrent medications (n [%]):** NR, but no BP lowering meds allowed **Comorbidities (n [%]):** NR **Recruitment setting:** NR	**1) Blood pressure:** Mean post-treatment BP values NR Primary outcome = least mean square change in DBP from baseline (all randomized patients, using last available posttreatment BP measurement): Valsartan 80/160: -8.29 mm Hg Valsartan 80/80x2: -8.67 Lisinopril 10/20: -9.97 p = NS Results for change in SBP reported to be comparable (quantitative data NR) Per-protocol results for 12 wk also reported, but only graphically (Figure 2) BP response rates (mean DBP < 90 or ≥ 10 decrease from baseline; all randomized patients, using last available posttreatment BP measurement): Valsartan 80/160: 44.1% Valsartan 80/80x2: 48.7% Lisinopril 10/20: 57.2% p = 0.012 for valsartan 80/160 vs. lisinopril p = NS for valsartan 80/80x2 vs. lisinopril **2) Rate of use of a single antihypertensive agent for BP control:** No additional antihypertensives allowed **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AE: Valsartan (any dose): 62.6% Lisinopril (either dose): 58.3% AEs considered to be drug-related: Valsartan: 22.8% Lisinopril: 27.8%	**General comments:** Population not well specified, randomization not specified **Quality assessment:** Overall rating: Fair Comments: - Population not well specified - Method of randomization not described - Potential confounders/comorbidities not discussed - Some important outcomes not assessed; did not report unadjusted posttreatment DBP and SBP values **Applicability:** - Setting not specified, study centers not reported - Unclear how patients recruited - Exclusion criteria vague on what "clinically significant" means

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	followup: NR	**Inclusion criteria:** - Age 21-80 yr - Stage I-III diastolic HTN (seated DBP ≥ 95 and ≤ 115 after placebo run-in period) **Exclusion criteria:** - Symptomatic CHF, MI, hypertensive encephalopathy, or CV accident < 6 mo - 2nd or 3rd degree heart block - Angina - Clinically relevant arrhythmias - Clinically significant valvular disease - Significant hepatic disease - Significant renal disease - Insulin-dependent diabetes - Women of childbearing age not using contraception	Serious AEs and/or withdrawals due to AEs: Valsartan: 14/364 (3.8%) Lisinopril: 8/187 (4.3%) Drug-related AEs leading to withdrawal: Valsartan: 7 (headache 3, lightheadedness 1, shortness of breath 1, rash 1, fatigue 1) Lisinopril: 6 (cough 3, chest pain 1, nausea/dizziness 1, fatigue 1) **6) Specific adverse events:**	

6) Specific adverse events:

	Valsartan (n = 364)	Lisinopril (n = 187)
Headache	7.7%	3.2%
Viral infection	0.3%	0%
URI	0.5%	0%
Fatigue	2.2%	3.7%
Back pain	0.3%	0%
Diarrhea	1.6%	2.1%
Cough	1.1%	8.0%
Dizzy	1.1%	3.7%
Sinusitis	0.3%	1.1%

7) Persistence/adherence: NR

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Bloom, 1998 **#12630** *and* **Conlin, Gerth, Fox, et al., 2001** **#12640**	**Geographical location:** Throughout US **Study dates:** Jul 1995 to Jun 1996; subsequent study reported followup to Jun 2000 **Funding source:** Merck & Co., Inc. **Interventions:** ARB (n = 567) ACE inhibitor (n = 5842) CCB (n = 5094) Beta-blocker (n = 4994) Thiazide diuretic (n = 5226) **Study design:** Retrospective cohort study **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NA **Duration of post-treatment followup:** 4 yr	**Number of patients:** - Screened for inclusion: 1.3 to 1.6 million - Eligible for inclusion: NA - Randomized: NA - Began treatment: 21,723 - Completed treatment: NA - Withdrawals/losses to followup: 6548 lost by 4-year followup **Age:** Mean (SD): 56 (NR) Median: NR Range: 35-71 **Sex (n [%]):** Female: 12,148 (55.9%) Male: 9575 (44.1%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** 0 [0%] (not allowed) **Comorbidities (n [%]):** NR (attempted to eliminate subjects with comorbid conditions based on concurrent prescriptions) **Recruitment setting:** Enrollees in pharmacy benefit management program which includes HMO, Blue Cross-Blue Shield, and union, corporate, and government clients **Inclusion criteria:** - Patients filling first antihypertensive drug prescription in one of 5 classes (ARB, ACEI, CCB, beta-blocker, thiazide) during study period - No prescription filled for any antihypertensive drug in prior 12 mo	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Based on prescription refill on or within 3 mo after 1-yr anniversary of initial prescription 1-year data: | Drug	Continued	Switched	D/c'd
---	---	---	---
ARB	64%	7%	29%
ACEI	58%	9%	33%
CCB	50%	9%	41%
Beta-B	43%	7%	50%
Thiaz	38%	6%	56% | In multivariable analysis: - Age ≥ 65 years was associated with higher persistence than age between 40 and 64 years (OR, 0.79; 95% CI, 0.74 to 0.84; p = 0.001) and age < 40 years (OR, 0.32; 95% CI, 0.29 to 0.35; p = 0.0001) - Dosing more than once daily was associated with lower persistence than once-daily dosing (OR, 1.40; 95% CI, 1.29 to 1.52; p = 0.0001) 4-year data: | Drug	Continued	Switched	D/c'd
---	---	---	---
ARB	50.8%	16.5%	32.7%
ACEI	46.5%	18.9%	34.6%
CCB	40.7%	19.3%	40.0%
Beta-B	34.7%	12.7%	52.6%
Thiaz	16.4%	32.6%	51.0%		**General comments:** - The large sample size and representative population of the PBM database are strengths of the study, but rating is downgraded because of lack of specificity regarding hypertensive diagnosis and comorbidity, as well as no dose info; correlation between dose and BP response and change in prescription - Reasons for discontinuing therapy are not captured (ineffective? adverse events?) - ARBs were introduced just 1 year before the study period, suggesting that prescribing patterns may have been in flux – may not be representative of current patterns **Quality assessment:** Overall rating: Fair Comments: - Appears to be well done study for administrative database **Applicability:** - Lack of clinical data on subjects means that baseline BP data, BP response, actual comorbidities are unknown

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: - Prescription for nitrate, antiarrhythmic, digoxin, warfarin, loop diuretic, or certain anti-migraine drugs - Concurrent prescriptions for two or more antihypertensive drug classes (including combination products) - Incomplete data on age and sex	- Persistence with ARB (92% losartan) was higher than persistence with CCBs, beta-blockers or thiazides (p < 0.03), but not higher than ACEI (p = 0.095). - Persistence was higher among women than men, and higher among patients ≥ 65 years of age than those < 65 years of age **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Bourgault, Senecal, Brisson, et al., 2005 **#12820**	**Geographical location:** Saskatchewan, Canada (database including > 90% of provincial residents) **Study dates:** Jan 1994-Sep 1999 **Funding source:** Merck Frosst Canada, Ltd. **Interventions:** Number of patients with data for at least 180 days: ARBs (n = 1002) ACEIs (n = 7104) Beta-blockers (n = 3989) CCBs (n = 2400) Diuretics (n = 6831) **Study design:** Retrospective cohort study **Blinding:** - Patients: No	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 21,326 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA **Age (ARBs and ACEIs):** Mean: 57.6 Median: NR Range: NR **Sex (ARBs and ACEIs; %):** Female: 45.7% Male: 54.3% **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Sample sizes at various timepoints: <table><tr><td></td><td>ARBs</td><td>ACEIs</td></tr><tr><td>1 year</td><td>463</td><td>3456</td></tr><tr><td>2 years</td><td>148</td><td>1541</td></tr><tr><td>3 years</td><td>5</td><td>265</td></tr></table> Persistence defined as continuously refilling a prescription for any antihypertensive drug within 90 days of previous dispensing (assumed to last 15-30 days), regardless of switches across drug	**General comments:** - Cohort studied overlaps with that studied in Marentette, Gerth, Billings, et al., 2002 (#12830); includes fewer total patients, but many more taking ARBs **Quality assessment:** Overall rating: Fair Comments: - Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs - Funded by pharmaceutical company **Applicability:** - Study period soon after introduction of ARBs; early use may not reflect current use patterns

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NR **Duration of post-treatment followup:** Mean length of followup in ARB and ACEI groups = 1.85 yr	**Comorbidities (n [%]):** NR **Recruitment setting:** Population-based prescription drug database **Inclusion criteria:** - ICD-9 code diagnosis of hypertension (401, 402, 403, 404, or 4-digit codes included in these categories) - Age 18-80 yr - New dispensed antihypertensive med between Jan 1997 and Sep 1999 - Antihypertensive prescribed was ARB, ACEI, beta-blocker, CCB, or diuretic **Exclusion criteria:** - Prescribed more than one antihypertensive agent at treatment initiation	classes and add-on therapies. Cumulative persistence: ARBs ACEIs 1 year 66% 59% 2 years 56% 47% 3 years 53% 40% Similar results were observed after controlling for age and sex, which were not explicitly noted as being statistically significant. Note: "Persistence" includes combinations and switches; in essence, what is being modeled is failure to discontinue. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Burke, Sturken-boom, Lu, et al., 2006
 	
#12880
	Geographical location: 694 general practices widely distributed across the UK (less coverage in Scotland and inner London)
	
	Study dates: Jan 1991 – Mar 2002
	
	Funding source: Merck & Co., Inc.
	
	Interventions:
	Numbers reported below are the % of patients given a drug from the specified class as their first prescription and the total number of "drug class episodes," respectively
		Number of patients:
		- Screened for inclusion: > 9 million
		- Eligible for inclusion: 109,454
		- Randomized: NA
		- Began treatment: 109,454
		- Completed treatment: NA
		- Withdrawals/losses to followup: NA
		
		Age:
		Mean (SD): 60.6 (13.4)
		Median: NR
		Range:
		  < 50 22.4%
		  50-59 25.1%
		  60-69 25.5%
		  ≥ 70 27.0%
			1) Blood pressure: NR
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety: NR
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence:
			Discontinuation was analyzed based on a Kaplan-Meier analysis of time until 90+ days
				General comments:
				- Outcomes of interest were analyzed on the basis of the number of drug-class episodes (223,228), not number of patients (109,454)
				
				Quality assessment:
				Overall rating: Poor
				
				Comments:
				- Non-random allocation to drugs
				- Time period of study includes considerable period before ARBs were available; allocation of patients to ACEIs versus ARBs may as a result be biased

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	ACEI (12.2%; 36,386) ARB (0.5%; 5184) α-antagonist (1.1%; 7823) Beta-blocker (27.4%; 54,973) CCB (12.5%; 41,019) Potassium-sparing diuretic (0.2%; 1831) Thiazide (42.0%; 71,331) Miscellaneous monotherapy (0.3%; 4681) Combination (3.7%; NA) **Study design:** Retrospective cohort study **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NA **Duration of post-treatment followup:** 4 yr	**Sex (n [%]):** Female: 56.5% Male: 43.5% **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Mean SBP (± SD): 173.5 ± 21.1 Mean DBP (± SD): 99.7 ± 27.3 **Concurrent medications (n [%]):** NR; patients with pre-existing diabetes prescription excluded **Comorbidities (n [%]):** NR; patients with pre-existing diabetes diagnosis excluded **Recruitment setting:** UK General Practice Research Database. Contains information (demographic descriptors, information from GP visits, GP prescription data [used to generate written prescriptions], diagnoses from specialist referrals and hospital admissions, and lab results) on > 9 million patients. **Inclusion criteria:** - Age ≥ 18 - New physician diagnosis of hypertension between 1 Jan and 31 Dec 2001 ("new" diagnosis = no hypertension diagnoses prior to 1 Jan 1991 and no antihypertensive prescription within 1 year of new diagnosis) **Exclusion criteria:** - Diabetes diagnosis or diabetes prescription before antihypertensive prescription	passed without a refill. Investigators also performed a Cox regression using the same outcome variable and controlling for various patient factors (age, number of previous antihypertensive drug classes, calendar year of antihypertensive therapy initiation, pretreatment SBP, duration of hypertension, smoking). The results of this modeling are substantially similar to the unadjusted analysis presented immediately below. Cumulative discontinuation rates: <table><tr><td></td><td>1 yr</td><td>2 yr</td><td>3 yr</td><td>4 yr</td></tr><tr><td>ACEIs</td><td>37.8%</td><td>48.0%</td><td>54.8%</td><td>60.4%</td></tr><tr><td>ARBs</td><td>29.4%</td><td>41.3%</td><td>50.3%</td><td>57.8%</td></tr><tr><td>α-antag</td><td>44.7%</td><td>56.5%</td><td>64.4%</td><td>69.9%</td></tr><tr><td>BB</td><td>44.0%</td><td>54.3%</td><td>61.2%</td><td>66.7%</td></tr><tr><td>CCB</td><td>41.2%</td><td>51.5%</td><td>58.8%</td><td>64.7%</td></tr><tr><td>K-diuretic</td><td>64.1%</td><td>74.9%</td><td>81.1%</td><td>84.9%</td></tr><tr><td>Thiazide</td><td>43.9%</td><td>55.4%</td><td>63.1%</td><td>69.3%</td></tr><tr><td>Misc</td><td>62.8%</td><td>75.0%</td><td>81.1%</td><td>84.8%</td></tr></table> Switching was defined only for the subset of patients that discontinued their first line antihypertensive: ACEIs 44.2% ARBs 36.5% α-antag 38.2% BB 44.8% CCB 43.4% K-diuretic 30.4% Thiazide 44.6% Misc 25.9% Even though the investigators' modeling controlled for various patient characteristics, it was not possible to determine which of these characteristics were predictive of persistence. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR	- No measurement, reporting, or adjustment for potential confounders - No data on comparability of patients on ACEIs versus ARBs **Applicability:** - UK location and different health system may affect use rates/patient characteristics - Study period soon after introduction of ARBs; early use may not reflect current use patterns - Specific ACEIs and ARBs not identified - Diabetics excluded

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR	
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	

Celik, Iyisoy, Kursak-lioglu, et al., 2005
 	
#890
	Geographical location: NR (author based in Turkey)
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Ramipril 10 mg (n = 50)
	- Telmisartan 80 mg telmisartan (n = 50)
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: NR
	- Providers: NR
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: NR
	
	Duration of treatment: 6 months
	
	Duration of post-treatment followup: NR
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 100
		- Began treatment: NR
		- Completed treatment: NR
		- Withdrawals/losses to followup: NR
		
		Age:
		Mean (SD): 51.79 ±6.01
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 44 (44%)
		Male: 56 (56%)
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		BP measured 3 times after a 10-min resting period using a standard mercury sphygmanometer; mean of 3 measurements used
		
		      Telmisartan Ramipril
		SBP 155.9 ± 6.75 154.3 ± 5.44
		DBP 96.4 ± 6.47 94.7 ± 5.83
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]):
		DM: 17 (17%)
		Family history of premature CAD: 19 (19%)
		Smoking: 26 (26%)
		
		Recruitment setting: NR
			1) Blood pressure:
			At 6 months, n = 50 each group:
			
			    Telmisartan Ramipril p-value
			SBP 133.5 ± 9.48 130.4 ± 13.39 0.18
			DBP 81.4 ± 6.06 80.2 ± 7.75 0.39
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity:
			Atrial fibrillations occurred in 4 patients in enalapril arm and 2 patients telmisartan arm
			
			5) Safety: NR
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function:
			LVEF
			       Telmisartan Ramipril
			Before 61.58 ± 2.06 61.96 ± 1.87
			After 61.70 ± 1.54 61.94 ± 1.40
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR
				General comments:
				None
				
				Quality assessment:
				Overall rating: Poor
				
				Comments:
				- Significant missing data – timing, funding of study, the number screened, the number that completed treatment
				- Study and assessment were not blinded; may lead to bias
				- No data on safety/adverse events
				
				Applicability:
				- Many common conditions excluded
				- No information on number screened or recruitment setting
				- No data on race/ethnicity of subjects

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Inclusion criteria: 100 newly diagnosed hypertensive patients without the below exclusions **Exclusion criteria:** - Secondary or malignant hypertension - Chronic obstructive lung disease - Atrial fibrillation, flutter, or any other atrial tachyarrhythmia's with 1 month - History of anti-arrythmic drugs, including digoxin, within 1 month - Hyperthyroidism - Severe valvular disease of hemodynamic significance - History of sensitivity to use of ACEIs or ARBs - Pregnancy or nursing - MI or cerebrovascular accident within 6 months - History of proven coronary artery disease - Concurrent therapy with medication that could affect blood pressure - Severe renal or hepatic failure		

Coca, Calvo, Garcia-Puig, et al., 2002
 	
#4500
	Geographical location: Multicenter trial: 17 centers in Spain
	
	Study dates: NR
	
	Funding source: Sanofi-Synthelabo Spain
	
	Interventions:
	Doses (titrated doses if DBP ≥ 90 after 4 or 8 weeks of treatment):
	- Irbesartan 150 mg/d (300 mg); n = 111, dose titration in 80 (72%)
	- Enalapril 10 mg/d (20 mg); n =115, dose titration in 88 (76.5%)
	
	Study design:
	RCT, parallel-group
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: 295
		- Randomized: 238
		- Began treatment: 238
		- Completed treatment: 226
		- Withdrawals/losses to followup: 12 (5 due to AEs, 4 lost to followup, 3 due to lack of efficacy)
		
		Age:
		Mean (SD): 52.7 ± 10.6 yr
		Median: NR
		Range: 22-73
		
		Sex (n [%]):
		Female: 52%
		Male: 48%
			1) Blood pressure:
			Posttreatment seated trough BP values not reported
			
			ABPM results:
			24-hr BP at 12 wk:
			    Irbesartan Enalapril
			    (n = 111) (n = 115)
			SBP 128.8 ± 13.8 127.2 ± 11.1
			DBP 79.9 ± 8.8 80.5 ± 8.1
			
			Baseline and 12-wk mean BPs also reported for ambulatory daytime BP (= average 10 a.m. to 8 p.m.) and nighttime BP (average 12 – 6 a.m.)
			
			Mean reductions in 24-hr ABPM BP:
			    Irbesartan Enalapril
			    (n = 111) (n = 115)
				General comments:
				- Baseline 24-hour SBP significantly higher in irbesartan group (mean 4 mm p = 0.003)
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Very little baseline information
				- Randomization process not described
				- Patients who failed treatment (BP ≥ 180/110 despite full-dose treatment) excluded (n = 3)
				
				Applicability:
				- All white patients
				- Recruitment setting not clearly

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Blinding:
	- Patients: Yes
	- Providers: NR
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 3-wk single-blind placebo phase; patients with mean daytime DBP < 85 mm Hg during this period were excluded
	
	Duration of treatment: 12 weeks
	
	Duration of post-treatment followup: 24 hours after last dose of study medication
		Race/ethnicity (n [%]): 100% white
		
		Baseline blood pressure:
		Clinic BP using mercury sphygmo-manometer: After resting for 10 minutes in seated position; non-dominant arm supported and cuff arm at heart level. 3 successive readings at 3 min intervals, mean of 3 values recorded.
		
		     Irbesartan Enalapril
		SBP 160.3 ± 14.1 158.2 ± 13.8
		DBP 101.6 ± 4.7 102.0 ± 5.2
		
		24-hr ABPM using a non-invasive automated oscillometric device (Spacelabs 90207); cuff placed on non-dominant arm, BP recorded at 20-min intervals automatically for 24 hr
		
		     Irbesartan Enalapril
		     (n = 115) (n = 123)
		SBP 144.2 ± 11.5 140.1 ± 11.9
		DBP 89.9 ± 6.3 89.6 ± 7.9
		
		Concurrent medications (n [%]): No other antihypertensives or any other drugs with effects on the cardiovascular system permitted
		
		Comorbidities (n [%]): NR; patients with severe concomitant disease excluded
		
		Recruitment setting: NR
		
		Inclusion criteria: Mild-moderate hypertension (clinic DBP 90-109 mm Hg on ≥ 3 occasions, SBP 140-179 mm Hg or uncontrolled hypertension (BP ≥ 140/90) despite monotherapy with antihypertensive drugs other than ACE inhibitors or ARBs
			SBP 14.7 ± 14.7 12.6 ± 13.1
			DBP 9.4 ± 8.5 8.8 ± 8.5
			Between-group p-value NS
			
			Mean reductions in seated trough BP:
			     Irbesartan Enalapril
			     (n = 111) (n = 115)
			SBP 19.0 ± 14.1 17.5 ± 14.0
			DBP 12.7 ± 8.8 12.4 ± 7.4
			Between-group p-value NS
			
			Seated trough BP – response rates:
			36% (40/111) of patients treated with irbesartan and 34.8% (40/115) of those treated with enalapril achieved strict BP control (clinic BP < 140/90 at 12 wk). Response rates based on the clinic criterion (DBP reduction of ≥ 10 mm Hg at 12 wk) were 64.0% (71/11) and 67.8% (78/115), respectively.
			
			24-hr ABPM – response rates:
			40.5% (45/111) of patients with irbesartan and 33.9% (39/115) with enalapril achieved strict BP control (daytime BP < 130/85 at 12 wk), with no significant difference between groups. Response rates (reduction in 24-hr DBP of ≥ 5 mm Hg at 12 wk independent of clinic values) were 71.2% (79/111) and 71.3% (82/115), respectively.
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			
			<table><tr><td></td><td>Irbesartan n (%)</td><td>Enalapril n (%)</td></tr><tr><td>Any AE</td><td>46 (40)</td><td>63 (51.2)</td></tr><tr><td>Discontinued due to AEs</td><td>2 (1.7)</td><td>3 (2.4)</td></tr></table>
			
			AEs deemed probably related to treatment were
				described
				- Process of inclusion of study centers not described
				- Comorbid conditions not described: they were "excluded" but list of criteria not mentioned

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: - Renal impairment (Ser Cr > 1.5 mg/dL), papilledema, or evidence of coronary heart disease or cardiac failure during the previous 3 months - Severe concomitant disease - Women who were pregnant or of childbearing potential	less frequent with irbesartan than with enalapril (9.2% vs. 24.6%, p = 0.026) Risk of AEs deemed probably related to treatment: 2.6 times higher in those treated with enalapril (OR 2.6, 95% CI 1.1 to 6.1) Discontinued due to AEs in irbesartan group (n = 2): GI disturbance, nausea, vomiting Discontinued due to AEs in enalapril group (n = 3): skin rash, persistent cough **6) Specific adverse events:** Most common AEs (> 5% in either group):	

	Irbesartan n (%)	Enalapril n (%)
Nervous system	22 (19.1)	33 (26.8)
Fatigue, back pain, fever	16 (13.9)	10 (8.1)
GI system	12 (10.4)	8 (6.5)
Headache	11 (9.6)	18 (14.6)
Dizziness	9 (7.8)	17 (13.8)
Cardiovascular system	8 (7.0)	9 (7.3)
Palpitations	7 (6.1)	8 (6.5)
Upper resp tract	4 (3.5)	18 (14.6)
Cough	1 (0.9)	10 (8.1)
Skin disorders	-	5 (4.1)

7) Persistence/adherence:
Compliance with treatment (assessed by pill counts at each visit) similar in two groups: 98.3% in patients treated with irbesartan and 98.4% in those treated with enalapril

Irbesartan once daily better tolerated than enalapril once daily

8) Lipid levels: NR

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			9) Progression to type 2 diabetes: NR	
			10) Markers of carbohydrate metabolism/diabetes control: NR	
			11) LV mass/function: NR	
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	

Cuspidi, Muiesan, Valagussa, et al., 2002
 	
#3790
	Geographical location: 36 sites in Italy, France, Germany
	
	Study dates: NR
	
	Funding source: Takeda Italia
	
	Interventions:
	- Candesartan 8-16 mg qd (n = 115)
	- Enalapril 10-20 mg qd (n = 124)
	
	Dose titration/co-interventions:
	- Higher dose of study drug used after 4 wk if BP not controlled (≥ 140/90 mmHg or DBP reduced < 10 mmHg and SBP < 20%)
	-After 4 additional wk, if BP not controlled, HCTZ 12.5 mg added and titrated up to 25 mg as needed
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: Yes
	
	Baseline/run-in period: 2- to 4-week run-in with single-blind placebo,
		Number of patients:
		- Screened for inclusion: 304
		- Eligible for inclusion: 239
		- Randomized: 239
		- Began treatment: 239
		- Completed treatment: 182
		- Withdrawals/losses to followup: 57 (19 due to AEs, 12 withdrew consent, 14 lack of efficacy, 12 "other")
		- ITT population = 196
		- Per-protocol population = 145
		
		Age:
		Mean (SD): 52.9
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 74/196 (38%)
		Male: 122/196 (62%)
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Seated trough BP measured using a mercury sphygmomanometer; 3 readings taken at 1-min intervals after patient seated for 5 min of rest. Mean of 3 readings used.
		
		     Candesartan Enalapril
		     (n = 91) (n = 105)
		SBP 163.1 ± 9.7 162.4 ± 8.9
			1) Blood pressure:
			BP was measured at the end of placebo period and at 4, 8, 12, 24, 36, and 48 weeks
			
			Mean post-treatment BP values NR
			
			Mean changes in SBP and DBP from baseline to last available timepoint (ITT population): No significant difference between the two treatments (no quantitative data or statistical tests shown)
			
			Similar results (no significant between-group differences) for mean changes in SBP and DBP at 24 and 48 wk in the per-protocol population (no quantitative data or statistical tests shown)
			
			The percentage of patients achieving BP normalization (defined as < 140/90 mmHg):
			Candesartan: 60.4%
			Enalapril: 60.0%
			No statistical testing shown; not clear whether ITT or per-protocol population
			
			2) Rate of use of a single antihypertensive agent for BP control:
			ITT analysis (n = 196 patients)
			Patients receiving study drug alone (with no HCTZ):
			Candesartan: 54.3%
			Enalapril: 45.8%
			
			Per-protocol analysis (n = 145 patients)
			Patients receiving study drug alone (with no
				General comments:
				- Emphasis on a non-biased approach and interpretation of results
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Would have been compelling if article included the mean BP measurements taken at 4, 8, 12, 24, 36, and 48 wk
				- May be error in randomization, as female low in the enalapril group (34% vs. 42% in candesartan group)
				
				Applicability:
				- No data on race/ethnicity of subjects
				- Restricted to patients with LVH

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	previous antihypertensive treatments withdrawn **Duration of treatment:** 48 weeks **Duration of post-treatment followup:** NA	DBP 101.5 ± 3.9 101.0 ± 4.4 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age 25-70 yr - Hypertension (SBP 150-200 mm Hg and DBP 95-115 mm Hg at end of placebo run-in period) - LVH (LVMI > 120g/m^2 in men and LVMI > 100g/m^2 in women) **Exclusion criteria:** - Adequate M-mode echo cardiogram not obtained - Clinical or echocardiographic evidence of significant valvular disease - Coronary heart disease - CHF - Dilated LV chamber (end diastolic diameter > 60 mm)	HCTZ): Candesartan: 61.0% Enalapril: 53.4% **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** There were no serious AEs Adverse events: |	N (%)	Withdrawals (n)
---	---	---
Candesartan	16 (14%)	6
Enalapril	24 (19%)	13 | **6) Specific adverse events:** Cough occurred in 9% of enalapril patients and in 3% of candesartan patients **7) Persistence/adherence:** Compliance measured by counting return tablets; no results reported. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LV mass estimated by Devereux's formula and normalized for body surface LVMI (g/m^2) measurements by echocardiographic and Doppler (ITT population): |	Baseline	Treatment (last available timepoint)
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Candesartan (n = 91)	141.0 ± 24.1	126.0 ± 32.4
Enalapril	143.4 ± 27.5	130.1 ± 29.3		

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			(n = 105)	
			The decrease in LV mass was accomplished by substantial reduction in interventricular septum and posterior wall thickness in both treatment groups. **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

De Rosa, Cardace, Rossi, et al., 2002
 	
#4470
	Geographical location: Naples, Italy
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Enalapril 5-20 mg (n = 24)
	- Losartan 12.5-50 mg (n = 26)
	
	Dose titration:
	- Enalapril started at 5 mg daily, titrated q 7 days, as tolerated, to 10 mg and 20 mg daily if DBP ≥ 90
	- Losartan started at 12.5 mg daily, titrated q 7 days, as tolerated, to 25 mg and 50 mg daily if DBP ≥ 90
	
	No co-interventions permitted
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes (double-dummy)
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2-wk placebo run-in
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 50
		- Began treatment: 50
		- Completed treatment: 42
		- Withdrawals/lost to followup: 8 (3 due to AEs, 2 lost to followup, 2 non-responders, 1 other)
		
		Age:
		For randomized group n = 50
		- Mean (SD): 52 yrs (7.7)
		- Median: NR
		- Range: NR
		
		For analyzed group completing study n = 42
		- Mean: 55 (SD not reported)
		- Range: 52-62
		-
		Sex (n [%]): (#s given are for analyzed 42 pts)
		Female: 21 (50%)
		Male: 21 (50%)
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Trough seated BP measured using a standard mercury sphygmomanometer after 5 min rest; average of 3 readings taken at 1-min intervals
			1) Blood pressure:
			Seated trough mean difference in BP (95% CI) at 3 yrs: p value - NS
			Losartan (n = 22)
			    Pre- 155/103
			    Post- 140/92
			    Mean diff SBP -14.5mmHg (-22.6, -6.4)
			    Mean diff DBP -10.5mmHg (-13.5, -7.6)
			
			Enalapril (n = 20)
			    Pre- 159/102
			    Post- 144/91
			    Mean diff SBP -14.6 (-27.4, -1.7)
			    Mean diff DBP -11.4 (-14.8, -8.1)
			
			2) Rate of use of a single antihypertensive agent for BP control: NA (no other antihypertensive meds permitted)
			
			3) Mortality: NR
			
			4) Morbidity:
			No quantitative data reported. Number of patients assessed unclear for most measures.
			
			QOL: "battery-of-scales" QOL instrument at baseline and after 12 wk of therapy. There were no statistical differences between the two therapies in the domains of general health, sexual functioning, or for the other scales of quality of life.
			
			For symptom bother, there was no between-group difference in HA or flushing, but there was
				General comments:
				- 2/26 pts in losartan group withdrew due to ineffective therapy and were excluded from analysis; 0/24 were excluded from enalapril for this reason. This biases BP results in losartan's favor.
				
				Quality assessment:
				Overall rating: Fair
				
				Comments: See comments above and below.
				
				Applicability:
				- Small number of patients from single center in Italy
				- Minimal information on patient characteristics
				- Analyzed according to treatment completion and excluded those in whom therapy was ineffective

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Duration of treatment: 3 years
	
	Duration of post-treatment followup: NA
		
		SBP Losartan Enalapril
		SBP 155 ± 17 159 ± 19
		DBP 103 ± 4 102 ± 5
		
		Concurrent medications (n [%]): NR; no non-study antihypertensives permitted
		
		Comorbidities (n [%]): See Exclusion criteria (below); otherwise NR
		
		Recruitment setting: Outpatient clinic
		
		Inclusion criteria:
		- Essential HTN
		- WHO stage II (SBP >140 and/or DBP > 90)
		
		Exclusion criteria:
		- Sig cardiovascular, cerebrovascular, renal, or hepatic disease.
		- Recent MI
		- Secondary HTN
		- "Clinicially significant lab abnormalities"
			a significantly higher incidence of "bother due to cough" in the enalapril patients than in losartan patients after 3 years of treatment, regardless of whether the symptom was present at baseline (12% vs. 2%; p = 0.01).
			
			5) Safety:
			Withdrawals due to AEs:
			Losartan: 0/26
			Enalapril: 3/24 (12.5%)
			
			6) Specific adverse events:
			In patients completing treatment (n = 42), frequency of cough was:
			- Losartan 2%
			- Enalapril 12% (p = 0.01)
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function:
			LV mass index change pre-/post- (baseline to 3 yr) using 2-D echocardiogram (g/m^2):
			
			                      Change
			        Pre- Post- (95% CI)
			Losartan: 176 ± 24 124 -52 (-110.5, 32)
			Enalapril: 170 ± 19 129 -41(-90.3, 21.9)
			P-value for between-group difference NR
			
			12) Creatinine/GFR:
			GFR measured by renal scintigraphy at baseline and 3 yr (mL/min ± SD):
			
			|
				Losartan	Enalapril

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Baseline	96.5 ± 32.3	94.8 ± 31.1
3 yr	108.6 ± 31.1	99.8 ± 19.6
P-value	< 0.005	0.085	 **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Degli Esposti, Degli Esposti, Valpiani, et al., 2002
 	
#12800
 	
(1-year results)
 	
and
 	
Degli Esposti, Sturani, Di Martino, et al., 2002
 	
#12810
 	
(3-year results)
	Geographical location: Ravenna, Italy (databases of a local health unit)
	
	Study dates: Jan-Dec 1997
	
	Funding source: Local health unit and Merck Sharp & Dohme Italia S.p.A.
	
	Interventions:
	ACEIs (n = 4986)
	ARBs (n = 317)
	CCBs (n = 4680)
	Diuretics (n = 4341)
	Beta-blockers (n = 2459)
	
	Study design:
	Retrospective cohort study
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: NA
	
	Baseline/run-in period: NA
	
	Duration of treatment: NR
	
	Duration of post-treatment followup: Data reported for 1 and 3 years
		Number of patients:
		- Screened for inclusion: 19,124
		- Eligible for inclusion: 16,783
		- Randomized: NA
		- Began treatment: NA
		- Completed treatment: NA
		- Withdrawals/losses to followup: NA
		
		Age (ACEIs and ARBs):
		Mean: 56.1
		Median: NR
		Range: 20-105
		
		Sex (ACEIs and ARBs, %]):
		Female: 52.6%
		Male: 47.4%
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure: NR
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]):
		              ACEIs ARBs
		Cardiopathy 1.3% 0.9%
		Diabetes 2.1% 1.3%
		Asthma/COPD 1.2% 1.3%
		Previous hosp
		for CV disease 7.9% 8.2%
		≥ 2 comorbidities 1.6% 3.2%
		
		Recruitment setting: Database of local health unit
		
		Inclusion criteria:
		- New user of antihypertensive drug (not prescribed any antihypertensive drugs during previous 12 mo)
		- Age ≥ 20 years
		- Received first prescription for a diuretic, beta-blocker, CCB, ARB, or ACEI during study period
			1) **Blood pressure:** NR
			
			2) **Rate of use of a single antihypertensive agent for BP control:** NR
			
			3) **Mortality:** NR
			
			4) **Morbidity:** NR
			
			5) **Safety:** NR
			
			6) **Specific adverse events:** NR
			
			7) **Persistence/adherence:**
			Persistence described under heading of "continuing," "switching," and "discontinuing" therapy; arbitrary minimum of 273 days used as cutoff.
			
			Continuing defined as persisting with original drug therapy, even if combined with an agent from another class.
			
			Switching defined as persisting with drug treatment, but switching to a drug of a different class.
			
			Discontinuing defined as giving up drug therapy altogether.
			
			1-year data:
			          Continue Switch Discontinue
			ACEIs 30.7% 9.4% 59.9%
			ARBs 33.4% 24.6% 42.0%
			
			Persistence was related to older age, taking medication for heart disease or diabetes, history of previous hospitalizations for CV events, and presence of ≥ 2 comorbidities.
			
			3-year results: No quantitative data reported. Persistence was related to older age, young general practitioner, male general practitioner, and male sex. ARBs had better persistence throughout the followup period, but precise
				General comments:
				- Small sample sizes for ARBs at 1 year (n = 317) and 3 years (n = 198)
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Non-random allocation to drugs
				- No data on comparability of patients on ACEIs versus ARBs
				- Funded by pharmaceutical company
				
				Applicability:
				- Study period soon after introduction of ARBs; early use may not reflect current use patterns

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: - Prescriptions for ≥ 2 antihypertensive agents or for a combination agent involving ≥ 2 classes - History of ≥ 3 prescriptions for cardiovascular, antidiabetes, or antiasthmatic/COPD drugs over previous 12 mo	estimates could not be derived from Figure 2. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Derosa, Cicero, Ciccarelli, et al., 2003 **#3140**	**Geographical location:** Pavia, Italy **Study dates:** NR **Funding source:** NR **Interventions:** - Perindopril 4 mg (n = 49) - Candesartan 16 mg (n = 47) Dose titration and co-interventions: No titration; no co-interventions allowed **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: NR - Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes **Baseline/run-in period:** 4-wk placebo run-in **Duration of treatment:** 12 mo	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 96 - Began treatment: 96 - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** Mean (SD): 54 median: NR Range: NR **Sex (n [%]):** Female: 49 (51%) Male: 47 (49%) **Race/ethnicity (n [%]):** NR, but presumably 100% Caucasian **Baseline blood pressure:** Trough seated BP measured 3 times at 1-min intervals after patient rested 10 min using a standard mercury sphygmomanometer (Erkameter 3000); average of 3 readings used <table><tr><td></td><td>Perindopril</td><td>Candesartan</td></tr><tr><td>SBP</td><td>147 ± 6</td><td>148 ± 6</td></tr><tr><td>DBP</td><td>94 ± 4</td><td>93 ± 5</td></tr></table>	**1) Blood pressure:** Mean change (± SD) in BP from baseline to 12 mo: <table><tr><td></td><td>Perindopril</td><td>Candesartan</td></tr><tr><td>SBP</td><td>-13 ± 4.5</td><td>-12 ± 4.1</td></tr><tr><td>DBP</td><td>-11 ± 3.6*</td><td>-8 ± 2.9</td></tr></table> * p < 0.05, perindopril vs. candesartan; no other between-group comparisons statistically significant 1-mo, 6-mo, 1-mo posttreatment followup data also reported **2) Rate of use of a single antihypertensive agent for BP control:** NA (no additional agents allowed) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Any AE: Perindopril: 5/49 (10%) Candesartan: 3/47 (6%) No serious AEs. No withdrawals due to AEs.	**General comments:** - Probably underpowered study **Quality assessment:** Overall rating: Good **Applicability:** - Very early diabetes with mild hypertension - Patients in academic medical center in Italy - Probably underpowered to detect true differences between the groups

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of post-treatment followup: Patients followed for an additional month at the end of the trial after discontinuation of study meds	**Concurrent medications (n [%]):** Glibenclamide: 43% Glipizide: 30% Gliclazide: 28%	**6) Specific adverse events:** Perindopril (n = 49): 2 (4%) cough, 4 (8%) abnormal taste, 1 (2%) epigastric discomfort Candesartan (n = 47): 1 (2%) headache, 2 (4%) dizziness, 1 (2%) nausea	
		Comorbidities (n [%]): NR	**7) Persistence/adherence:** NR	
		Recruitment setting: Department of Internal Medicine and Therapeutics at a single university hospital **Inclusion criteria:** - Type 2 diabetes diagnosed < 6 mo before - Mild hypertension (DBP 90-105 without meds) - Non-smokers - Adequate glycemic control (HbA1c < 7.5%) with diet or oral hypoglycemic drugs - Not on hypocholesterolemic drugs - No retinopathy, neuropathy, or nephropathy **Exclusion criteria:** - Secondary hypertension - Malignant hypertension - Unstable angina - MI within 6 months - Liver disease - Renal disease - Contraindication to ACEI or ARB - Already receiving ACEI or ARB	**8) Lipid levels:** Values are mean ± SD: |	Perindopril	Candesartan	|---|---|---|	LDL baseline	120 ± 18	125 ± 15		LDL change 12 mo	-14 ± 7.4*	-4 ± 1.8		HDL baseline	43 ± 4	40 ± 5		HDL change 12 mo	-2 ± 0.5	+2 ± 0.4		TG baseline	160 ± 18	149 ± 10		TG change 12 mo	-22 ± 11.6	+2 ± 0.8	 * $p < 0.05$, perindopril vs. candesartan 6-mo and 1-mo posttreatment followup data also reported **9) Progression to type 2 diabetes:** All already have type 2 diabetes **10) Markers of carbohydrate metabolism/diabetes control:** Values are mean ± SD: |	Perindopril	Candesartan	|---|---|---|	HbA1c baseline	6.4 ± 0.9	6.5 ± 1.1		HbA1c change 12 mo	-0.2 ± 0.1	-0.2 ± 0.1		Fasting glucose baseline	155 ± 15	160 ± 13		

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Fasting glucose 1 yr −15 ± 4* −8 ± 2 * p < 0.05, perindopril vs. candesartan 6-mo and 1-mo posttreatment followup data also reported **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** Values are mean ± SD: Perindopril Candesartan AER/24 hr baseline 17 (10) 18 (11) AER/24 hr change 12 mo −8 ± 3.6 −8 ± 4.1 6-mo and 1-mo posttreatment followup data also reported	
Eguchi, Kario, and Shimada, 2003 **#3150**	**Geographical location:** Tochigi, Japan **Study dates:** NR **Funding source:** NR **Interventions:** - Candesartan (4-12 mg) (n = 37) - Lisinopril (5-20 mg) (n = 36) Dose titration/co-interventions: Initially, all patients treated with candesartan (4-8 mg) or lisinopril (5-10 mg) (choice of dose not explained). Dosage of candesartan was then increased by 4 mg and dosage of lisinopril by 5-10 mg for 4 wk up to the maximum. If response	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 73 - Began treatment: 73 - Completed treatment: NR - Withdrawals/losses to follow-up: NR; all 12 patients who experienced AEs were "excluded from the study" - Population analyzed = 61 **Age:** Mean (SD): 69.3 ± 7.4 Median: NR Range: NR **Sex (n [%]):** Female: 57% Male: 43%	**1) Blood pressure:** Mean seated trough BP at 12 wk: Candesartan Lisinopril (n = 61) (n = 61) SBP 148 ± 16 144 ± 18 DBP 79 ± 11 77 ± 9.8 No significant difference between groups (p-values NR) Other outcomes reported: 24-hr ABPM outcomes **2) Rate of use of a single antihypertensive agent for BP control:** Trichlormethazide added per protocol: Candesartan: 79% Lisinopril: 80% p = NS	**General comments:** - Meds taken before randomization (no clear run-in period described): ACEI 41% ARB 6.6% Diuretics 16% Calcium antagonist 64% None 6.6% **Quality assessment:** Overall rating: Poor Comments: - Protocol not clearly defined, blinding not reported, no washout after period 1 of crossover, imbalance in treatment groups (apparently due to more patients discontinuing lisinopril and not continuing to period 2)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	not satisfactory (BP systolic < 140 and BP diastolic < 90) at 4-8 wk, then trichlormethazide 1-2 mg added. At 12 wk, patients crossed over to the alternative drug as monotherapy, with dose titration and addition of diuretic repeated as above. **Study design:** RCT, crossover **Blinding:** - Patients: NR - Providers: NR - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 1-week "washout" after randomization **Washout period(s):** No washout between study periods **Duration of treatment:** 2 x 12-week treatment periods **Duration of post-treatment followup:** NA	**Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Seated trough BP measured after patient seated for 5 min rest using a standard mercury sphygmomano-meter Mean baseline values for analyzed population (n = 61): DBP: 163 ± 17 SBP: 85 ± 11 **Concurrent medications (n [%]):** **Comorbidities (n [%]):** Diabetes 48% Smoker 23% **Recruitment setting:** Clinic office **Inclusion criteria:** - Ambulatory, asymptomatic older patients with > 3 visits in a 14- to 28-day period with mean SBP > 150 mm Hg or mean DBP > 90 on > 2 occasions **Exclusion criteria:** - Serum creatinine > 2.5 mg/dL - Major stroke, congestive heat failure, malignancy or other severe concomitant disease - BP > 180/110 mm Hg on medication - Note: Patients with MI with preserved LV contractility and those with "minor" stroke were *not* excluded	**3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Patients with AEs requiring their "exclusion" from analysis: Candesartan: 2 patients (2.7%; 1 dim vision and 1 facial edema) Lisinopril: 10 patients (13.7%; 9 cough, 2 fatigue) (numbers given here as reported) **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	- Of the 61 patients analyzed, 35 received candesartan first and 26 lisinopril first - Patients with AEs (n = 12) excluded from efficacy analysis **Applicability:** - Apparently limited to Japanese patients in a single clinic

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Elliott, 1999
 	
#5950
 	
and
 	
Gavras and Gavras, 1999
 	
#6030
 	
and
 	
Levine, 1999
 	
#6020
 	
and
 	
Argenziano and Trimarco, 1999
 	
#6040
 	
and
 	
Breeze, Rake, Donoghue, et al., 2001
 	
#4660
	Geographical location: North America, Europe, and South Africa
	
	Study dates: NR
	
	Funding source: SmithKline Beecham Pharma (Collegeville, PA; since merged with GlaxoSmithKline, now GSK)
	
	Interventions:
	- Enalapril 5 mg qd, with titration up to 20 mg qd (n = 264)
	- Eprosartan 200 mg bid, with titration up to 300 mg bid (n = 264)
	
	Both groups: HCTZ 12.5-25 mg qd added at 12 wk if DBP ≥ 90)
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes (titration/maint)
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 3- to 5-wk single-blind placebo run-in
	
	Duration of treatment: 26 wk: 18-wk titration period + 8-wk maintenance period
	
	Duration of post-treatment followup: None
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 528
		- Began treatment: NR
		- Completed treatment: 447
		- Withdrawals/losses to followup: NR (≥ 16)
		
		Age:
		Mean (± SEM): 55.6 ± 0.7
		Median: NR
		Range: 23-84
		
		Sex (n [%]):
		Female: 56.5%
		Male: 43.5%
		
		Race/ethnicity (n [%]):
		Caucasian 456 (86%)
		Black 40 (8%)
		Asian 6 (1%)
		Other 26 (5%)
		
		Baseline blood pressure (± SEM);
		Sitting BP measured in triplicate "according to standard techniques"
		
		    Enalapril Eprosartan
		SBP 156.2 ± 0.9 156.4 ± 0.9
		DBP 101.2 ± 0.3 100.7 ± 0.3
		
		Baseline values also reported for ≥ 65 years subgroup and black subgroup
		
		Concurrent medications (n [%]):
		NR; concomitant use of medications know to affect BP prohibited
		
		Comorbidities (n [%]):
		Current smoker:
		Enalapril: 31 (12%)
		Eprosartan: 36 (14%)
			1) Blood pressure:
			Mean post-treatment BP values NR
			
			Overall study population
			Mean change in BP from baseline (at 26 wk):
			    Enalapril Eprosartan
			Sit SBP -14.7 -15.5 mm Hg
			Sit DBP -11.9 -12.9 mm Hg
			
			Response rates (DBP < 90 or DBP < 100 and a reduction of ≥ 10 mm Hg from baseline):
			    Enalapril Eprosartan
			12 wk 62.6% 70.3% (p < 0.05)
			26 wk 73.4% 81.7% (p < 0.02)
			
			≥ 65 years subgroup
			Mean change in BP from baseline (at 26 wk):
			    Enalapril Eprosartan
			Sit SBP -15.3 ± 2.2 -18.9 ± 2.1 (NS)
			Sit DBP -12.2 ± 1.1 -13.9 ± 1.1 (NS)
			
			Response rates:
			    Enalapril Eprosartan
			26 wk 48 (77.4%) 55 (87.3%) (NS)
			
			Black patient subgroup
			Mean change in BP from baseline (at 26 wk):
			    Enalapril Eprosartan
			Sit SBP -10.5 ± 3.7 -18.8 ± 3.5 (NS)
			Sit DBP -9.6 ± 2.4 -10.5 ± 1.9 (NS)
			
			Response rates:
			    Enalapril Eprosartan
			12 wk 5 (26.3%) 11 (52.4%) (p < 0.05)
			26 wk 8 (42.1%) 14 (66.7%) (p = 0.02)
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Eprosartan group: HCTZ added in 81 patients
			Enalapril group: HCTZ added in 81 patients
			
			3) Mortality:
			One death in eprosartan group; judged to be unrelated
				General comments:
				- An analysis comparing the subgroups < 65 years and ≥ 65 years of age found that the elderly subpopulation "mirrored the response of the study as a whole"
				- An analysis of a subgroup of 40 black patients found that the black subpopulation "mirrored the response of the study as a whole"
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Method of BP ascertainment not described
				- Uncertainty about number of withdrawals (enumerated those w/d for serious AE and cough; but not for any other causes, if any)
				- One report described 529 patients instead of 528; other minor discrepancies across reports
				
				Applicability:
				- No list of participating centers (described as multinational)
				- Poor description of subjects' comorbidities, although exclusion criteria suggest a comparatively healthy group

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

		See also Exclusion criteria, below
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Age ≥ 18 yr
		- Essential HTN (sitting DBP 95-114 mm Hg)
		
		Exclusion criteria:
		- Secondary forms of hypertension
		- Advanced hypertensive retinopathy
		- Sitting SBP > 200 mmHg
		- MI or CVA < 90 days
		- CHF or angina
		- Advanced AV conduction defects, ventricular tachyarrhythmias, bradycardia
		- Unstable DM
		- Clinically significant renal or hepatic disease
		- Other concurrent severe disease
		- Emphysema, chronic bronchitis, asthma with cough, URI < 2 wks
			4) Morbidity:
			One MI in eprosartan group, judged to be unrelated to treatment.
			
			The between-group differences in changes in Psychological General Well Being (PGWB) scores were -2.48 (95% CI -4.63 to -0.32) for the study end point and -0.79 (-2.72 to 1.15) for monotherapy end point.
			
			At monotherapy end point there were no significant differences between treatments (data not presented).
			
			5) Safety:
			
			               Enalapril Eprosartan
			Severe AE 32 (12.1%) 24 (9.1%)
			Tx-related 16 (6.1%) 10 (3.8%)
			Serious nonfatal 8 (3.0%) 4 (1.5%)
			≥ 1 AE 213 (80.7%) 201 (76.1%)
			
			≥ 65 years subgroup
			All AE 48 (77.4%) 46 (73.0%)
			All Serious 7 (11.3%) 4 (6.3%)
			Serious - w/d 1 1
			Serious - no w/d 3 0
			
			6) Specific adverse events:
			               Enalapril Eprosartan
			Definite cough 14 (5.4%) 4 (1.5%)
			Cough (p = 0.01) 59 (22.3%) 34 (12.9%)
			Pharyngitis 64 (24.2%) 44 (16.7%)
			Headache 37 (14.0%) 39 (14.8%)
			Rhinitis 43 (16.3%) 33 (12.5%)
			URI 43 (16.3%) 33 (12.5%)
			Myalgia 16 (6.1%) 25 (9.5%)
			Dyspnea 17 (6.4%) 14 (5.3%)
			Dizziness 21 (8.0%) 13 (4.9%)
			Fatigue 18 (6.8%) 13 (4.9%)
			
			*definite cough – persistent, non-productive (dry) cough assoc. with tx and not due to URI as judged by investigator
			
			7) Persistence/adherence: NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

			8) Lipid levels:
			
			      Eprosartan Enalapril
			      baseline end baseline end
			LDL-c 3.5±0.8 3.6±0.9 3.5±0.9 3.7±0.9
			HDL-c 1.4±0.3 1.4±0.4 1.4±0.4 1.4±0.3
			TG 1.6±1.0 1.6±1.1 1.6±1.0 1.7±1.1
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control:
			"Neither eprosartan nor enalapril significantly affected … blood glucose" at any time point.
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR:
			"The degree and direction of … renal function tests were comparable in both treatment groups."
			
			13) Proteinuria: NR	

Erkens, Panneman, Klungel, et al., 2005 **#12840**	**Geographical location:** 25 medium-sized cities in The Netherlands **Study dates:** Included patients received treatment between 1997 and 2001 **Funding source:** Novartis Pharma, B.V. (The Netherlands) **Interventions:** Diuretics (n = 458) Beta-blockers (n = 471) CCBs (n = 455) ACEIs (n = 412) ARBs (n = 447) **Study design:** Retrospective cohort study **Blinding:** - Patients: No - Providers: No	**Number of patients:** - Screened for inclusion: 48,234 - Eligible for inclusion: 2243 (after random selection of 500 per group and post-selection exclusions) - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA **Age:** Mean (SD): NR Median: NR Range: - 0-19: 1.6% - 20-39: 11.5% - 40-59: 42.6% - 60-79: 37.0% - ≥ 80: 7.4% **Sex (n [%]):** Female: 1276 (56.9%) Male: 967 (43.1%)	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** 1-yr persistence (defined as the % of patients who used a given drug for ≥ 270 days and had an additional drug dispensing in the 3 mo after the followup period): Diuretics: 33.0% Beta-blockers: 35.0% CCBs: 34.7% ACEIs: 59.7% ARBs: 62.0%	**General comments:** - High-quality administrative data in a population-based sample **Quality assessment:** Overall rating: Fair Comments: - Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs - Funded by pharmaceutical company **Applicability:** - Specific ACEIs and ARBs not identified

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NR **Duration of post-treatment followup:** Patients followed for 15 mo after their index data	**Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** Antidiabetic drugs: 11.3% Lipid-lowering drugs: 9.4% Antiasthmatic drugs: 14.2% **Comorbidities (n [%]):** Prior CV hospitalizations: 8.2% **Recruitment setting:** **-** Data drawn from community-based database linking drug-dispensing records from pharmacies and hospital discharge records - Patients receive first antihypertensive prescription from GP (85%), internist (5.8%), cardiologist (4.0), or other (5.2%) **Inclusion criteria:** - From base cohort (n = 48,234), patients selected who: (1) did not use antihypertensive drugs in the year before the index date; (2) were registered in the database for ≥ 1 yr before and ≥ 15 mo after their first prescription for antihypertensive drugs; and (3) received at least two prescriptions for antihypertensive drugs - From this group, 500 per drug class randomly drawn for analysis **Exclusion criteria:** Patients using fixed combination drugs	Persistence increased with male sex, increasing age, use of antidiabetic drugs, use of lipid-lowering drugs, and prior cardiovascular hospitalizations (all in univariable analyses) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Fogari, Mugellini, Zoppi, et al., 2002
 	
#4320
	Geographical location: Pavia, Italy
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Perindopril 4 mg daily (n = 42)
	- Losartan 50 mg daily (n = 43)
	
	No dose titration; no co-interventions specified
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 4-wk placebo run-in
	
	Duration of treatment: 12 wk
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 85
		- Began treatment: 85
		- Completed treatment: 82
		- Withdrawals/losses to followup: 3 (2 due to AEs, 1 failure to appear at visit)
		
		Age:
		Mean (SD): 58.4 (8.0)
		Median: NR
		Range: 46-64
		
		Sex (n [%]):
		Female: 40 (47%)
		Male: 45 (53%)
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Trough seated BP assessed using a standard mercury sphygmanometer; 3 readings taken at 1-min intervals after patient rested 10 min; average of 3 readings used
		
		        Perindopril Losartan
		SBP 163.2 ± 12.9 162.9 ± 12.6
		DBP 102.8 ± 6.1 102.7 ± 5.9
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]):
		100% type 2 diabetes
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Adult men and women
		- Documented mild-to-moderate essential HTN (DBP 90-110)
		- Concomitant type 2 diabetes in
			1) Blood pressure:
			Mean trough seated BP at 12 wk:
			        Perindopril Losartan
			SBP 146 ± 10 147 ± 11
			DBP 87 ± 5 88 ± 5
			p = 0.001 for all pre-/post- comparisons
			p = NS for between-treatment comparisons
			
			Mean change in BP at 12 wk:
			        Perindopril Losartan
			SBP -16 -15
			DBP -15 -14
			p < 0.001 for all pre-/post- comparisons
			p = NS for between-treatment comparisons
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			2 withdrawals due to AEs – treatment group(s) not specified
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			
			Mean HDL (mg/dL):
			      Baseline 12 wk p-value
			Perindopril 44 ± 5 46 ± 6 NS
			Losartan 44 ± 5 44 ± 6 NS
			
			Mean total cholesterol (mg/dL):
			      Baseline 12 wk p-value
			Perindopril 197 ± 23 186 ± 19 NS
			Losartan 191 ± 20 188 ± 19 NS
			
			Mean triglycerides (mg/dL):
			      Baseline 12 wk p-value
			Perindopril 142 ± 49 127 ± 44 NS
				General comments:
				None
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Numbers screened and eligible NR
				- AEs not well reported
				- Details of dose titration and concomitant med use (if any) not given
				
				Applicability:
				- 100% of study population also has type 2 diabetes
				- Racial diversity not described (? 100% Caucasian)
				- Recruitment setting(s) not described
				- 44 patients never treated before for hypertension

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

		stable metabolic control with diet and oral hypoglycemic agents	Losartan 145 ± 50 140 ± 48 NS
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control:
			Mean FBG (mg/dL):
			          Baseline 12 wk p-value
			Perindopril 112 ± 7.3 107 ± 6.9 NS
			Losartan 113 ± 7.5 111 ± 7.0 NS
			
			Mean HbA1c (%):
			          Baseline 12 wk p-value
			Perindopril 7.2 ± 1.9 7.1 ± 1.7 NS
			Losartan 6.9 ± 2.0 7.0 ± 1.8 NS
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR:
			Mean serum creatinine (mg/dL):
			          Baseline 12 wk p-value
			Perindopril 1.1 ± 0.4 1.1 ± 0.4 NS
			Losartan 1.1 ± 0.5 1.1 ± 0.4 NS
			
			13) Proteinuria: NR	

Fogari, Mugellini, Zoppi, et al., 2004
 	
#2490
	Geographical location: NR (authors based in Pavia, Italy)
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Valsartan 160 mg (n = 75)
	- Enalapril 20 mg (n = 75)
	
	No dose titration; no co-interventions permitted
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: No
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 150
		- Began treatment: 150
		- Completed treatment: 140
		- Withdrawals/losses to followup: 6 (2 due to lack of compliance, 3 due to missed clinic visit, and 1 due to concomitant illness)
		
		Age:
		Mean (SD): 70.3 ± 5.7
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 79/144 (54%)
		Male: 65/144 (46%)
			1) Blood pressure:
			Trough seated BP at 16 wk:
			      Valsartan Enalapril
			      (n = 73) (n = 71) P-value
			SBP 147.3 ± 7.3 150.2 ± 8.0 < 0.01
			DBP 87.1 ± 4.7 90.4 ± 5.0 < 0.001
			
			BP normalized at 16 wk (DBP < 90 mm Hg):
			Valsartan: 60.2%
			Enalapril: 52.1%
			p = NS
			
			2) Rate of use of a single antihypertensive agent for BP control:
			See immediately above on % of patients who normalized at 16 wk on monotherapy.
			
			3) Mortality: NR
				General comments:
				None
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Not everyone blinded
				- No titration for increase blood pressure
				
				Applicability:
				- Many comorbidities excluded in this elderly population and again comorbidities not presented
				- No data on race/ethnicity of subjects

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Providers: No - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2-wk run-in; previous anti-HTN treatment withdrawn **Duration of treatment:** 16 wk **Duration of post-treatment followup:** NA	**Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Trough seated BP measured using a standard mercury sphygmomano-meter after patient rested in sitting position for 5 min; mean of 3 measurement taken at 2-min intervals used 　　　　Valsartan　　Enalapril SBP　165.9 ± 7.3　165.8 ± 6.8 DBP　100.8 ± 3.7　100.9 ± 3.9 **Concurrent medications (n [%]):** NR; concomitant drugs with antihypertensive properties prohibited **Comorbidities (n [%]):** NR **Recruitment setting:** Outpatient clinics **Inclusion criteria:** Outpatients 61-80 years of age with mild-moderate hypertension (DBP ≥ 95 and ≤ 110) at end of 2-wk run-in **Exclusion criteria:** - Secondary arterial hypertension, sitting systolic blood pressure > 200, malignant hypertension, K_W retinopathy III or IV, a hx of HTN encephalopathy - CVA within 6 months, previous or current heart failure, MI within 6 months, angina, valvulopathy or relevant arrythmia - Hepatic or renal dysfunction - Clinical hypo or hyperthyroidism - Known hypersensitivity to ACEI or ARB	**4) Morbidity:** NR **5) Safety:** Any AE: Valsartan: 5 (6.8%) Enalapril: 9 (12.6%) No serious AEs that were considered to be drug-related **6) Specific adverse events:** Cough n = 4 enalapril and n = 1 valsartan HA　V = 2 and E = 2 Nausea V = 1 E = 2 **7) Persistence/adherence:** "Patient compliance to both treatments was satisfactory" (no quantitative data reported) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Fogari, Zoppi, Preti, et al., 2001 **#4790**	**Geographical location:** Pavia, Italy **Study dates:** NR **Funding source:** NR **Interventions:** - Trandolapril 2 mg daily (n = 45) - Losartan 50 mg daily (n = 44) **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 4-wk placebo run-in period **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 89 - Began treatment: 89 - Completed treatment: 89 - Withdrawals/losses to followup: NA **Age:** Mean (SD): 55.5 (2) Median: NR Range: 51-60 **Sex (n [%]):** Female: 89 (100%) Male: 0 **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Seated trough BP measured using a standard mercury sphygmanometer; mean of 3 readings at 1-min intervals after 10 min rest <table><tr><td></td><td>Trandolapril</td><td>Losartan</td></tr><tr><td>SBP</td><td>162.1 ± 12</td><td>160.6 ± 12</td></tr><tr><td>DBP</td><td>101.2 ± 5</td><td>100.5 ± 5</td></tr></table> **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Mild-moderate essential HTN (DBP 90-110 mm Hg - Postmenopausal women (defined by cessation of menses ≥ 1yr; confirmed by: (1) plasma FSH > 20 U/L; (2) FSH > LH levels; and (3) plasma 17-β-estradiol < 50 pmol/L)	**1) Blood pressure:** Mean trough seated BP at 12 wk: <table><tr><td></td><td>Trandolapril</td><td>Losartan</td></tr><tr><td>SBP</td><td>145.2 ± 10</td><td>145.5 ± 11</td></tr><tr><td>DBP</td><td>88.1 ± 4</td><td>88.6 ± 5</td></tr></table>p < 0.01 for all pre-/post- comparisons p = NS for between-treatment comparisons Mean change in BP at 12 wk: <table><tr><td></td><td>Trandolapril</td><td>Losartan</td></tr><tr><td>SBP</td><td>-17</td><td>-15</td></tr><tr><td>DBP</td><td>-13</td><td>-12</td></tr></table>p < 0.01 for all pre-/post- comparisons p = NS for between-treatment comparisons **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Mean HDL (mg/dL): <table><tr><td></td><td>Baseline</td><td>12 wk</td><td>p-value</td></tr><tr><td>Trandolapril</td><td>50 ± 15</td><td>50 ± 16</td><td>NS</td></tr><tr><td>Losartan</td><td>49 ± 16</td><td>48 ± 17</td><td>NS</td></tr></table> Mean total cholesterol (mg/dL): <table><tr><td></td><td>Baseline</td><td>12 wk</td><td>p-value</td></tr><tr><td>Trandolapril</td><td>231 ± 31</td><td>226 ± 29</td><td>NS</td></tr><tr><td>Losartan</td><td>227 ± 33</td><td>224 ± 31</td><td>NS</td></tr></table> Mean triglycerides (mg/dL): <table><tr><td></td><td>Baseline</td><td>12 wk</td><td>p-value</td></tr><tr><td>Trandolapril</td><td>128 ± 59</td><td>125 ± 57</td><td>NS</td></tr><tr><td>Losartan</td><td>120 ± 51</td><td>123 ± 50</td><td>NS</td></tr></table> **9) Progression to type 2 diabetes:** NR	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Numbers screened and eligible NR - AEs not well reported - Details of dose titration and concomitant med use (if any) not given **Applicability:** - 100% of study population post-menopausal women - Racial diversity not described (? 100% Caucasian) - Recruitment setting(s) not described

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: - Hormone replacement therapy < 6 mo - Diabetes mellitus, obesity, smoking, MI, or stroke < 6 mo - History of breast cancer or thromboembolic disease - Major systemic diseases - Any condition that would require use of concomitant medications	**10) Markers of carbohydrate metabolism/diabetes control:** Mean FBG (mg/dL): 　　　　　　　Baseline　12 wk　　p-value Trandolapril　92 ± 10　89 ± 10　NS Losartan　　　93 ± 9　　92 ± 10　NS Mean glucose infusion rate (GIR) (mg/min/kg): 　　　　　　　Baseline　　12 wk　　　p-value Trandolapril　6.67 ± 0.56　7.99 ± 0.65　< 0.05 Losartan　　　6.74 ± 0.47　6.96 ± 0.50　NS p = significant (but not specified) for between-group comparison **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Franke, 1997 **#11930**	**Geographical location:** Saarlouis, Germany **Study dates:** NR **Funding source:** NR **Interventions:** - Placebo (n = 65) - Candesartan 4 mg (n = 66) - Candesartan 8 mg (n = 68) - Candeartan 12 mg (n = 65) - Enalapril 10 mg (n = 71) No dose titration; no co-interventions **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: Yes	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 364 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR (11 due to AEs, rest uncertain) - ITT population = 335 **Age:** Mean (SD): NR Median: NR Range: NR **Sex (n [%]):** NR **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR Seated trough BP measured using a fully automated device (Bosotron 2) Baseline values NR	**1) Blood pressure:** Baseline BP values NR (except DBP in Figure 1) Mean post-treatment BP values NR Mean changes (± SD) in seated trough DBP (mm Hg) at 12 wk: Candesartan 4 mg (n = 66):　-8.4 ± 10.5 Candesartan 8 mg (n = 68):　-10.5 ± 9.9 Candesartan 12 mg (n =65):　-10.0 ± 10.0 Enalapril 10 mg (n = 71):　　-10.6 ± 9.8 No between-group statistical results shown Response rates (reduction in seated DBP of ≥ 10 mm Hg and/or seated DBP < 90 mm Hg): Candesartan 4 mg (n = 66):　53.0% Candesartan 8 mg (n = 68):　69.1% Candesartan 12 mg (n =65):　NR Enalapril 10 mg (n = 71):　　69.0% No between-group statistical results shown **2) Rate of use of a single antihypertensive agent for BP control:** No other antihypertensives permitted	**General comments:** - Short report with minimal details **Quality assessment:** Overall rating: Poor Comments: - Extremely brief, few details **Applicability:** - Minimal information provided about study population, recruitment sites, etc.

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Was allocation concealment adequate?: NR **Baseline/run-in period:** Washout of at least 2 weeks, followed by 2-week placebo run-in **Duration of treatment:** 12 weeks **Duration of post-treatment followup:** NA	**Concurrent medications (n [%]):** NR; concomitant treatment with other antihypertensives not permitted **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age 18-70 yr - Mild-to-moderate essential hypertension (sitting DBP 95-114 mmHg) **Exclusion criteria:** None specified	**3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 186 adverse events, equally distributed among all groups Patients experiencing ≥ 1 AE: Candesartan groups: 28-33% Enalapril: 35% Withdrawals due to AEs: 11 (treatment groups not specified) **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Ghiadoni, Magagna, Versari, et al., 2003 **#3330**	**Geographical location:** NR **Study dates:** June 1999-Dec 2001 **Funding source:** NR **Interventions:** Multi-therapy trial (nifedipine, amlodipine, atenolol, nebivolol, telmisartan, and perindopril); total study was 40 normotensive controls and 180 treated patients	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 180 - Began treatment: 180 - Completed treatment: 168 - Withdrawals/losses to followup: 12, all due to treatment failure (required additional drugs beyond those specified in study protocol) **Age:** Mean (SD): 50.5 ± 10	**1) Blood pressure:** At 6 months: |	Telmisartan	Perindopril | SBP 133 ± 10 134 ± 10 DBP 86 ± 5 86 ± 6 Responders at 6 mo (BP < 140/90 mm Hg): Telmisartan: 22/29 (76%) Perindopril: 22/28 (79%) **2) Rate of use of a single antihypertensive agent for BP control:** HCTZ added in 21% of telmisartan patients (6/29)	**General comments:** - Patients in multiple arms with small control group **Quality assessment:** Overall rating: Poor Comments: - No comment on blinding of endpoints - Study population not well defined (how they were recruited, which patients from which groups dropped out, etc.)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	- Telmisartan 80 to 160 mg (n = 29)
	- Perindopril 2 to 4 mg (n = 28)
	
	HCTZ 12.5 mg added if needed to each compound
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: NR
	- Providers: NR
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: None
	
	Duration of treatment: 6 months
	
	Duration of post-treatment followup: NR
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 22/57 = 37%
		Male: 36/57 = 63%
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Mean of 3 measurements taken at 3-min intervals using an automatic digital device (Omron HEM-705CP)
		
		        Telmisartan Perindopril
		SBP 151 ± 10 153 ± 9
		DBP 100 ± 7 100 ± 6
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: Outpatient clinics
		
		Inclusion criteria:
		- Patients with essential hypertension who were never treated or had discontinued treatment for HTN
		- Non-smokers or < 5 cigarettes per day
		- Alcohol consumption < 50 mg/day
		
		Exclusion criteria:
		- Diabetes
		- Renal dysfunction
		- Total cholesterol > 240
			and 25% of perindopril patients (7/28)
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety: NR
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence:
			164 out of 180 – 16 BP rose too high to continue in study protocol
			
			8) Lipid levels:
			Total cholesterol:
			           Telmisartan Perindopril
			Baseline 218 ± 24 214 ± 252
			6 mo 216 ± 21 209 ± 21
			
			HDL:
			           Telmisartan Perindopril
			Baseline 53 ± 15 53 ± 11
			6 mo 52 ± 14 53 ± 9
			
			LDL:
			           Telmisartan Perindopril
			Baseline 136 ± 16 131 ± 18
			6 mo 134 ± 17 128 ± 15
			
			9) Progression to type 2 diabetes: Plasma glucose levels remained essentially unchanged (see immediately below)
			
			10) Markers of carbohydrate metabolism/diabetes control:
			Plasma glucose:
			           Telmisartan Perindopril
			Baseline 97 ± 8 96 ± 7
			6 mo 97 ± 8 97 ± 5
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR
				- No data on race/ethnicity of subjects
				- No data on safety/adverse events
				
				Applicability:
				- Limited by few comorbidities and multiple comparisons

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Gregoire, Moisan, Guibert, et al., 2001 **#5090**	**Geographical location:** 173 pharmacies across Canada **Study dates:** Feb 1996-Oct 1997 **Funding source:** Merck Frosst Canada **Interventions:** - Losartan (n = 80) - ACEI (n = 369) - CCB (n = 214) **Study design:** Prospective cohort study **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: Yes (research assistants unaware of study's objectives telephoned participants) **Was allocation concealment adequate?:** NR **Baseline/run-in period:** NA **Duration of treatment:** NR **Duration of post-treatment followup:** 3 months (assessments at baseline, 1mo, and 3mo)	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 692 recruited - Completed treatment: 663 - Withdrawals/losses to followup: 29 (9 lost to followup, 20 discontinued before end of study for reasons other than AEs) **Age:** Mean (SD): 58.3 Median: NR Range: 20.4-87.7 **Sex (n [%]):** Female: 369 (55.7%) Male: 294 (44.3%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** 173 pharmacies in Canada **Inclusion criteria:** - HTN patients ≥ 18 yr - Received 1st prescription for losartan, ACEI, or CCB as hypertensive monotherapy **Exclusion criteria:** - Pregnant women - Taking other anti-HTN meds - Taking meds for CHF or angina - Previously given samples of study medication by their physicians	1) **Blood pressure:** NR 2) **Rate of use of a single antihypertensive agent for BP control:** NR 3) **Mortality:** NR 4) **Morbidity:** NR 5) **Safety:** ≥ 1 AE related to antihypertensive medication: Losartan: 42/80 (52.5%) ACEI: 222/369 (60.2%) CCB: 149/214 (69.6%) Odds of reporting an AE were significantly higher among patients treated with an ACEI (adjusted odds ratio = 1.78; 95% CI, 1.02 to 3.12) or a CCB (2.65; 1.47 to 4.78) than among patients treated with losartan. Estimates adjusted for age, sex, level of education, number of symptoms due to health problems pereived the week prior to entering the study, prior use of antihypertensive drugs, current use of any other medication, insurance coverage, and duration of hypertension). 6) **Specific adverse events:** Specific AEs (numbers are n [%]): |	Losartan	ACEI	CCB
---	---	---	---
Dizziness	16 (20)	49 (13.3)	51 (23.8)
Headache	11 (13.8)	53 (14.4)	49 (22.9)*
Dry cough	4 (5.0)	55 (14.9)*	5 (2.3)
Tiredness	4 (5.0)	23 (6.2)	15 (7.0)
Nausea	2 (2.5)	19 (5.1)	17 (7.9)*
Dry mouth	4 (5.0)	19 (5.1)	11 (5.1)
Swollen ankles	2 (2.5)	1 (0.3)	27 (12.6)* | * Adjusted odds of experiencing AE significantly greater than with losartan (see Table 3 for details) 7) **Persistence/adherence:** NR 8) **Lipid levels:** NR	**General comments:** - Obvious limitations from prospective cohort design with no info on those screened but not included - Statistically significant differences at baseline between 3 groups with respect to proportion who were "new users" vs. "discontinuers" and numbers who switched previous medication due to AEs and uncontrolled hypertension - No data on BP **Quality assessment:** Overall rating: Poor Comments: - Numbers screened and eligible NR - AEs relatively well reported - Adjustment generally good, but lacks adjustment for comorbid conditions (e.g., CHF) which could confound presence of AEs **Applicability:** - No assessment of severity of disease or comorbidities - No adjustment or evaluation for comorbitiies or severity of disease - Patients selected by pharmacies - No blood pressure data

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			9) Progression to type 2 diabetes: NR	
			10) Markers of carbohydrate metabolism: NR	
			11) LV mass/function: NR	
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Hasford, Mimran, and Simons, 2002 **#4090**	**Geographical location:** France, Germany, and UK **Study dates:** Initial antihypertensive prescription given Oct 1997-Sep 1998; patients followed retrospectively for 1 yr **Funding source:** Sanofi-Synthelabo and Bristol-Myers Squibb **Interventions:** Monotherapy with one of the following single agents: - ACEIs: 333 - Irbesartan: 380 - Losartan: 188 - Valsartan: 69 - Candesartan: 82 - Eprosartan: 35 - Beta-blockers (BBs): 441 - Calcium channel blockers (CCBs): 466 - Diuretics: 422 Dose titration and co-interventions: Dose titration of initial medication allowed **Study design:** Retrospective cohort database study Matched those initially not prescribed irbesartan to those prescribed irbesartan by diabetes, angina, CVA, CHF, MI **Blinding:** - Patients: NA - Providers: NA - Assessors of outcomes: NA **Was allocation concealment adequate?:** NA	**Number of patients:** - Screened for inclusion: 3026 - Eligible for inclusion: 2416 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NR **Age:** Mean (SD): 60.3 Median: NR Range: NR **Sex (n [%]):** Female: 1269 (54%) Male: 1147 (46%) **Race/ethnicity (n [%]):** NR, presumably 100% Caucasian **Baseline blood pressure:** Method of assessing BP not described <table><tr><td></td><td>SBP</td><td>DBP</td></tr><tr><td>ACEIs</td><td>159.8 ± 22.5</td><td>94.6 ± 14.1</td></tr><tr><td>Irbesar-tan</td><td>164.3 ± 22.4</td><td>93.5 ±16.7</td></tr><tr><td>Losartan</td><td>160.4 ± 19.5</td><td>91.4 ± 13.8</td></tr><tr><td>Other ARBs</td><td>164.7 ± 21.8</td><td>95.9 ± 20.6</td></tr><tr><td>BBs</td><td>162.2 ± 23.6</td><td>94.4 ± 14.4</td></tr><tr><td>CCBs</td><td>162.9 ± 22.1</td><td>93.6 ± 17.5</td></tr><tr><td>Diuretics</td><td>160.7 ± 20.4</td><td>93.8 ± 12.6</td></tr></table> **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR	**1) Blood pressure:** BP reduction not a predefined study outcome Minimal results reported for subgroup of all patients with on-treatment BP data (n = 717); precise timepoint(s) of BP measurement(s) not specified; not clear whether restricted to patients who persisted with their original monotherapy General estimating equation (GEE) analysis showed that, in above-described subgroup, patients who were originally prescribed irbesartan had a greater average decrease in SBP (5.91 mm Hg; p = 0.053) and DBP (4.10 mm Hg; p = 0.090) than patients who were initially prescribed losartan and a greater average decrease in SBP (4.95 mm Hg; p = 0.022) and DBP (3.59 mm Hg; p = 0.053) than patients who were initially prescribed any of the remaining agents **2) Rate of use of a single antihypertensive agent for BP control:** Assessed on basis of prescriptions filled By 1 yr: 46.8% persisted with initially prescribed monotherapy (see below, under Persistence/adherence) 12.9% (9% irbesartan, 8% losartan, 13.6% all other agents) had switched to a different single agent 23.8% had been prescribed adjunctive antihypertension treatment in addition to initially prescribed med (16.1% irbesartan, 24.5% losartan, 25.3% all other agents) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 12.9% overall (9% irbesartan, 8% losartan,	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Does not report those who were lost from the system at 1 yr - Outcome measured not useful (lumped together multiple reasons for not being on monotherapy after 1 yr) **Applicability:** - Does not report prevalence of the comorbidities patients were matched on (diabetes, angina, CVA, CHF, MI)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Baseline/run-in period: NA **Duration of treatment:** 1-yr follow up after identification **Duration of post-treatment followup:** NA	**Recruitment setting:** Database study from a health database maintained in UK, France, and Germany that covers "hundreds" of practices that "represent the characteristics of the general medicine practices in each country" **Inclusion criteria:** - Newly diagnosed hypertension (< 1 yr) - Initial therapy with single agent **Exclusion criteria:** - Hypertension > 1 yr - Initial prescription for dual agents	13.6% all other agents) switched to another agent and 16.5% (14.2% irbesartan, 22.9% losartan, 16.6% all other agents) discontinued all antihypertensive therapy , but not clear whether this had to do with efficacy or AEs or something else **6) Specific adverse events:** NR **7) Persistence/adherence:** Persistence status determined on basis of filled prescriptions See outcome 2, above, for overall persistence rates Persistence by treatment group (defined as percentage of patients who remained on their initially prescribed monotherapy at 1 yr): Persistence ACEIs 42% Irbesartan 60.8%* Losartan 44.7% Other ARBs 51.3% BBs 49.7% CCBs 43.6% Diuretics 34.4% * $p \leq 0.001$ for irbesartan vs. diuretics, ACEIs, CCBs, BBs, and losartan; $p \leq 0.009$ for irbesartan vs. other ARBs **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Karlberg, Lins, and Hermans- son, 1999 **#6090**	**Geographical location:** 22 sites, 2 Denmark, 6 Finland, and 14 Sweden **Study dates:** NR **Funding source:** NR **Interventions:** - Telmisartan (20, 40-80 mg) (n = 139) - Enalapril (5, 10-20 mg) (n = 139) Titrated to higher dose if mean DBP > 90 at 4-wk intervals until wk 16, then add HCTZ 12.5-25 mg for DBP > 90 **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 3- to 5-wk double-dummy placebo run-in period to determine eligibility **Duration of treatment:** 26 wk: 16 wk titration; 10 wk maintenance **Duration of post-treatment followup:** NR	**Number of patients:** - Screened for inclusion: 356 - Eligible for inclusion: NR - Randomized: 278 - Began treatment: 278 - Completed treatment: 251 - Withdrawals/losses to followup: 36, 2 due to lack of efficacy, 27 due to AEs, 7 for administrative or other reasons (note: reported numbers do not total correctly) - ITT population = 272 **Age:** Mean (SD): 71.0±4.9 Median: NR Range: NR **Sex (n [%]):** Female: 160 (58%) Male: 118 (42%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Trough BP measured 3 times at 2- min intervals after patient rested in supine position for 5 min using a standard mercury sphygmo- manometer Baseline supine values: <table><tr><td></td><td>Telmisartan</td><td>Enalapril</td></tr><tr><td>SBP</td><td>180.6 ± 18.4</td><td>177.4 ± 16.6</td></tr><tr><td>DBP</td><td>101.9 ± 5.2</td><td>100.7 ± 5.1</td></tr></table> **Concurrent medications (n [%]):** Outside of HCTZ added per protocol, not assessed or mentioned **Comorbidities (n [%]):** NR (though see Exclusion criteria)	**1) Blood pressure:** Placebo-adjusted mean change from baseline in trough supine BP (mm Hg; means NR): <table><tr><td></td><td>Telmisartan</td><td>Enalapril</td><td>p-value</td></tr><tr><td>SBP</td><td>-22.1</td><td>-20.1</td><td>0.350</td></tr><tr><td>DBP</td><td>-12.8</td><td>-11.4</td><td>0.074</td></tr></table> Response rates (trough supine BP, last available assessment): <table><tr><td>Definition of "response"</td><td>Telmisartan</td><td>Enalapril</td></tr><tr><td>DBP < 90</td><td>86 (63%)</td><td>84 (62%)</td></tr><tr><td>DBP < 90 or decrease ≥ 10 mm Hg vs. baseline</td><td>96 (71%)</td><td>93 (68%)</td></tr><tr><td>SBP reduced ≥ 10 mm Hg vs. baseline</td><td>95 (70%)</td><td>91 (67%)</td></tr></table> Note: Also reports subgroup analyses for: - Age < 75 vs. ≥ 75 - Male vs. female Results also reported for ABPM **2) Rate of use of a single antihypertensive agent for BP control:** 87 (64%) telmisartan and 84 (63%) enalapril used one agent **3) Mortality:** NR **4) Morbidity:** Quality of life scales administered, but simply states scores were high at baseline in both groups and did not change during study; no quantitative data **5) Safety:** 98/139 patients in each treatment group (71%) experienced ≥ 1 AE. 35 (35%) in the telmisartan group and 52 (37%) in the enalapril group were considered by investigators to have treatment- related AEs.	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: **Applicability:** - No real baseline co-morbidity information - Recruitment strategy not clear, run in period took 20% out - No data on race/ethnicity of subjects

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Recruitment setting: NR – assume outpatient clinics **Inclusion criteria:** - Age ≥ 65 years with mild to moderate HTN - Mean DBP ≥ 95 and ≤ 114 mmHg at final two consecutive visits of the 3- to 5-wk placebo run-in phase, and if mean supine DBP vary by more than 10 mmHg **Exclusion criteria:** - Known or suspected secondary hypertension - Hepatic or renal dysfunction - Bilateral renal artery stenosis or post-renal transplant - NYHA class III or IV CHF - Recent MI or CABG - Clinically relevant arrhythmias - Clinically significant sodium depletion - Hypokalemia or hyperkalemia - Poorly controlled diabetes - Chronic use of oral anti-coagulants - High doses NSAIDs or acetaminophen - Salt substitutes or KCL - Use of investigational drugs - Patients with mean supine SBP > 220 or supine DBP > 114 mm Hg at any time during the placebo run-in phase	Serious AEs considered by investigators to be treatment-related (number of patients): Telmisartan: - Glaucoma (1) - Strabismus (1) Enalapril: - Dizziness, vertigo and chest pain (1) - Constipation (1) - Stroke (1) - Severe disabling Quincke's angioneurotic edema (1) Withdrawals due to AEs: Telmisartan: 11 (7.9%) Enalapril: (11.5%) **6) Specific adverse events:** Treatment-related AEs (n [%]; n = 139 each group): |	Telmisartan	Enalapril
Any event	35 (25.2%)	52 (37.4%)
Cough	9 (6.5)	22 (15.8)
Diarrhea	6 (4.3)	3 (2.2)
Dizziness	4 (2.9)	4 (2.9)
HA	3 (2.2)	4 (2.9)
Flatulence	2 (1.4)	2 (1.4)
Nausea	2 (1.4)	2 (1.4)
Increased sweating	2 (1.4)	2 (1.4)
Erythematous rash	2 (1.4)	2 (1.4)
Rhinitis	2 (1.4)	2 (1.4)
Impotence	2 (1.4)	1 (0.7)	 **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Proteinuria: NR	

Kavgaci, Sahin, Onder Ersoz, et al., 2002
 	
#4040
	Geographical location: Trabzon, Turkey
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Losartan 50 mg daily (n = 20)
	- Fosinopril 10 mg daily (n = 10)
	
	Dose titration/co-interventions:
	Amlodipine 5 mg add at 1 mo if BP ≥ 140/85; titrated up to 10 mg if BP still uncontrolled at 2 mo
	
	Study design:
	RCT, parallel-group (open-label)
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 15-day washout if previously on anti-HTN meds (n = 18)
	
	Duration of treatment: 6 mo
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion:
		- Eligible for inclusion: 33
		- Randomized: 33
		- Began treatment: 33
		- Completed treatment: 33
		- Withdrawals/losses to followup: 0
		
		Age:
		Mean (SD): 52.9
		Median: NR
		Range: 40-66
		
		Sex (n [%]):
		Female: 20 (61%)
		Male: 13 (39%)
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Seated trough BP measured using a sphygmomanometer after a 15-min rest; mean of 3 measurements taken at 5-min intervals
		
		        Losartan Fosinopril
		SBP 159 ± 21 156 ± 21
		DBP 99 ± 11 97 ± 9
		
		Concurrent medications (n [%]):
		Usual antidiabetic medication continued during trial:
		        Losartan Fosinopril
		Oral meds 13 (65%) 9 (69%)
		Insulin 3 (15%) 2 (15%)
		
		Comorbidities (n [%]):
		- 100% with diabetes type 2
		
		Recruitment setting: Internal medicine outpatient clinics of a university hospital
			1) Blood pressure:
			Mean seated trough BP at 6 mo:
			        Losartan Fosinopril
			SBP 132 ± 10 136 ± 8
			DBP 84 ± 7 84 ± 4
			All comparisons with baseline statistically significant
			Between-group p-values NS
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Patients using adjunctive amlodipine:
			Losartan: 7 (35%)
			Fosinopril: 4 (31%)
			
			3) Mortality: No deaths during study
			
			4) Morbidity: NR
			
			5) Safety: NR
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			Mean total cholesterol (mmol/L):
			         Baseline 6 mo p-value
			Losartan 5.65 ± 1.24 5.7 ± 1.25 NS
			Fosinopril 5.97 ± 1.3 5.34 ± 0.72 < 0.05
			
			Mean triglycerides (mmol/L):
			         Baseline 6 mo p-value
			Losartan 2.17 ± 1.1 1.66 ± 0.72 < 0.05
			Fosinopril 2.36 ± 1.2 1.87 ± 1.0 < 0.05
			
			9) Progression to type 2 diabetes: NA
			
			10) Markers of carbohydrate metabolism/diabetes control:
			Mean total glucose (mmol/L):
			         Baseline 6 mo p-value
				General comments:
				- All patients recommended to be on low-protein diet, ? benefit/ impact
				
				Quality assessment:
				Overall rating: Poor
				
				Comments:
				- Inconsistent use of significant digits raises more general suspicions
				- Large amounts of missing details
				
				Applicability:
				- Patients poorly characterized
				- Not clear how many other comorbidities present

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

			Losartan 8.93 ± 3 7.76 ± 1.96 NS
			Fosinopril 9.87 ± 3.4 9.327 ± 1.9 NS
			
			Mean HbA1c (%):
			          Baseline 6 mo p-value
			Losartan 7.53 ± 2.50 6.58 ± 1.18 NS
			Fosinopril 8.15 ± 1.64 7.57 ± 1.65 NS
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR:
			Mean creatinine (μmol/L):
			          Baseline 6 mo p-value
			Losartan 78.7 ± 17.7 84.8 ± 10.6 NS
			Fosinopril 86.6 ± 17.7 84.8 ± 10.6 NS
			
			Mean creatinine clearance (mL/min):
			          Baseline 6 mo p-value
			Losartan 186.5 ± 68.2 122.2 ± 38.3 < 0.0001
			Fosinopril 156.0 ± 56.6 113.1 ± 36.5 < 0.05
			
			13) Proteinuria:
			Mean albumin excretion (mg/day) in subgroup with microalbuminuria:
			          Baseline 6 mo p-value
			Losartan 121 54.8
			(n = 8) (32.0-264.5) (8.6-261.0) < 0.05
			Fosinopril 154 14
			(n = 7) (44-300) (10.6-46.0) < 0.05	

Inclusion criteria: - Type 2 diabetes - SBP 140-180 **Exclusion criteria:** - Albuminuria > 300 mg/day - Cr Cl < 100 mlLmin - Taking ACEIs or AT1 blockers				
Koylan, Acarturk, Canberk, et al., 2005 **#860**	**Geographical location:** Turkey **Study dates:** May 2000-May 2001 **Funding source:** NR **Interventions:** - Irbesartan (n = 337) - ACE inhibitors (n = 298) - CCB (n = 308) Administered "according to approved prescribing guidelines" (details not provided)	**Number of patients:** - Screened for inclusion: 1053 - Eligible for inclusion: 998 - Randomized: NA - Began treatment: 983 - Completed treatment: 872 - Withdrawals/losses to followup: 118 (25 due to AEs; 8 due to lack of efficacy; 85 failed to return) **Age:** Mean (SD): 52.7 to 54 Median: NR Range: NR	**1) Blood pressure:** No quantitative data reported. Investigators reported no significant differences among the three treatments for: - Reduction in supine SBP and DBP values (vs. baseline) at 1, 3, and 6 months - Percentage of patients with normalized SBP and DBP (≤ 140 mmHg and ≤ 90 mmHg, respectively) at 1, 3, and 6 months **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR	**General comments:** None **Quality assessment:** Overall rating: Poor Comments: - Used supine BP - Primary objective was to evaluate compliance, not efficacy **Applicability:** - Unusual recruitment strategy that seems highly susceptible to selection bias, as reflected by baseline

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Study design: RCT, parallel-group
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: No, consecutive patients allocated to treatment group in order (max of 6 patients/physician)
	
	Baseline/run-in period: None
	
	Duration of treatment: 6 months
	
	Duration of post-treatment followup: NR
		Sex (n [%]):
		Female: 56.6%
		Male: 43.4%
		
		Race/ethnicity (n [%]):
		NR
		
		Baseline blood pressure:
		BP measured in morning after 15 min of rest in the supine position
		
		Baseline values (± SEM):
		      Irbe ACE CCB
		Supine 160.9 159.6 160.7
		SBP ± 16.2 ± 15.2 ± 14.0
		Supine 96.2 96.5 95.9
		DBP ± 7.4 ± 7.5 ± 7.2
		
		Concurrent medications (n [%]):
		None
		
		Comorbidities (n [%]):
		LVH 6.6-8.9%
		Angina/previous MI 5.4-6.3%
		Prior cor revasc 1.4-2.8%
		Heart failure <1-1.8%
		Stroke/TIA 0-1.1%
		Nephropathy <1-3.6%
		Periph art disease <1- 2.9%
		Retinopathy 2.4-2.9%
		
		Recruitment setting:
		Patients recruited by internists or cardiologists at multiple university hospitals
		
		Inclusion criteria:
		- Age > 18 yr
		- Mild-to-moderate HTN (90 ≤ DBP ≤ 110 mm Hg)
		- Newly diagnosed with HTN or patients on HTN monotherapy for whom a change in treatment was indicated
		
		Exclusion criteria:
			4) Morbidity: NR
			
			5) Safety:
			        Irbesartan ACE CCB
			Any AE 54 (14.3%) 76 (25.5%) 60 (19.5%)
			P = 0.001
			
			Withdrawals due to AEs:
			Irbesartan: 0
			ACEI: 23/298 (7.7%)
			CCB: 2/308 (< 1%)
			
			6) Specific adverse events: n (%)
			          Irbe ACE CCB
			Ankle edema 3 (<1%) 5 (1.7%) 20 (6.5%)
			Constipation 6 (1.6) 2 (<1) 10 (3.2)
			Cough 3 (<1) 28 (9.4) 4 (1.3)
			Dry mouth 14 (3.7) 19 (6.4) 11 (3.6)
			Dizziness 4 (1.1) 7 (2.3) 5 (1.6)
			Headache 7 (1.9) 12 (4.0) 7 (2.3)
			Nausea 7 (1.9) 9 (3.0) 3 (<1)
			Feeling sick 15 (4.0) 7 (2.3) 14 (4.5)
			Pyrosis 9 (2.4) 8 (2.7) 6 (1.9)
			Insomnia 6 (1.6) 7 (2.3) 8 (2.6)
			
			7) Persistence/adherence:
			A higher proportion of patents receiving irbesartan took their daily dose of medication than ACE or CCB (p = 0.0005) (see Figure 1)
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR
				differences in Table 1

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Secondary HTN - DBP ≥ 110 mmHg - Currently treated with 2-3 anti-HTN drugs or combo agents - Pregnant or lactating - Neurological or mental disorders - MI or CVA < 6 mo - Severe renal or liver failure		

Lacourciere, Belanger, Godin, et al., 2000
 	
 #5550
	Geographical location: 8 centers in Canada
	
	 Study dates: NR
	
	 Funding source: Merck
	
	 Interventions:
	 - Losartan 50-100 mg daily (n = 52)
	 - Enalapril 5-20 mg daily (n = 51)
	
	 Dose titration/co-interventions:
	 - Losartan: Start at 50 mg daily x 8 wks. If DBP > 85, then increase to 100 mg daily. If DBP >85 at week 12, then add HCTZ 12.5 mg daily titrated to 25 mg until DBP ≤ 85 (could then add other BP meds to achieve goal, but not specified by protocol)
	 - Enalapril: Start at 5 mg daily x 4 wk. If DBP > 85, then increase to 10 mg daily. At week 8, if DBP still > 85, then increase to 20 mg daily. At week 12, if DBP still > 85, then add HCTZ 12.5 mg daily and titrate to 25 mg until DBP ≤ 85 (could then add other BP meds to achieve goal, but not specified by protocol)
	
	 Patients with DBP > 100 at week 20 were discontinued from study.
	
	 Early titration allowed in patients at week 4 if DBP > 105.
		Number of patients:
		 - Screened for inclusion: NR
		 - Eligible for inclusion: NR
		 - Randomized: 103
		 - Began treatment: 102
		 - Completed treatment: 92
		 - Withdrawals/losses to followup: 11
		
		 Age:
		 Mean: 58.5
		 Median: NR
		 Range: NR
		
		 Sex (n [%]):
		 Female: 20 (19.4%)
		 Male: 83 (80.6%)
		
		 Race/ethnicity (n [%]):
		 Caucasion: 99 (96%)
		 Asian: 3 (3%)
		 Black: 1 (1%)
		
		 Baseline blood pressure:
		 Trough BP measured using standard mercury sphygmomanometer after 5 min rest; average of 3 measurements:
		
		        Losartan Enalapril
		 SBP 162.3 ± 16.2 157.7 ± 15.9
		 DBP 97.2 ± 6.3 95.3 ± 4.8
		
		 Concurrent medications (n [%]): NR
		
		 Comorbidities (n [%]): NR (all
			1) Blood pressure:
			 Average of 3 seated trough clinic values (SD):
			                   SBP DBP
			 Losartan:
			 Pre: 163.3 ± 16.2 97.2 ± 6.3
			 Post (52 wk): 148.3 ± 17.1 86.8 ± 9.6
			
			 Enalapril:
			 Pre: 157.7 ± 15.9 95.3 ± 4.8
			 Post (52 wks): 145.5 ± 18.2 84.4 ± 8.4
			
			 Clinic BP at other time points measured, but not reported.
			
			 Also report 24-h ambulatory BP at 4 time points during study (baseline, week 12, 28, and 52) – but only 5 of 8 sites did this.
			
			 2) Rate of use of a single antihypertensive agent for BP control:
			 Losartan group on monotherapy – 20/52 (38.5%)
			 Enalapril group on monotherapy – 31/52 (59.6%)
			
			 3) Mortality: No deaths
			
			 4) Morbidity: No CV events
			
			 5) Safety:
			 Withdrawals due to AEs:
			    Enalapril – 1 (cough)
			    Losartan – 2 (1 w/ dyspnea and 1 w/ urticaria)
			
			 6) Specific adverse events:
			 Cough:
			    Enalapril – 7 patients (14%)
			    Losartan - 0 patients
				General comments:
				 - Small study
				 - No description of recruiting strategy or number of patients screened to generate study sample
				 - Do not present complete data for many outcomes, only those that are statistically significant
				 - 2 patients (1 in each group) excluded from analysis due to uncontrolled hypertension
				
				 Quality assessment:
				 Overall rating: Fair
				
				 Comments: See above
				
				 Applicability:
				 - Placebo run-in limits assessment of discontinuation rates
				 - Missing a great deal of data on the number of analyses performed and specific data; they seem to report selectively the statistically significant findings
				 - Long list of exclusions for patients with CV comorbidities

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Study design:
	RCT- parallel group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2-wk placebo run-in. Was preceded by 7-day wash out of previous HTN meds (14-day wash out of ACEIs)
	
	Duration of treatment: 52 wk
	
	Duration of post-treatment followup: NA
		diabetic)
		
		Recruitment setting: NR (seems like outpatient clinics)
		
		Inclusion criteria:
		- DM2 dx at age ≥ 30
		- Sitting DBP 90-115
		- Urinary albumin excretion 20-350 mcg/min
		
		Exclusion criteria:
		*There was a placebo run-in period. Didn't indicate how many were excluded by run-in.
		- Suspicion of renovascular disease
		- History of malignant htn (SBP>210 mmHg)
		- Stroke, TIA, or MI in previous 12 months
		- Significant heart conduction distubances or arrhythmia
		- Unstable angina
		- History of heart failure
		- Serum Cr ≥ 200 mmol/L
		- Serum potassium ≥ 5.5 mmol/L or ≤ 3.5mmol/L
		- Treatment with oral corticosteroids
		- Concomitant use of agents that may affect BP except B-blockers and nitrates
		- Drug or alcohol abuse
		- Pregnancy or breast feeding
		- Ineffective contraception
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			Total cholesterol difference at 52 wk compared to baseline (pre-/post- values NR):
			   Losartan: 2.1% decrease
			   Enalapril: 4.2% decrease
			   $P < 0.05$
			
			Also report limited data on LDL for losartan only and triglycerides for enalapril only.
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control:
			HbA1c change at 52 wks compared to baseline (pre-/post- values NR):
			 Losartan: + 0.006
			 Enalapril: + 0.0025
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR:
			GFR declined approx 9% in each group by week 52 ($P < 0.001$ for pre-/post- analysis). Values not given for GFR at 52 wk.
			
			13) Proteinuria:
			Urine albumin excretion based on average of 3 measurements:
			
			Losartan:
			Pre: 64.1 mcg/min (no SD given)
			Post (52 wk): 41.5mcg/min
			
			Enalapril:
			Pre: 73.9mcg/min
			Post (52 wk): 33.5 mcg/min
			
			P-value for pre-post was < 0.001 for both.
			No significant difference between treatments (no p-value given).	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Lacourciere, Neutel, Davidai, et al., 2006
 	
#100
	Geographical location: 81 U.S. and Canadian sites
	
	Study dates: Oct 1, 2002 to July 17, 2003
	
	Funding source: NR
	
	Interventions:
	Forced titration of:
	- Ramipril 2.5, 5, and 10 mg (n = 407)
	- Telmisartan 40 and 80 mg (n = 405)
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate? NR
	
	Baseline/run-in period: Screening 1-7 days, placebo run-in phase 2-4 wk
	
	Duration of treatment: 14 wk
	
	Duration of post-treatment followup: NR
		Number of patients:
		- Screened for inclusion: 1998
		- Eligible for inclusion:
		- Randomized: 812
		- Began treatment: 812
		- Completed treatment: 722
		- Withdrawals/losses to followup: 90, 35 due to AEs, 12 due to lack of efficacy, 13 lost to followup, 14 "investigator decision", 18 patient decision (note: reported numbers do not total correctly)
		
		Age:
		Mean (SD): 52.5 ± 9.8
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 269 (33.1%)
		Male: 543 (66.9%)
		
		Race/ethnicity (n [%]):
		87.7% white (712)
		
		Baseline blood pressure:
		Seated trough BP measured by manual cuff sphygmomanometer:
		
		      Telmisartan Ramipril
		SPB 153.9 ± 12.2 152.5 ± 12.8
		DBP 99.7 ± 4.2 99.8 ± 4.3
		
		Concurrent medications (n [%]):
		NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: Clinic setting
		
		Inclusion criteria:
		- Age ≥ 18 yr
		- Mild-moderate hypertension at baseline (mean DBP ≥ 95 and ≤ 109
			1) Blood pressure:
			Seated trough BP at 14 wk:
			
			     Telmisartan Ramipril p-value
			SBP 139.6 143.4 < 0.0000
			DBP 88.7 92.0 < 0.0001
			
			SBP response at 14 wk (trough seated SBP < 140 mm Hg or reduction from baseline of ≥ 10 mm Hg):
			Telmisartan: 70.7%
			Ramipril: 62.7%
			$p < 0.01$
			
			DBP response at 14 wk (trough seated DBP < 90 mm Hg or reduction from baseline of ≥ 10 mm Hg):
			Telmisartan: 60.5%
			Ramipril: 46.8%
			$p < 0.01$
			
			ABPM outcomes also reported (primary)
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			Severe AEs:
			Telmisartan: 15 (3. 8%)
			Ramipril: 30 (7.4%)
			
			Serious AEs: 14 patients (treatment group NR), none considered to be drug-related
			
			Withdrawals due to AEs:
			Telmisartan: 12 (3.0%)
			Ramipril: 23 (5.7%)
			
			6) Specific adverse events:
			AEs occurring at a rate of ≥ 1% and judged to be drug-related:
				General comments:
				None
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Patients and providers not blinded
				
				Applicability:
				- Significant number of limitations to inclusion in the study as evidence by number of screened patients to enrolled

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		mm Hg measured by manual cuff and 24-hr DBP > 85 mm Hg measured by ABPM [Spacelabs 90207] during the morning, daytime, and nighttime periods	<table><tr><td></td><td>Telmisartan</td><td>Ramipril</td></tr><tr><td>Peripheral edema</td><td>4 (1%)</td><td>0</td></tr><tr><td>Dizziness</td><td>6 (1.5%)</td><td>4 (1%)</td></tr><tr><td>HA</td><td>4 (1%)</td><td>6 (1.5%)</td></tr><tr><td>Cough</td><td>1 (0.2%)</td><td>33 (8%)</td></tr></table>	
		Exclusion criteria: - Mean seated SBP ≥ 180 or mean seated DBP ≥ 110 mm Hg during any visit of the placebo run-in or if they had secondary hypertension, CHF, stroke within 6 months, PTCA within 3 months, hemodynamically significant valvular heart disease, myocardial obstructive pathologic conditions, or clinical relevant arrhythmias - Night shift workers excluded - Excluded for relevant organ system disease (poorly controlled diabetes, significant hepatic, renal dysfunction, - Any hypersensitivity or reaction (including angioedema) to ACEI or ARB, history of non-compliance, substance abuse, sodium depletion, hypokalemia, or hyperkalemia, hereditary fructose intolerance, bililary tract obstruction	**7) Persistence/adherence:** Monitored via an unspecified process but NR. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Larochelle, Flack, Marbury, et al., 1997 **#6790**	**Geographical location:** NR; investigators from Canada, Brazil, S. Africa, US **Study dates:** NR **Funding source:** Bristol-Myers Squibb **Interventions:** - Irbesartan (n = 121) 150 mg once daily - Enalapril (n = 61) 20 mg once daily At end of 1 week if seated DBP was ≥ 90, then titration of irbesartan to	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 182 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** Mean (SD): NR Median: NR Range: NR **Sex (n [%]):** Female: 72 (40%) Male: 110 (60%)	**1) Blood pressure:** Reduction in trough seated DBP from baseline at 12 wk: Percentage of patients "normalized" (trough seated DBP < 90 mm Hg) at 12 wk: Irbesartan: 59% Enalapril: 57% p = 0.97 Percentage of "responders" (trough seated DBP normalized or reduced ≥ 10 mm Hg from baseline) at 12 wk: Irbesartan: 100% Enalapril: 98% p = 0.97	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Setting of study; no description (country? system? center selection? study clinicians?) - No data regarding numbers of patients screened or eligible for inclusion - Raw numbers not reported, only percentages

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	300 mg, enalapril to 40 mg
	
	After week 4, if seated DBP was ≥ 90, open-label once-daily adjunctive antihypertensive medications were added (HCTZ 25-50 mg/day, followed by long-acting nifedipine 30-60 mg.day and/or atenelol 50-100 mg/day)
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: Diuretics withdrawn for at least 3 days, other anti-hypertensives for at least 24 hr. Patients with seated DBP > 115-130 entered to double-blind phase Those with DBP ≤ 115 entered a single-blind placebo lead-in period of up to 7 days
	
	Duration of treatment: 12 weeks
	
	Duration of post-treatment followup: NA
		Race/ethnicity (n [%]):
		White: 98 (54%)
		Black: 58 (32%)
		Other: 26 (14%)
		
		Baseline blood pressure:
		Trough-seated DBP 24 ± 3 hr after ingestion of previous day's medication
		
		       Irbesartan Enalapril
		SBP 176.7 ± 17.8 175.4 ± 15.2
		DBP 119.2 ± 3.9 119.0 + 3.3
		
		Concurrent medications (n [%]):
		NR (though see Exclusion criteria)
		
		Comorbidities (n [%]): NR (though see Exclusion criteria)
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Seated diastolic BP 115-130
		- Men and surgically sterile or post-menopausal women > 18 yr
		- Signed an informed consent
		
		Exclusion criteria:
		- Concomitant disease that would present safety hazards
		- Concomitant medications known to affect BP
		- Patients with seated BP < 115 at day 7 of wash-out period
			2) Rate of use of a single antihypertensive agent for BP control (%):
			On monotherapy at 12 wk:
			Irbesartan: 9%
			Enalapril: 7%
			
			Also taking HCTZ:
			Irbesartan: 24%
			Enalapril: 18%
			
			Taking ≥ 3 adjunctive meds:
			Irbesartan: 67%
			Enalapril: 75%
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			No changes in lab parameters, ECG findings or physical exam findings
			
			Patients with AEs (%):
			Irbesartan: 55%
			Enalapril: 64%
			
			6) Specific adverse events (%):
			          Irbesartan Enalapril
			Headache 17.4% 19.7%
			Dizziness 9.1% 18.0%
			Cough 2.5% 13.1%*
			URI 9.9% 13.1%
			*p= 0.007
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
				Applicability:
				- Patient compliance not assessed

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Mackay, Pearce, and Mann, 1999 **#12650**	**Geographical location:** United Kingdom **Study dates:** Immediate post-marketing period for 4 drugs, through 6 mo followup Enalapril (1985) Lisinopril (1988) Perindopril (1990) Losartan (1995) **Funding source:** Pharmaceutical companies **Interventions:** - Enalapril (dose NR; n = 15,361 analyzed) - Lisinopril (dose NR; n = 12,438 analyzed) - Perindopril (dose NR; n = 9089 analyzed) - Losartan (dose NR; n = 14,522 analyzed) **Study design:** Prospective cohort **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** Up to 6 mo **Duration of post-treatment followup:** Up to 6 mo	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: NR - Completed treatment: 51,410 analyzed - Withdrawals/losses to followup: NR (except for withdrawals due to cough) **Age:** Mean (SD): 61.9 (~ 13) Median: NR Range: NR **Sex (n [%]):** Female: 28,215 (55.7%) Male: 22,478 (44.3%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** Cardiac failure 8.8% **Recruitment setting:** Initial post-marketing surveillance cohort **Inclusion criteria:** All patients dispensed incident prescriptions for each drug in the immediate post-marketing period in England; and their prescribing general practitioners were mailed a questionnaire **Exclusion criteria:**	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** Patients with cough: | Drug	Pts w/ cough	Rate per 1000 pt-mo	95% CI
---	---	---	---
Enalapril	86	3.9	3.1 to 4.8
Lisinopril	270	14	13 to 16
Perindopril	210	16	14 to 19
Losartan	64	3.1	2.4 to 4.0 | Rate ratios for cough, day 8 to 60, compared to losartan: | Drug	RR crude	RR adj for age and sex	95% CI
---	---	---	---
Enalapril	1.3	1.5	1.2 to 2.2
Lisinopril	4.6	4.8	3.6 to 6.5
Perindopril	5.3	5.7	4.2 to 7.6 | Rate ratios for cough; females compared with males | Drug	RR crude	RR adj for age	95% CI
---	---	---	---
Enalapril	1.5	1.4	0.8 to 2.5
Lisinopril	1.6	1.6	1.2 to 2.2
Perindopril	1.6	1.6	1.2 to 2.1
Losartan	1.7	1.5	0.8 to 2.6		**General comments:** - Authors suggest most cough associated with losartan is due to carry over from ACEI , since most patients put on losartan were switched for ACEI-related cough **Quality assessment:** Overall rating: Poor Comments: - Non-concurrent time periods for assessment of different drugs - Assembly of cohort not well-described **Applicability:** - Assessment in first few months of use of new drug products suggests that prescribing patterns may no longer be the same

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		NR, but presumably failure of GP to return questionnaire	**7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Malacco, Santona-staso, Vari, et al., 2004
 	
#2130
	Geographical location: 88 outpatient centers in Italy
	
	Study dates: NR
	
	Funding source: Novartis
	
	Interventions:
	- Valsartan 160 mg (n = 604)
	- Lisiniopril 20 mg (n = 609)
	
	Dose titration and co-interventions: No dose titration; HCTZ 12.5 mg added at 4 wk for non-responders (SBP > 150 or decrease < 20 [if SBP < 180] or decrease < 30 [if SBP ≥ 180])
	
	Study design: RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: NR
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: Yes
	
	Baseline/run-in period: 2-wk
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 1213
		- Began treatment: 1213
		- Completed treatment: 1100
		- Withdrawals/losses to followup: 113 (32 due to AEs, other causes NR)
		
		Age:
		Mean (SD): 54.1 (10.1)
		Median: NR
		Range: 28-78
		
		Sex (n [%]):
		Female: 578 (48%)
		Male: 635 (52%)
		
		Race/ethnicity (n [%]):
		White: 100%
		
		Baseline blood pressure:
		Trough seated BP measured 3 times after 5-min rest using mercury sphygmomanometer; mean of 3 readings used
		
		Mean baseline values (± SD):
			1) Blood pressure:
			Mean BP (± SD) at 16 wk (ITT population):
			
			        Valsartan Lisinopril
			        (n = 594) (n = 591)
			SBP 137.2 ± 13.3 136.8 ± 12.2
			DBP 83.9 ± 7.1 83.7 ± 7.0
			
			Rates of BP control (SBP ≤ 150 or decrease ≥ 20 [if baseline SBP < 180] or ≥ 30 [if baseline SBP ≥ 180]):
			Valsartan: 428 (82.6%)
			Lisinopril: 409 (81.6%)
			p = NS
			
			Also reported:
			Mean BP at 16 wk for per-protocol population
			Mean reductions in BP vs. baseline (ITT and per-protocol populations)
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Valsartan: 79.3%
			Lisinopril: 78.7%
			
			3) Mortality:
			No deaths occurred during trial
			
			4) Morbidity: NR
				General comments:
				None
				
				Quality assessment:
				Overall rating: Good
				
				Applicability:
				- Setting/recruitment/selection NR
				- Exclusion criteria strict and vague

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	placebo run-in **Duration of treatment:** 16 wk **Duration of post-treatment followup:** NA	Valsartan (n = 594) / Lisinopril (n = 591) SBP 167.4 ± 10.2 / 167.2 ± 9.5 DBP 99.3 ± 4.2 / 99.1 ± 4.3 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Age ≥ 18 yrs - Mild to severe HTN (SBP 160-220 and DBP 95-110) **Exclusion criteria:** - Malignant HTN - TIA, CVA, or MI within 6 months - Secondary HTN - CHF - Clinically relevant arrhythmia - Clinically significant valvular heart disease - Liver disease - Hyperkalemia - Serum creatinine > 1.5 times normal - Type 1 diabetes - Type 2 diabetes with poor glucose control or neuropathy - Known hypersensitivity to ARB, ACEI, or thiazides - Pregnant, possibly pregnant, or breastfeeding women - Women of childbearing age not using birth control	**5) Safety:** Any drug-related AE: Valsartan: 31/604 (5.1%) Lisinopril: 65/609 (10.7%) p = 0.001 Severe AEs: Valsartan: 3/604 (< 0.5%) Lisinopril: 3/609 (< 0.5%) Withdrawals due to AEs: Valsartan: 9/604 (1.5%) Lisinopril: 23/609 (3.8%) p = 0.01 **6) Specific adverse events:** Drug-related AEs: 　　　　　　　Valsartan / Lisinopril 　　　　　　　(n = 604) / (n = 609) Cough*　　　6 (1%) / 44 (7.2%) Headache　4 (0.7%) / 9 (1.5%) Vertigo　　4 (0.7%) / 1 (0.2%) Asthenia　3 (0.5%) / 4 (0.7%) Palpitations　2 (0.3%) / 2 (0.3%) Hypotension　1 (0.2%) / 3 (0.5%) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Mallion, Bradstreet, Makris, et al., 1995
 	
#12090
	Geographical location: Multicenter, with sites in Italy, Costa Rica, France, Switzerland, New Zealand, Germany, Austria, The Netherlands, and Portugal
	
	Study dates: NR
	
	Funding source: NR (multiple authors from Merck)
	
	Interventions:
	- Losartan 50-100 mg (n = 109)
	- Captopril 50-100 mg (n = 54)
	
	Dose titration and co-interventions: Patients started on 50 mg and titrated up to 100 mg if BP not controlled (DBP 90-115 mm Hg) at 6 wk; no co-interventions allowed
	
	Study design: RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: Yes – details not specified
	
	Baseline/run-in period: 4-wk placebo run-in
	
	Duration of treatment: 12 wk
	
	Duration of post-treatment followup: 1 wk without study drugs to determine rebound HTN
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 163
		- Began treatment: 163
		- Completed treatment: 142
		- Withdrawals/losses to followup: 21 (15 due to AEs, 3 lost to followup, 3 not described)
		
		Age:
		Mean (SD): 54.1
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 63 (39%)
		Male: 100 (61%)
		
		Race/ethnicity (n [%]):
		Caucasian: 145 (89%)
		Oriental: 2 (1%)
		Latin American: 9 (6%)
		Black: 4 (2%)
		Asian: 3 (2%)
		
		Baseline blood pressure:
		Trough seated BP measured 3 times at 1-min intervals after 5 min rest (instrument not specified); average of 3 readings used
		
		          Losartan Captopril
		SBP 159.3 (16.8) 159.4 (16.2)
		DBP 103.1 (5.3) 103.7 (5.5)
		
		Concurrent medications (n [%]):
		- Non-study BP meds not permitted
		- Allowed acetaminophen, aspirin, NSAIDs
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: NR
			1) Blood pressure:
			Mean BP at 12 wk:
			         Losartan Captopril
			        (n = 109) (n = 51)
			SBP 149.8 (20.3) 151.4 (16.4)
			DBP 93.9 (9.3) 97.9 (9.2)
			
			Adjusted* mean change in BP at 12 wk:
			      Losartan Captopril
			      (n = 109) (n = 51) P-value
			SBP -9.1 -7.9 NS
			DBP -9.1 -5.7 ≤ 0.01
			*Adjusted for baseline BP
			
			BP response rates at 12 wk (DBP < 90 or DBP ≥ 90 with reduction of ≥ 10 from baseline):
			Losartan: 55/109 (50.5%)
			Captopril: 15/51 (29%)
			p ≤ 0.05
			
			Subgroup analyses (no formal statistical testing done):
			
			Mean reduction in DBP at 12 wk, age < 65 vs. ≥ 65:
			               Age < 65 Age ≥ 65
			Losartan DBP -9.4 -8.1
			Captopril DBP -5.1 -7.7
			
			Sex "not a significant demographic factor, although DBP reductions were slightly higher in men at all time-points within both treatment groups"
			
			2) Rate of use of a single antihypertensive agent for BP control: NA (no other antihypertensive meds allowed)
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
				General comments:
				- Patients withdrawn if DBP not ≥ 95 during placebo run-in period resulting in some potential exclusions
				- Primary outcome was change in DBP, but one wonders if this was established a priori since it was the only significant BP change during the study.
				- Randomization stratified by degree of hypertension (mild vs. moderate)
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Numbers of screened and eligible patients NR
				
				Applicability:
				- Minimal racial diversity (89% Caucasian)
				- Recruitment setting(s) not described
				- Minimal comorbidities in study population of hypertensive patients

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Inclusion criteria: - Age ≥ 18 yr - Mild-to-moderate essential HTN (mean sitting DBP 90-115 before placebo run-in, then 95-115 after 2 and 4 wk on placebo) **Exclusion criteria:** - Known hypersensitivity/ contraindication (including angioedema, cough) to captopril or other ACEI - Significant cardiovascular, cerebrovascular, renal/ hepatic disease - Secondary or malignant HTN - Recent MI - Serum K <3.5 or > 5.5 mmol/L or other laboratory values outside of the normal ranges - Women of child-bearing age if not surgically sterile or using effective contraception	Losartan (n [%]) / Captopril (n [%]) ≥ 1 AE: 42 (38.5%) / 20 (37.0%) Withdrawals due to AEs: 10 (9.2%) / 5 (9.3%) Drug-related AEs: 16 (14.7%) / 10 (18.5%) **6) Specific adverse events:** AEs occurring in > 4% of patients in either group: Losartan (n = 109) — n (%), DR / Captopril (n = 54) — n (%), DR Headache 8 (7.3) 2 / 4 (7.4) 3 Nausea 6 (5.5) 1 / 2 (3.7) 2 Dizziness 4 (3.7) 1 / 3 (5.6) 2 URI 5 (4.6) 0 / 0 DR = # AEs considered to be drug-related **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Malmqvist, Kahan, and Dahl, 2000 **#5650**	**Geographical location:** 56 centers, locations not reported **Study dates:** NR **Funding source:** Astra Hässle AB **Interventions:** - Candesartan 8 to 16 mg (n = 140) - Enalapril 10 to 20 mg (n = 146) - HCTZ 12.5 to 25 mg (n = 143)	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 512 - Randomized: 429 - Began treatment: 429 - Completed treatment: 404 - Withdrawals/losses to followup: 26 (17 due to AEs, 9 for other reasons) **Age:** Mean: 57.7	**1) Blood pressure:** Mean post-treatment BP values NR Mean change in seated trough BP from baseline to 12 wk (no variance data reported): Candesartan / Enalapril SBP -19 / -13 DBP -11 / -9 Mean difference between treatments (candesartan vs. enalapril) in change in seated	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Mean baseline and post-treatment BP values NR - Patients withdrawn from study if mean seated SBP > 200 mm Hg or DBP >

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Dose titration/co-interventions: Higher doses used if DBP > 90 mm Hg after 6 wk; no co-interventions **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes (double-dummy) - Providers: NR - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 3- to 6-wk placebo run-in **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	Median: Range: 40 to 70 **Sex (n [%]):** Female: 100% Male: 0% **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Trough seated BP measured in duplicate, with an interval of at least 1 min, after patient rested in seated position for 5 min Mean baseline values NR **Concurrent medications (n [%]):** Non-study medication that would affect BP not allowed; no changes permitted to hormone replacement therapy **Comorbidities (n [%]):** History of habitual smoking: 9% Estrogen replacement: 22% **Recruitment setting:** NR **Inclusion criteria:** - Women age 40-69 yr - Untreated or treated primary hypertension (seated DBP 95-115) from a mean of 2 measurements at the end of placebo run-in period **Exclusion criteria:** - Secondary or malignant hypertension - Seated SBP > 200 mm Hg - MI, stroke, coronary bypass surgery, TIA within prior 6 mo - Angina, aortic/mitral valve stenosis, heart failure, or arrhythmia - Insulin-treated diabetes - Gout	trough BP from baseline to 12 weeks: |	Mean diff	95% CI	P-value
---	---	---	---
SBP	-5.5	-9.1 to -1.9	< 0.01
DBP	-2.2	-3.9 to -0.5	= 0.01 | BP control rates (seated DBP ≤ 90 mm Hg) at 12 wk: Candesartan: 60% Enalapril: 51% p = NS **2) Rate of use of a single antihypertensive agent for BP control:** No other antihypertensives permitted **3) Mortality:** NR **4) Morbidity:** No difference in Psychological General Well-Being, McMaster Overall Treatment Evaluation Questionnaire (data not reported) **5) Safety:** Any AEs: Candesartan: 60% Enalapril: 67% 10 serious AEs were reported (treatment groups not specified); none assessed as related to study drug 17/429 randomized patients (4%) withdrew due to AEs; treatment groups not specified **6) Specific adverse events:** Number of patients (%): |	Candesartan	Enalapril
---	---	---
Respiratory infection	12 (8)	7 (5)
Fatigue	11 (8)	7 (5)
Headache	10 (7)	27 (19)
Dizziness	6 (4)	10 (7)
Cough	0 (0)	19 (13)
Palpitations	5 (4)	0 (0)	 **7) Persistence/adherence:** Compliance (defined as amount of prescribed	110 mm Hg on > 2 occasions in 1 wk **Applicability:** - High loss during placebo run-in period (62/512 initially enrolled) - 100% women - Exclusion of patients who did not respond to therapy (seated SBP > 200 mm Hg or DBP > 110 mm Hg on > 2 occasions in 1 wk) means that analyzed population is a selected group of those who did respond; leads to bias

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Severe concomitant disease that may interfere with assessment - Any condition associated with poor compliance (e.g., drug or alcohol abuse)	medication taken) was between 75 and 125% in all but 2 patients; not reported by treatment group **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Marentette, Gerth, Billings, et al., 2002 **#12830**	**Geographical location:** Saskatchewan, Canada (database including > 90% of provincial residents) **Study dates:** Jan 1994-Dec 1998 **Funding source:** Merck Frosst Canada, Ltd. **Interventions:** Number of patients with data for at least 180 days: ARBs (n = 267) ACEIs (n = 7466) Beta-blockers (n = 4295) CCBs (n = 3200) Diuretics (n = 9623) Alpha-blockers (n = 731) Alpha-agonists (n = 575) Vasodilators (n = 25) Mixed classes (more than 1 class concurrently or sequentially during study period; n = 20,276) **Study design:** Retrospective cohort study **Blinding:**	**Number of patients:** - Screened for inclusion: 51,029 - Eligible for inclusion: 46,458 - Randomized: NA - Began treatment: NA - Completed treatment: NA - Withdrawals/losses to followup: NA **Age (ARBs and ACEIs):** Mean: 58 Median: NR Range: 1-85 **Sex (ARBs and ACEIs; %):** Female: 48.8% Male: 51.2% **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** NR **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Population-based prescription drug database	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Sample sizes at various timepoints: ARBs ACEIs 180 days 267 7466 360 days 170 6539 540 days 44 5699 720 days 3 4826 Small ARB sample explained by fact that ARBs not listed in provincial formulary until March 1996. Patient classified as persistent at a given period of observation (180, 360, 540, or 720 days) if patient filled at least one prescription within 90 days of the end of the given period and within 90 days of the end of each prior interval.	**General comments:** - Relatively small number of patients in ARB subgroup **Quality assessment:** Overall rating: Fair Comments: - Non-random allocation to drugs - No data on comparability of patients on ACEIs versus ARBs - Funded by pharmaceutical company **Applicability:** - Study period soon after introduction of ARBs; early use may not reflect current use patterns

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NR **Duration of post-treatment followup:** Patients followed for minimum of 180 days to a maximum of 720 days	**Inclusion criteria:** - ICD-9 code diagnosis of hypertension (401, 402, 403, 404, or 4-digit codes included in these categories) - At least 1 antihypertensive prescription during first 4.5 yr of study period - No antihypertensive prescription in the 12 mo before the first prescription **Exclusion criteria:** None specified	Extrapolating from Figure 2, persistence was: ARBs ACEIs 180 days 87% 75% 360 days 85% 65% 540 days - 60% 720 days - 55% When considering all drug classes, persistence was higher for males and for older ages. Persistence was reported by age for ACEIs (but not ARBs): 1-47 yr: 71.7% 48-57: 76.1% 58-66: 74.5% 67-74: 76.5% 75-95: 77.0% Note: "Persistence" includes combinations and switches; in essence, what is being modeled is failure to discontinue. **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Matsuda, Hayashi, and Saruta, 2003 **#12110**	**Geographical location:** Honjo, Ashikaga, Tochigi, Japan **Study dates:** 1998-1999 **Funding source:** NR **Interventions:** - ACE group - perindopril 2 mg or	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 52 - Began treatment: 52 - Completed treatment: 52 - Withdrawals/losses to followup: 0 **Age:**	**1) Blood pressure:** Mild proteinuria Mod proteinuria SBP ACE ARB ACE ARB Baseline 148±3 154±4 152±4 150±3 12 wk 135±3 137±3 134±4 137±4 24 wk 132±4 NR 120±3 NR 48 wk 131±4 NR 124±3 NR	**General comments:** - All data were presented to compare subgroups with mild and moderate proteinuria with regard to effect of ACEI versus ARB **Quality assessment:** Overall rating: Poor

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	trandolapril 1 mg (dose titrated to achieve SBP < 135 and DBP < 85) (n = 27) - ARB group – losartan 25 mg or candesartan 4 mg (dose titrated to achieve SBP < 135 and DBP < 85) (n = 25) **Study design:** RCT, parallel-group **Blinding:** - Patients: NR - Providers: NR - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** NR **Duration of treatment:** 48 weeks **Duration of post-treatment followup:** NR	Mean (SD): 52 Median: NR Range: NR **Sex (n [%]):** Female: 23 (44%) Male: 29 (56%) **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Average of 2 measurements taken after 5 min in sedentary position (seated or supine NR) Mild proteinuria Mod proteinuria ACE ARB ACE ARB n = 13 n = 13 n = 14 n = 12 S 148 ± 3 154 ± 4 152 ± 4 150 ±3 D 86 ± 5 86 ± 3 90 ± 3 89 ± 3 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Outpatient clinic **Inclusion criteria:** - Hypertension (SBP > 140 and/or DBP > 90 mmHg) - Proteinuria (> 0.3 g/24 hr) - Serum creatinine level < 265 μmol/L or creatinine clearance > 30 mL/min/1.72 m^2 **Exclusion criteria:** - Diabetic nephropathy - Polycystic kidney disease - Chronic pyelonephritis	Mild proteinuria Mod proteinuria DBP ACE ARB ACE ARB Baseline 86±5 86±3 90±3 89±3 12 wk 76±4 71±2 78±3 79±3 24 wk 80±3 NR NR NR 48 wk 74±4 NR NR NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** "Neither ACE-I nor ARB had any effect on creatinine clearance" **13) Proteinuria:** No change in patients with mild proteinuria. In patients with moderate proteinuria, ACEI reduced proteinuria by 44 ± 6% (from 2.7 ± 0.5 to 1.5 ± 0.4 g/d; p < 0.05, n = 14) at 12 wks and 54 ± 7% at 48 wk (1.2 ± 0.2 g/d) ARB caused a 23 ± 8% decrease (from 2.7 ± 0.4 to 2.0 ± 0.4 g/d, p > 0.2, n = 12) at 12 wk (p < 0.05 versus ACEI) and 41% at 48 wk (p > 0.5 versus ACEI)	Comments: - Poorly described methods regarding washout, co-interventions, dose titration - Position of BP measurement not described - No data on safety/adverse events **Applicability:** - Patient ethnicity not described, but likely all Japanese

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Mazzaglia, Mantovani, Sturken-boom, et al., 2005
 	
#390
	Geographical location: Italy
	
	Study dates: 2000-2001
	
	Funding source: Pfizer Italia
	
	Interventions:
	A single antihypertensive in one of the following classes:
	- α-blockers (n = 662)
	- Diuretics (n = 2177)
	- β-blockers (n = 1780)
	- Calcium channel blockers (CCBs, n = 2700)
	- ACE inhibitors (n = 4602)
	- ARBs (n = 1382)
	
	Study design: Retrospective cohort study
	
	Blinding: NA
	
	Was allocation concealment adequate?: NA
	
	Baseline/run-in period: NA
	
	Duration of treatment: 365 days
	
	Duration of post-treatment followup: NA
		Number of patients:
		Of 409,724 in the Health Search Database, 24,540 were newly diagnosed with hypertension; of these, 13,303 satisfied inclusion criteria (4967 did not receive antihypertensive therapy within 90 days of diagnosis, 6270 were started on combination therapy)
		
		Age (ACEI/ARB):
		Mean (SD): 66.0 (12.8)/64.0 (12.6)
		Median: NR
		Range: NR
		
		Sex (ACEI/ARB; n [%]):
		Female: 2484 (54.0%)/770 (55.7%)
		Male: 2118 (46.0%)/612 (44.3%)
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Average of last 2 separate measurements made by physicians within 3 mo before index date; method of assessment not specified
		
		    ACEI ARB
		SBP 153.1 ± 19.1 153.2 ± 18.6
		DBP 90.1 ± 10.6 90.6 ± 10.2
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]):
		
		    ACE ARB
		CAD 179 (3.9) 54 (4.0)
		HF 45 (0.98) 14 (1.01)
		DM 564 (12.3) 101 (7.3)
		Stroke 141 (3.1) 43 (3.1)
		Dyslip 415 (9.0) 220 (8.7)
		COPD 244 (5.3) 85 (6.2)
			1) **Blood pressure:** NR
			
			2) **Rate of use of a single antihypertensive agent for BP control:** See below, under Persistence/adherence
			
			3) **Mortality:** NR
			
			4) **Morbidity:** NR
			
			5) **Safety:** NR
			
			6) **Specific adverse events:** NR
			
			7) **Persistence/adherence:**
			Patients classified into one of the following groups:
			Continuers: Patients continuing the first-line medication for at least 1 yr;
			Combiners: Patients receiving an additional type of antihypertensive drug and continuing the initial medication;
			Switchers: Patients changing from the first-line to another antihypertensive class and discontinuing the initial treatment;
			Discontinuers: Patients stopping the first-line therapy without having another antihypertensive prescription during followup.
			
			|
				ACEI	ARB

---	---	---
Continuers	23.3%	25.2%
Combiners	26%*	25%*
Switchers	10%*	8%*
Discontinuers	40%*	42*	 * Estimates based on Figure 1; values not reported in text or tables Adjusted hazard ratio for discontinuation = 0.5 (95% CI 0.47 to 0.54) for ACEI, and 0.44 (0.41 to 0.48) for ARB. Adjusted hazard ratio for combining = 1.45 (1.29 to 1.64) for ACEI, and 1.35 (1.16 to 1.57) for ARB.	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Cohort study, requiring multivariate adjustment to make groups more comparable **Applicability:** - Reflects Italian practice patterns and study population

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Prostate 218 (4.7) 53 (3.8) 2+ 479 129 (9.3) comor- (10.4) bidities **Recruitment setting:** Primary care clinics engaged in the Health Search Database **Inclusion criteria:** - Newly diagnosed hypertensives (ICD-9: 401-404, 437.2) - Age ≥ 35 yr during 2000-1 - Registered with one of the participating GPs for at least 1 yr before entry into the study - Received at least one antihypertensive medication within 3 mo of diagnosis **Exclusion criteria:** - Received antihypertensive drugs within 6 months prior to index date - Less than 365 days of valid follow-up after entry to the cohort - Received one-pill combination therapy or multiple pill medications as first-line therapy	(Adjustment included age, sex, baseline BP, comorbidities, and family history) **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

McInnes, O'Kane, Istad, et al., 2000
 	
#5680
	Geographical location: Multicenter: Glasgow, UK; Oslo, Norway; Oula, Finland; Oude Wetering, The Netherlands
	
	Study dates: NR
	
	Funding source: Astra Hassle
	
	Interventions:
	- Candesartan cilexetil 8 mg + HCTZ 12.5 mg (n = 237)
	- Lisinopril 10 mg + HCTZ 12.5 mg (n = 116)
	
	No dose titration; no co-interventions
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: 418
		- Randomized: 355
		- Began treatment: 353
		- Completed treatment: 286
		- Withdrawals/losses to followup: 67
		
		Age:
		Mean (SD): 57.5 ± 9.7
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 158 (45%)
		Male: 195 (55%)
			1) Blood pressure:
			Results for ITT population (n = 237 candesartan, 116 lisinopril)
			
			Seated BP at 26 weeks:
			            Candesartan/ Lisinopril/
			            HCTZ HCTZ
			SBP 151.1± 19.1 145.9 ± 18.4
			DBP 93.0 ± 9.3 91.2 ± 8.4
			
			Direct statistical testing NR; analyses of adjusted mean change results have p-values > 0.05.
			
			Response rates at 26 wk (seated DBP ≤ 90 mm Hg and/or reduction of ≥ 10 mm Hg from baseline):
				General comments:
				- Patients withdrawn if mean sitting BP > 180/100 at 2 visits 2-4 weeks apart, resulting in high level of withdrawal prior to 26-wk endpoint
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Not clear if there was a run-in period (mentioned in results, but not methods)
				- Because no clear run-in, comparison is of patients' prior BP treatment and treatment with study drug; since prior treatment varied, significance of

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Study design: RCT, parallel-group
	
	Blinding:
	- Patients: Yes (double-dummy)
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: Yes (although blocks of 3 were used, central randomization should have controlled for this)
	
	Baseline/run-in period: NR
	
	Duration of treatment: 26-30 wk; outcomes reported at 26 wk
	
	Duration of post-treatment followup: NA
		Race/ethnicity (n [%]):
		Caucasian: 348 (99%)
		
		Baseline blood pressure:
		Seated trough BP assessed using a fully automated device (Omron HEM-705CP). Mean of 3 measurements taken at 2-min intervals after patient seated for 5 min.
		
		        Candesartan/ Lisinopril/
		        HCTZ HCTZ
		SBP: 169.2 ± 17.2 163.3 ± 16.9
		DBP: 102.9 ± 5.5 101.8 ± 4.9
		
		Concurrent medications (n [%]):
		No other antihypertensives allowed
		
		Comorbidities (n [%]):
		NR (patients reported to be similar across groups in race, height, BMI, medical history, duration of hypertension, and WHO stage.)
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Age 20-80 yr
		- Primary HTN
		- Diastolic BP 95-115 on 2 occasions 1-2 wk apart, 24 hr after antihypertensive monotherapy
		
		Exclusion criteria:
		- Women of child-bearing potential
		- Recent significant CV event or condition
		- Concomitant drugs with BP modulating effects
		-Contraindications to any of study drugs
		-Severe concomitant disease
		-Conditions associated with poor compliance
			Candesartan/HCTZ: 129/237 (54.4%)
			Lisinopril/HCTZ: 72/116 (62.1%)
			p = 0.094
			
			Other outcomes reported:
			BP control rates (seated DBP ≤ 90 mm Hg)
			Mean seated BP at 2 and 12 wk (Figure 1)
			Standing BP outcomes
			Some outcomes also reported for per-protocol population
			
			2) Rate of use of a single antihypertensive agent for BP control: Study drugs both combination agents; no other antihypertensives medications allowed
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			                Candesartan Lisinopril
			Pts with AEs 164 (68.9%) 93 (79.5%)
			Atrributable AEs 80 (33.6%) 54 (46.2%)
			Withdrawn d/t AE 14 (5.9%) 14 (12.0%)
			
			2 cases of angioedema were reported in the lisinopril group (2/116 = 1.7%) vs. none in the candesartan group
			
			6) Specific adverse events:
			                 Candesartan Lisinopril
			Dizziness/vertigo 11.8% 15.4%
			Headache 11.8% 8.5%
			Viral infection 8.8% 7.7%
			Fatigue 5.9% 6.0
			Back pain 5.5% 5.1%
			Resp infection 5.5% 9.4%
			Pain 5.0% NR
			Cough 4.6% 23.1%
			Myalgia 4.2% 6.0%
			Nausea 4.2% NR
			Accident/injury NR 4.3%
			Pharyngitis NR 4.3%
			
			7) Persistence/adherence: As assessed by
				change observed is unclear; would have been better to have placebo run-in to get baseline BP or at least to group results by prior drug type
				- Difficult to tell how many patients withdrew and the reasons for withdrawal
				- Very little baseline information about the patients
				
				Applicability:
				- Racially homogenous – all white northern European patients
				- Recruitment setting not described
				- Low dose of lisinopril used

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			tablet count, 90% of patients took 90-110% of study medications – similar in two treatment groups	
			8) Lipid levels: NR	
			9) Progression to type 2 diabetes: NR	
			10) Markers of carbohydrate metabolism/diabetes control: NR	
			11) LV mass/function: NR	
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	
Mimran, Ruilope, Kerwin, et al., 1998 **#6640**	**Geographical location:** Multicenter trial (France??, Spain ??) **Study dates:** NR **Funding source:** Bristol-Myers Squibb/Sanofi **Interventions:** - Irbesartan 75 mg (n = 98) - Enalapril 10 mg (n = 102) One capsule once a day between 6 and 10 a.m. If DBP at trough was ≥ 90 mm at weeks 4 or 8, dosage was doubled (irbesartan increased from 150 mg, enalapril to 20 mg). If SBP remained ≥ 90 mm at week 8 doses doubled again (300 mg and 40 mg). **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes	**Number of patients:** - Screened for inclusion: - Eligible for inclusion: - Randomized: 200 - Began treatment: 200 - Completed treatment: 191 - Withdrawals/losses to followup: 9, 4 due to AEs, 3 at patient request, 2 lost to followup **Age:** Mean (SD): 58.3 Median: NR Range: 145 < 65 yr; 55 ≥ 65 yr; 15 ≥ 75yr **Sex (n [%]):** Female: 99 Male: 101 **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Measured by a standard calibrated mercury sphygmomanometer. Mean of 3 readings take 1 min apart used. Seated and standing readings taken.	**1) Blood pressure:** Numerical results not reported. Both groups: Statistically significant decreases from baseline trough SBP and DBP at all measured time points (weeks 2-12). No statistically significant difference between regimes with respect to decrease in SBP or DBP. Results consistent across both sexes and all age groups. Pts maintained on lowest doses: DBP decreased by 15 mm within 4 weeks with no further decreases. Patients whose dose was doubled once: Mean DBP decreased by 8 mm with lowest doses, but mean DBP was above 90 mm. Doubling was associated with additional decrease of 5 mm between wks 4 and 8 for both groups, resulting in a decrease from baseline of 13 mm with little change thereafter. Patients whose dose was doubled twice: DBP decreased by 5 mm and 1 mm in both groups, resulting in a total decrease from baseline of 11 mm and 8 mm in enalapril and irbesartan groups. At 12 wks:	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: No description of sites, or criteria for selection of sites **Applicability:** Race of patients not mentioned

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 4-to 5-wk single-blind placebo lead-in period **Duration of treatment:** 12 weeks **Duration of post-treatment followup:** NA	Baseline seated BP: |	Enalapril	Irbesartan | SBP: 164.9 ± 12.8 163.9 ± 12.5 DBP: 101.8 ± 4.2 101.0 ± 4.1 **Concurrent medications (n [%]):** NR (though see Exclusion criteria) **Comorbidities (n [%]):** NR (though see Exclusion criteria) **Recruitment setting:** NR **Inclusion criteria:** - Lead-in medication consumption > 80% and < 120% - DBP on days 22-29 (or days 29 and 36) between 95 mm Hg and 110 mm Hg inclusive, values on each day not differing by more than 8 mm Hg - Age ≥ 18 yr **Exclusion criteria:** - Concomitant diseases or medications that would present a safety hazard or interfere with assessment of safety or efficacy of study medications - Women who were pregnant, lactating, or of child-bearing potential	- Mean DBP was higher in those titrated than those maintained at lowest dosages. - 66% of irbesartan and 63% of enalapril group were normalized (DBP < 90mm). **2) Rate of use of a single antihypertensive agent for BP control (different doses):** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** |	Enalapril (%) (n = 102)	Irbesartan (%) (n = 98)
Adverse drug experience	26	19
AE	43	45
Serious AE	1.0	4.1
Discontinued	2.9	1.0 | **6) Specific adverse events:** Patients with cough (%): Enalapril: 15% Irbesartan: 7% **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** Mean change in lab parameters at week 12 (95% CI): |	Enalapril n = 96	Irbesartan n = 94		

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

			Creatinine (mg/dL) — 0.03 (0 to 0.06) — 0.01 (-0.02 to 0.04)	

13) Proteinuria: NR

Mogensen, Neldam, Tikkanen, et al., 2000

#5340

Interventions and study design:

Geographical location: 37 sites in Australia, Denmark, Finland, and Israel

Study dates: NR

Funding source: AstraZeneca

Interventions:
Randomized to 1 of 4 groups by treatment in 2 x 12-week periods:
- Candesartan/candesartan (n = 66)
- Lisinopril/lisinopril (n = 64)
- Candesartan/candesartan + lisinopril (n = 34)
- Lisinopril/candesartan + lisinopril (n = 35)

Doses were: candesartan 16 mg, lisinopril 20 mg

Co-interventions:
Some patients also received HCTZ 12.5, but protocol for giving this not described

Study design:
RCT, parallel-group (performed as a mixed study; analyzed as a parallel-group study)

Blinding:
- Patients: Yes (double-dummy)
- Providers: Yes
- Assessors of outcomes: Yes

Was allocation concealment adequate?: NR

Baseline/run-in period: 4-wk

Patient characteristics:

Number of patients:
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 199
- Began treatment: 198
- Completed treatment: NR
- Withdrawals/losses to followup: 2 excluded from 12- and 24-wk analyses (1 never took study med, 1 provided no efficacy data); additional 53 excluded from 24-wk analysis ("most because their DBP was below 80 mm Hg")

Age:
Mean (SD): 59.8
Median: NR
Range: NR

Sex (n [%]):
Candesartan/lisinopril:
Female: 99 (50%)
Male: 98 (50%)

Race/ethnicity (n [%]): NR

Baseline blood pressure:
Seated trough BP measured after 5-min rest using automatic device (Omron HEM-705 CP). Mean of 3 measures separated by 2 min analyzed.

	Candesartan (n = 99)	Lisinopril (n = 98)
SBP	162.7 ± 17.7	162.6 ± 17.6
DBP	96.0 ± 6.2	95.7 ± 6.2

Concurrent medications (n [%]):
Oral anti-diabetic drugs: "about 80%"

Results:

1) Blood pressure:
Mean post-treatment BP values NR (except in Figure 2)

Mean reduction (95% CI) in seated trough BP at 12 wk:

	Candesartan (n = 99)	Lisinopril (n = 98)	Adjusted* mean diff. between groups
SBP	12.4 (9.1 to 15.8)	15.7 (12.2 to 19.2)*	3.3 (-1.5 to 8.2) p = 0.18
DBP	9.5 (7.7 to 11.2)	9.7 (7.9 to 11.5)	0.02 (-2.3 to 2.7) p > 0.20

*Adjusted for center, treatment, baseline value, weight, and change in DBP

Mean reduction (95% CI) in seated trough BP at 24 wk:

	Candesartan (n = 49)	Lisinopril (n = 46)
SBP	14.1 (8.9 to 19.2)	16.7 (11.4 to 21.9)
DBP	10.4 (7.7 to 13.1)	10.7 (8.0 to 13.5)

No statistical tests reported for comparison between candesartan and lisinopril monotherapies at 24 wk

2) Rate of use of a single antihypertensive agent for BP control:
Number of patients given HCTZ in addition to study drugs at 12 wk:
Candesartan: 18/99 (18%)
Lisinopril: 27/98 (28%)

Number of patients given HCTZ in addition to

Comments/ quality/applicability:

General comments:
None

Quality assessment:
Overall rating: Fair

Comments:
- Primary results (mean post-treatment values) NR; report only differences from baseline
- 24-wk results not analyzed for candesartan vs. lisinopril, only the combination vs. each individual
- Addition of HCTZ permitted, but protocol for this not described

Applicability:
- All patients had type 2 diabetes and microalbuminuria
- Recruitment not described

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	placebo run-in **Duration of treatment:** 24 wk **Duration of post-treatment followup:** NA	of patients in both groups Insulin: 20% in both groups **Comorbidities (n [%]):** All patients with hypertension, diabetes type 2 and microalbuminuria **Recruitment setting:** Tertiary hospitals and primary care clinics **Inclusion criteria:** - Age 30-74 yr - Type 2 diabetes - Urinary albumin:creatinine ratio 2.5-25 mg/mmol, diastolic BP 90-110 mmHg after 2 and 4 wk of placebo, respectively **Exclusion criteria:** - BMI ≥ 40 kg/m^2 - SBP > 200 mm Hg - Non-diabetic cause of secondary hypertension - Cardiovascular event < 6 mo - Serum creatinine ≥ 130 x6d mol/L in women and ≥ 150 x 6d ml/L in men - Serum potassium > 5.5 mmol/L - HbA1c > 10% - Pregnancy or potential pregnancy or breastfeeding	study drugs at 24 wk: Candesartan: 7/49 (14%) Lisinopril: 6/46 (13%) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** 14/197 stopped treatment due to AEs: 5 due to dizziness, weakness, or both (candesartan 2, lisinopril 2, combination 1); 3 due to cough (all lisniopril). Others not specified. **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above) **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** No clear changes in mean values for HbA1c from baseline to 12 or 24 wk in any of the treatment groups (no quantitative data reported) **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** Mean post-treatment urinary albumin:creatinine ratios NR Mean reduction in urinary albumin:creatinine ratio (%, with 95% CI) at 12 wk:	

Candesartan (n = 99)	Lisinopril (n = 98)	Adjusted* mean diff. between treatments
30 (15 to 42)	46 (35 to 56)	30 (1 to 71) p = 0.58

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			*Adjusted for center, treatment, baseline value, weight, and change in DBP Mean reduction in urinary albumin:creatinine ratio (%, with 95% CI) at 24 wk: *Adjusted for center, treatment, baseline value, weight, and change in DBP	

Mean reduction in urinary albumin:creatinine ratio (%, with 95% CI) at 24 wk:

Candesartan (n = 49)	Lisinopril (n = 46)	Adjusted* mean diff. between treatments
24 (0 to 43)	39 (20 to 54)	Not reported

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Naidoo, Sareli, Marin, et al., 1999 **#6140**	**Geographical location:** 21 centers in South Africa, Hungary, Czech Republic, Slovak Republic, Argentina, Brazil, and Colombia **Study dates:** NR **Funding source:** Merck **Interventions:** - Losartan 100 mg + HCTZ 25 mg (n =176) - Enalapril 10 mg ± HCTZ 25 mg (n =173) Dose titration and co-interventions: Beginning at wk 2, amlodipine 5 mg could be added if DBP > 105, with titration to 10 mg if DBP > 90 at next visit Patients with inadequate BP control (SBP > 220 and/or DBP > 120 or increased > 15 from baseline) at 2 successive measurements at least 3 days apart were discontinued from the trial **Study design:** RCT, parallel-group	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 349 - Began treatment: 325 - Completed treatment: 311 - Withdrawals/losses to followup: 38, some before and some after starting treatment (12 due to AEs, 12 due to protocol violations, 7 lost to followup, 5 lack of cooperation, 2 insufficient response) **Age:** Mean (SD): 53.25 Median: NR Range: NR **Sex (n [%]):** Female: 201 (58%) Male: 148 (42%) **Race/ethnicity (n [%]):** Caucasian: 174 (50%) Black: 98 (28%) Other: 77 (22%) **Baseline blood pressure:** Seated trough BP measured 3 times after a 5-min rest using a standard	**1) Blood pressure:** Mean BP at 12 wk (entire sample):	**General comments:** - Patients with inadequate BP control (SBP > 220 and/or DBP > 120 or increased > 15 from baseline) at 2 successive measurements at least 3 days apart were discontinued from the trial **Quality assessment:** Overall rating: Fair Comments: - Varying numbers of patients reported in text and tables - 12-wk outcomes compared with prestudy treatment in primary statistical analysis **Applicability:** - Recruitment setting not described - Extensive exclusion criteria

1) Blood pressure:
Mean BP at 12 wk (entire sample):

	Losartan/HCTZ (n = 173)	Enalapril/HCTZ (n = 173)
SBP	139.7 ± 17.6	140.5 ± 15
DBP	88.7 ± 10.1	88.4 ± 8.3

Mean BP for patients *not* receiving adjunctive amlodipine:

	Losartan/HCTZ (n = 129)	Enalapril/HCTZ (n = 124)
SBP baseline	159.8 ± 13.7	161.5 ± 15.1
SBP 12 wk	137.3 ± 16.6	139.2 ± 14.6
DBP baseline	103.0 ± 5.8	103.2 ± 7.0
DBP 12 wk	87.1 ± 10	87.5 ± 8.7

Note: Ns reported above are as given in the relevant data tables; varying figures given in text and other tables

Authors reported that "both regimens were effective in black (n = 54 losartan/HCTZ; n = 44 enalapril/HCTZ) and non-black patients (data not shown)"

BP control rates (control not clearly defined):

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2 days no meds
	
	Duration of treatment: 12 wk
	
	Duration of post-treatment followup: NA
		mercury sphygmomanometer; average of 3 readings used
		
		        Losartan/ Enalapril/
		        HCTZ HCTZ
		SBP 162.9 ± 16.1 163.8 ± 16.1
		DBP 104.2 ± 6.3 103.6 ± 7.4
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Moderate or severe hypertension (DBP > 105)
		- Inadequate control on 2 or more agents (DBP > 90)
		- At least on drug-related symptom that might be alleviated by medication switch
		
		Exclusion criteria:
		- On ACEI prior to study start
		- Serious AE on ACEI, diuretic, or ARB
		- Malignant or secondary hypertension
		- SBP > 220
		- Significant CV, GI, hepatic, or blood/coagulation disorders
		- Unstable diabetes
		- Obesity (arm girth > 41 cm)
		- Potassium < 3.5 or > 5.5 mEq/L
		- Serum creatinine > 150 umol/L
		- Bun > 12.5 mmol/L
		- Alanine or aspartate amino-transferase value > 50% upper limit normal
		- Proteinuria or hematuria
		- Cancer
		- AIDS
		- Absence of a kidney
		- Alcohol or drug abuse
			Losartan/HCTZ: 63%
			Enalapril/HCTZ: 58.4%
			
			2) Rate of use of a single antihypertensive agent for BP control:
			NA; all patients taking a combination agent ± additional therapy
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			No. of patients with ≥ 2 drug-related AEs:
			Losartan/HCTZ: 29 (16.5%)
			Enalapril/HCTZ: 37 (21.4%)
			
			Withdrawals due to AEs:
			Losartan/HCTZ: 5 (2.8%)
			Enalapril/HCTZ: 7 (4.0%)
			
			Withdrawals due to drug-related AEs:
			Losartan/HCTZ: 3 (1.7%)
			Enalapril/HCTZ: 3 (1.7%)
			
			No serious AEs judged to be drug-related
			
			6) Specific adverse events:
			AEs not necessarily drug-related:
			            Losartan/ Enalapril/
			            HCTZ HCTZ
			            (n = 173), % (n = 170), %
			Headache 19.1 20.6
			Palpitations 15.6 13.5
			Tired 14.5 17.1
			Dizzy 11.0 5.3
			Nervous 12.1 9.4
			Flushing 10.4 6.5
			Weakness 9.2 7.1
			Swollen 5.8 5.3
			ankles
			Muscle pain 6.4 8.8
			Cough 6.9 16.5*
			Cold 6.4 7.6
			hands/feet
			* p = 0.005, enalapril/HCTZ vs. losartan/HCTZ	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Need for treatment with beta-blockers, psychotropics, antidepressants, cimetidine, oral contraceptives, steroids, corticotropin, or lithium	7) **Persistence/adherence:** NR 8) **Lipid levels:** NR 9) **Progression to type 2 diabetes:** NR 10) **Markers of carbohydrate metabolism/diabetes control:** NR 11) **LV mass/function:** NR 12) **Creatinine/GFR:** NR 13) **Proteinuria:** NR	

Neutel, Frishman, Oparil, et al., 1999
 	
#5930
	Geographical location: 44 centers across US
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Telmisartan 40-160 mg qd (n = 385)
	- Lisinopril 10-40 mg qd (n = 193)
	
	Dosage titration and co-interventions: At wk 4, patients with uncontrolled DBP (≥ 90 mm Hg) were titrated to dose level 2 (telmisartan 80 mg, lisinopril 20 mg); if DBP still uncontrolled at wk 8, then titrated to dose level 3 (telmisartan 160 mg, lisinopril 40 mg). If DBP still uncontrolled at wk 12, but DBP reduced by ≥ 10 mm Hg from baseline, then HCTZ 12.5 mg added; remaining uncontrolled patients dropped from study. For patients on HCTZ, this could be titrated up to 25 mg if BP control lost during maintenance phase.
	
	If DBP ≥ 90 mm Hg on 2 consecutive
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 578
		- Began treatment: 578
		- Completed treatment: 448?
		- Withdrawals/losses to followup: 136 during dose-titration period (125 treatment failures, 11 no post-randomization BP data); 25 during maintenance phase (protocol deviations or invalid data)
		
		Age:
		Mean (SD): 53.5
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 195 (34%)
		Male: 383 (66%)
		
		Race/ethnicity (n [%]):
		White: 433 (75%)
		Black: 102 (18%)
		Hispanic: 35 (6%
		Other: 8 (1%)
		
		Baseline blood pressure:
			1) **Blood pressure:**
			Mean change in BP at 48 wk (in mm Hg; all analyzable completers, n's uncertain):
			
			    Telmisartan Lisinopril
			SBP -21.1 -19.3
			DBP -16.3 -15.4
			p = NS
			
			Mean change in BP at 48 wk among patients who completed on monotherapy (in mm Hg; n's uncertain):
			    Telmisartan Lisinopril
			SBP -17.7 -18.6
			DBP -15.9 -15.5
			
			2) **Rate of use of a single antihypertensive agent for BP control:**
			Telmisartan: 44%
			Lisinopril: 48%
			
			3) **Mortality:** NR
			
			4) **Morbidity:** NR
			
			5) **Safety:**
			Drug-related AEs:
			Telmisartan: 28%
			Lisinopril: 40%
			p = 0.001
				General comments:
				- Study excluded large number of patients post-randomization who failed to respond to treatment (DBP ≥ 90)
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Randomization not described
				- Large number of non-responders excluded post-randomization
				- N's unclear for many outcomes
				
				Applicability:
				- Recruitment not described
				- Non-responders excluded during study
				- Supine BP used

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	study visit while patient taking max dose of HCTZ, then patient dropped from study
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2- to 14-day withdrawal of previous antihypertensive med; 4-wk placebo run-in
	
	Duration of treatment: 48 wk after dose titration achieved
	
	Duration of post-treatment followup: NA
		Supine BP measured 3 times at 2-min intervals after patient rested in supine position for 5 min using mercury sphygmomanometer; average of 3 readings used
		
		   Telmisartan Lisinopril
		SBP 153.4 152.5
		DBP 100.8 100.5
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: NR- 44 centers
		
		Inclusion criteria:
		- Mean supine DBP 95-114 on placebo (run-in period)
		
		Exclusion criteria:
		- Secondary hypertension
		- Patients excluded at various points during study if DBP ≥ 90
			Discontinuations due to cough:
			Telmisartan: 0.3%
			Lisinopril: 3.1%
			$p = 0.007$
			
			Discontinuations due to angioedema:
			Telmisartan: 0
			Lisinopril: 2 patients
			
			6) Specific adverse events:
			AEs considered to be drug-related:
			
			               Telmisartan Lisinopril
			               (n = 385), % (n = 193), %
			Impotence 3 2
			Headache 5 6
			Fatigue 4 7
			Cough 3 7*
			Dizzy 7 8
			Dyspepsia 0 2
			*$p = 0.18$ vs. telmisartan
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Rabbia, Silke, Carra, et al., 2004
 	
#12280
	Geographical location: NR; investigators from Italy and Ireland
	
	Study dates: NR
	
	Funding source: No external funding
	
	Interventions:
	- Fosinopril 10-20 mg (n = 19)
	- Irbesartan 150-300 mg (n = 19)
	- Atenolol 50-100 mg (n = 20)
	All once daily at 8 am
	
	Doses doubled if office BP was ≥ 140/90 mm
	
	No sodium or liquid intake restriction
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2-wk placebo-run-in period
	
	Duration of treatment: 14 weeks
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 58
		- Began treatment: NR
		- Completed treatment: NR
		- Withdrawals/losses to followup: NR
		
		Age:
		Mean (SD): 38 ± 10 yr
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 27
		Male: 31
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Office BP measured 3 times by same physician in sitting position after 10 min of rest using a mercury sphygmomanometer, disappearance of phase V Korotkoff sound = diastolic pressure
		
		Baseline values:
		    Fosinopril Irbesartan
		SBP: 152 ± 11 151 ± 11
		DBP: 97 ± 7 97 ± 6
		
		ABPM obtained for 24 hr (results also reported)
		
		Concurrent medications (n [%]):
		None allowed during study
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Never treated mild hypertension
			1) Blood pressure:
			Office BP at 14 wk (p < 0.001 for all comparisons with baseline):
			
			        Fosinopril Irbesartan
			SBP: 129 ± 7 133 ± 9
			DBP: 85 ± 4 87 ± 8
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety: NR
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: Nr
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR
				General comments:
				- No racial distribution
				- Setting of study; no description (country? system? center selection? study clinicians?)
				- No data regarding numbers of patients screened, eligible for inclusion, or lost to followup
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Setting of trial not described
				- Single-blind
				
				Applicability:
				- Race of patients not mentioned

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		with no evidence of target organ damage - SBP and DBP were ≥ 140 and ≥ 90 mm, respectively, on 3 consecutive days (3 measurements /day separated by 10-mm interval) after 15 min sitting position **Exclusion criteria:** - Clinical, biochemical, ECG or radiological evidence of end-organ damage or reported history of coronary artery disease - History of heavy alcohol consumption - Sec. hypertension def. as ABPM < 130/80 with persistently elevated office BP) and poor sleep quality during ABPM - No medications allowed during study		

Ragot, Ezzaher, Meunier, et al., 2002
 	
#3630
	Geographical location: 105 outpatient French Centers
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Telmisartan 40-80 mg (n =220)
	- Perindopril 4-8 mg (n = 221)
	
	Doses doubled at 6 wk if necessary
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: NR
	- Providers: NR
	- Assessors of outcomes: No – patients self measure BP
	
	Was allocation concealment
		Number of patients:
		- Screened for inclusion: 671
		- Eligible for inclusion: 441
		- Randomized: 441
		- Began treatment: 441
		- Completed treatment: NR
		- Withdrawals/losses to followup: 73, 5 no BP measurements on treatment, 1 did not receive study med, 54 due to poor quality self BP measurement, 13 due to unspecified protocol violations
		- Per protocol population = 368
		
		Age:
		Mean (SD): 55.3 ± 11.8
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 197/435 (45%)
		Male: 238/435 (ITT pop) (55%)
			1) Blood pressure:
			Mean trough office BP at 12 wk (taken from Fig 3; SDs not reported):
			
			          Telmisartan Perindopril
			          (n = 217) (n = 218) P-value
			SBP 144.0 148.0 p < 0.05
			DBP 88.7 91.3 p < 0.005
			
			Mean decrease in trough office DBP from baseline to 12 wk:
			Telmisartan: - 8.8 mm Hg
			Perindopril: -6.3 mm Hg
			$p = 0.002$
			
			Adjusted mean difference (telmisartan vs. perindopril) for reduction in trough office SBP was -3.4 mm Hg ($p = 0.016$). Mean decreases NR.
			
			Normalized SBP at 12 wk (SBP < 140 mm Hg):
			Telmisartan: 97/217 (45%)
			Perindopril: 67/218 (31%)
			$p < 0.005$
				General comments:
				- Focus of article was comparison of self-measurement of BP and office measurement
				
				Quality assessment:
				Overall rating: Poor
				
				Comments:
				- Not blinded
				- Large number of patients (n = 59) excluded from per-protocol analysis due to poor quality self-measurement of BP
				
				Applicability:
				- Results are more applicable than most of HTN trials review in that co-morbidities are presented in baseline table

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	adequate?: Yes - IVRS
	
	Baseline/run-in period: 3-wk run-in placebo period sitting DBP ≥ 90 and ≤ 110 and SBP < 180
	
	Duration of treatment: 12 wk
	
	Duration of post-treatment followup: NR
		Race/ethnicity (n [%]):
		421/435 = 97.5% white
		
		Baseline blood pressure:
		Trough office BP assessed using semiautomatic device (OMRON 705 CP); 3 measurements taken at 1-min intervals with patient sitting and after 5 min rest; mean analyzed
		
		      Telmisartan Perindopril
		      (n = 217) (n = 218)
		SBP 158 ± 13 159 ± 13
		DBP 98 ± 6 98 ± 6
		
		Concurrent medications (n [%]):
		Anti-HTN therapy prior to study entry: 236 (54%)
		
		Comorbidities (n [%]):
		Obesity 111 (25.5%)
		History of CV events 58 (13.5%)
		Type II DM 27 (6.5%)
		
		Recruitment setting: Outpatient French clinics
		
		Inclusion criteria:
		- Age ≥ 18 yr
		- Mild-moderate hypertension
		- Inadequate BP control or treatment side effect
		- 3-wk run-in placebo period sitting DBP ≥ 90 and ≤ 110 and SBP < 180
		
		Exclusion criteria:
		- Patients with self BP measurement of poor quality during run-in period, poor compliance with treatment during run-in period
		- History of non response to ACEI or ARB
		- Suspicion of secondary HTN
		- Biliary disease
		- Non-postmenopausal women not using reliable contraception
			Normalized DBP at 12 wk (DBP < 90 mm Hg):
			Telmisartan: 122/217 (56%)
			Perindopril: 96/218 (44%)
			p < 0.01
			
			Results for self-BP measurement also reported
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			Any AE:
			Telmisartan: 74 (34%)
			Perindopril: 70 (32%)
			
			6) Specific adverse events:
			Cough:
			Telmisartan: 2 (< 1%)
			Perindopril: 12 (5%)
			p = 0.007
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Rajzer, Klocek, and Kawecka-Jaszcz, 2003 **#3320**	**Geographical location:** Krakow, Poland **Study dates:** NR **Funding source:** University grant **Interventions:** - Quinapril 20 mg qd (n = 38 BP responders) - Losartan 100 mg (50 mg bid) (n = 24 BP responders) - Amlodipine 10 mg qd (n = 37 BP responders) Dose titration and co-interventions: None, as subjects represent subgroup from larger trial who responded (BP ≤ 140/90 mm Hg) to monotherapy at 3 mo **Study design:** RCT, parallel-group **Blinding:** - Patients: No - Providers: Yes - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2-wk antihypertensive-free run-in period **Duration of treatment:** 6 mo **Duration of post-treatment followup:** NR	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 118 (for the larger study) - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: NR **Age (n = 118 larger trial):** Mean (SD): 53.7 ± 9.06 Median: NR Range: NR **Sex (n [%]; n = 118 larger trial)*:** Female: 64 (54%) Male: 54 (46%) **Race/ethnicity (n [%]):** NR, but presumably 100% white **Baseline blood pressure:** Mean of 3 sphygmomanometer measurements "in standard conditions" Mean baseline values: $\quad$ Quinapril (n = 38) $\quad$ Losartan (n = 24) SBP $\quad$ 154 ± 22.5 $\quad$ 155 ± 18.6 DBP $\quad$ 97 ± 14.1 $\quad$ 91 ± 13.5 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** - Mild to moderate hypertension according to WHO/ISH guidelines - BP adequately controlled (BP ≤ 140/90 mm Hg at 3 mo) on study	**1) Blood pressure:** Mean BP at 3 mo: $\quad$ Quinapril (n = 38) $\quad$ Losartan (n = 24) SBP $\quad$ 141 ± 23.7 $\quad$ 132 ± 15.8 DBP $\quad$ 92 ± 8.7 $\quad$ 83 ± 9.2 Mean BP at 6 mo: $\quad$ Quinapril (n = 38) $\quad$ Losartan (n = 24) SBP $\quad$ 113 ± 14.6 $\quad$ 125 ± 16.8 DBP $\quad$ 86 ± 7.1 $\quad$ 84 ± 8.1 No significant differences between groups for decrease from baseline at either timepoint (p-values NR) 24-hr ABPM values also reported **2) Rate of use of a single antihypertensive agent for BP control:** NA (response to monotherapy was the criterion for inclusion in this subgroup report) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** Measured but NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** LVMI was comparable across groups at baseline (116.9 ± 23.9 g/m^2) and did not change at 6 mo for any of the groups (data not shown)	**General comments:** - Subgroup analysis of patients from a larger trial who responded to monotherapy at 3 mo (99/118) - Focus of article is effect of treatment on pulse wave velocity and plasma collagen markers **Quality assessment:** Overall rating: Poor Comments: - No information on recruitment setting, exclusion criteria, or comorbidities - No data on safety/AEs - Inclusion of only responders to monotherapy biases the results toward the null hypothesis of no difference in BP response, especially since there were fewer responders in the losartan group **Applicability:** - Subgroup of patients who responded to monotherapy - No information on recruitment setting, exclusion criteria, or comorbidities

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		drug monotherapy **Exclusion criteria:** NR	**12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Robles, Angulo, Grois, et al., 2004
 	
#12300
	Geographical location: Badajoz, Spain
	
	Study dates: NR
	
	Funding source: NR
	
	Interventions:
	- Irbesartan 150 mg/day (n = 15)
	- Fosinopril 20 mg/day (n = 15)
	
	After 4 weeks: If BP ≥ 140/90 titrated by adding 12.5mg/day
	
	After 8 weeks: Non-controlled patients excluded
	
	Sodium intake limited
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: NR
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period:
	After withdrawal of any antihypertensive therapy, if needed, eligible patients entered a 2-week washout phase
	
	Duration of treatment: 12 weeks
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 30
		- Began treatment: NR
		- Completed treatment: NR
		- Withdrawals/losses to followup: NR
		
		Age:
		Mean: 61.3 yr
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 15
		Male: 15
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Method of assessment NR
		     Irbesartan Fosinopril
		SBP: 157.7 ± 11.2 147.9 ± 11.7
		DBP: 94.1 ± 5.6 92.3 ± 6.3
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Mild or moderate essential HTN (BP ≥ 140/90 and < 180/100)
		
		Exclusion criteria:
		- Creatinine ≥ 1.5 mg/dL
		- Unstable angina
		- MI/stroke in last 3 mo
			1) Blood pressure:
			BP at 12 wk (method of assessment NR; $p < 0.001$ for all comparisons vs. baseline):
			
			       Irbesartan Fosinopril
			SBP: 131.0 ± 8.7 132.2 ± 12.4
			DBP: 82.7 ± 4.2 84.0 ± 5.4
			
			2) Rate of use of a single antihypertensive agent for BP control:
			HCTZ was added to 6 pts with inadequate BP control at 4 wk (3 in Irb gp) and 8th wk (2 in Irb gp and 1 in Fos gp)
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety: NR
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: NR
			
			13) Proteinuria: NR
				General comments:
				None
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Setting and some of the subjects not described
				
				Applicability:
				- Primary objective: effect of drugs on hematopoiesis
				- Setting and some of the subjects not described

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Heart failure - Hypokalemia - COPD - Hematological disease - Hb ≤ 13 gm or >17 gm - Hypersensitivity to test drugs - Pre-menopausal women		

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Roca-Cusachs, Oigman, Lepe, et al., 1997
 	
#6710
	Geographical location: Multicenter, with sites in Spain, Austria, Brazil, Czech Republic, China, Colombia, Croatia, Dominican Republic, Ecuador, Jamaica, Mexico, Pakistan, Peru, Russia, Slovak Republic, Slovenia, Taiwan, Ukraine, UAE
	
	Study dates: NR
	
	Funding source: Merck & Co
	
	Interventions:
	- Losartan 50-100 mg (n = 192)
	- Captopril 25 mg twice daily-50 mg twice daily (n = 204)
	
	Dose titration and co-interventions: Titrated to higher dose at 6 wk if seated DBP ≥ 90; no other antihypertensives allowed
	
	Study design: RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 1-wk drug washout; 4-wk placebo run-in
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 396
		- Began treatment: 396
		- Completed treatment: 356
		- Withdrawals/losses to followup: 40 (17 due to AEs, 7 lost to followup, 7 insufficient response, 7 protocol violations, 2 uncooperative)
		
		Age:
		Mean (SD): 51.4 (10.9)
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 174 (44%)
		Male: 222 (56%)
		
		Race/ethnicity (n [%]):
		Black: 36 (9%)
		Non-black: 360 (91%)
		
		Baseline blood pressure: Trough seated BP assessed using mercury sphygmomanometer after 5-min rest; average of 3 readings
		
		Losartan Captopril
		SBP 158.2 ± 16.5 157.2 ± 16.7
		DBP 103.9 ± 6.5 103.2 ± 7.1
		
		Concurrent medications (n [%]): Other BP meds not permitted
		
		Comorbidities (n [%]): NR
			1) Blood pressure:
			Main results in Figure 1 (change in seated DBP) and Figure 2 (change in seated SBP), but mean posttreatment BP values NR in tables or text.
			
			Mean change in seated BP from baseline to 12 wk:
			
			  Losartan Captopril
			  (n = 190) (n = 203) P-value
			SBP -15.4 -12.2 = 0.023
			DBP -11.5 -9.3 = 0.010
			
			BP control rates at 12 wk (DBP < 90 or decrease in DBP from baseline of ≥ 10 mm Hg):
			Losartan: 60.0%
			Captopril: 54.7%
			p > 0.10
			
			2) Rate of use of a single antihypertensive agent for BP control: NA (no other antihypertensives allowed)
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			
			  Losartan Captopril
			  (n = 192) (n = 204)
			
			≥ 1 clinical AE 63 (33%) 83 (41%)
			≥ 1 drug-related clinical AE 20 (10%) 27 (13%)
			≥ 1 serious clinical AE 4 (2%) 10 (5%)
			Withdrawn due to clinical AEs 5 (3%) 12 (6%)
				General comments:
				- Patients withdrawn if DBP not ≥ 95 during placebo run-in period resulting in some potential exclusions
				- Primary outcome was change in DBP/SBP, but one wonders if this was established a priori since final SBP/DBP are not reported in study.
				
				Quality assessment: Overall rating: Fair
				
				Comments:
				- Numbers screened and eligible NR
				
				Applicability:
				- Minimal racial diversity (91% Caucasian)
				- Recuitment setting(s) not described
				- Minimal comorbities in study population; difficult to extrapolate to the general population

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Duration of treatment: 12 wk
	
	Duration of post-treatment followup: NA
		Recruitment setting: NR
		
		Inclusion criteria:
		- Adult male and female outpatients
		- Mild-to-moderate HTN (DBP 90-115 before placebo, then 95-115 after 2 & 4 wks on placebo during run-in
		- No concurrent medical conditions
		- No therapy that might affect BP
		
		Exclusion criteria:
		- Malignant or secondary HTN
		- Untreated thyrotoxicosis or hypothyroidism
		- Significant cardiovascular, cerebrovascular, hepatic, renal, GI, hematologic, pulmonary, or neurologic disorders
		- Uncontrolled diabetes
		- Concurrent disease that would preclude participation or survival (e.g., AIDs or neoplasm)
		- Alcohol or drug abuse
		- Clinically significant lab values outside normal range (e.g., serum K < 3.5 or > 5.5 mol/L
		- Women who were pregnant or lactating
		- Known sensitivity to captopril or other ACEIs
		- Concomitant therapy with other investigational drugs, beta-blockers, steroids, ACTH, or lithium
			≥ 1 laboratory AE 24 (13%) 24 (12%)
			≥ 1 drug-related
			laboratory AE 11 (6%)* 3 (2%)
			* p = 0.029; all other between-group comparisons NS
			
			Withdrawals for serious clinical AEs included 1 losartan for encephalopathy and HTN crisis, 1 captopril for HA with TIA and hemiparesis. Other withdrawals were "considered unrelated to study treatment."
			
			Withdrawals for clinical AEs included 3 losartan for urticaria + pruritis, chest pain, taste perversion (first 2 related to study treatment); 9 captopril for pruritis, headache (2), vomiting, taste loss, dizziness with headache, rash, dyspnea with heart failure, anxiety with tachycardia (all but last one considered drug-related).
			
			Laboratory AEs included: losartan (increased ALT in 4, hyperbilirubinemia in 2, increased serum creatinine in 2, increased BUN in 1, hyperkalemia in 1); captopril (1 drug-related hyperuricemia and 1 hyperkalemia).
			
			6) Specific adverse events:
			
			            Losartan Captopril
			            (n = 192) (n = 204)
			Headache 8% 10%
			Cough 6% 7%
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function: NR
			
			12) Creatinine/GFR: see above
			
			13) Proteinuria: NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Rosei, Rizzoni, Muiesan, et al., 2005
 	
#1480
	Geographical location: Italy
	
	Study dates: NR
	
	Funding source: Takeda Italia Farmeceutici S.p.A., Rome, Italy
	
	Interventions:
	- Candesartan 8-16 mg (n = 66)
	- Enalapril 10-20 mg (n = 63)
	
	Dose titration/co-interventions: Patients started on lower dose of study drug; moved to higher dose if BP ≥ 130/85 after 6 wk. If BP still uncontrolled after 12 wk, HCTZ 12.5 mg added. If BP not controlled at 18 wk, HCTZ increased to 25 mg.
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2-wk placebo run-in
	
	Duration of treatment: 24 wk
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 129
		- Began treatment: 129
		- Completed treatment: 118
		- Withdrawals/losses to followup: 11
		
		Age:
		Mean (SD): 58.4
		Median: NR
		Range: 30 to 70
		
		Sex (n [%]):
		Female: 36%
		Male: 64%
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Seated trough BP measured after 5-min rest; mean of 3 measurements taken at 1-min intervals
		
		BP measured using a mercury sphygmomanometer *and* a validated automatic device (Omron 705 CP)
		
		Baseline mean values NR (from Abstract; see also Figures 1 and 2):
		Candesartan: 148/90 ± 11/8 mm Hg
		Enalapril: 148/91 ± 12/8 mm Hg
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]):
		Candesartan/Enalapril:
		No alcohol: 49%/52%
		No smoking: 83%/75%
		Retinopathy: 6%/3%
		Heart disease: 9%/13%
		Kidney disease: 2%/3%
		
		Recruitment setting: NR
			1) Blood pressure:
			Mean BP at 24 weeks (from Abstract; not clear whether taken using sphygmomanometer [see Figure 1] or automatic device [see Figure 2]):
			Candesartan: 132/82 ± 12/7 mm Hg
			Enalapril: 131/85 ± 14/6 mm/Hg
			p = NS
			
			BP response rates at 24 wk (response not defined):
			Candesartan: 70.5%
			Enalapril: 71.9%
			p = NS
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Monotherapy at 18-24 weeks:
			Candesartan: 59%
			Enalapril: 63.8%
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			Any AEs:
			Candesartan: 27/66 (40.9%)
			Enalapril: 31/63 (49.2%)
			p = NS
			
			1 non-drug-related serious AE (diabetes decompensation in patient in candesartan group)
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence:
			Mean compliance:
			Candesartan: 98.2 ± 13.16%
			Enalapril: 97.8 ± 13.67%
			
			8) Lipid levels:
			Triglycerides (mg/dL):
			
			           Candesartan Enalapril
			           (n = 60) (n = 57)
			Baseline 145.5 ± 79.5 143.9 ± 111.5
				General comments:
				None
				
				Quality assessment:
				Overall rating: Fair
				
				Comments:
				- Assembly of patients not described
				
				Applicability:
				- Patient identification, study site not clear
				- All patients had NIDDM

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			24 wk 159.1 ± 95.3 154.8 ± 160.5	

Inclusion criteria:
- Grade 1 essential hypertension (SBP 140-159; DBP diastolic 90-99) at the end of 2-wk run-in period
- Age 30-70 yr
- Previous diagnosis of NIDDM with or without hypoglycemic therapy
- Previously treated with antihypertensive drugs (including ACEs or ARBs) for ≤ 1 mo in the 3 mo preceding enrollment
- If previously treated, enrolled only if did not tolerate or respond to previous antihypertensive medication

Exclusion criteria:
- Secondary hypertension
- SBP > 159, DBP > 99
- IDDM, intolerance or contraindications to study drugs
- Use of study drug within 4 wk of enrolment
- Major cardiac arrhythmias, hemodynamically relevant valvular heart disease, AV blocks grade 2 or 3
- CHF (NYHA II-IV)
- MI, stroke, coronary surgery, TIA within previous 3 mo
- Angina
- Autonomic neuropathy
- PVD with lesions
- Known renal artery stenosis, kidney transplantation
- Serum creatinine > 1.6 mg/dL
- Severely impaired liver function, serum sodium ≤ 130 mmol/L, serum K ≤ 3.6 mmol/L

Total cholesterol (mg/dL):

	Candesartan (n = 60)	Enalapril (n = 57)
Baseline	212.8 ± 39.4	221.2 ± 37.0
24 wk	210.0 ± 35.4	228.1 ± 37.3

LDL cholesterol (mg/dL):

	Candesartan (n = 60)	Enalapril (n = 57)
Baseline	142.4 ± 34.8	152.0 ± 35.5
24 wk	140.9 ± 28.8	157.5 ± 34.9

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: No difference (data not reported)

13) Proteinuria:
Candesartan: 33.9 (92.6)
Enalapril: 58.3 (195.3)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruff, Gazdick, Berman, et al., 1996 **#7110**	**Geographical location:** 12 centers in the U.S. **Study dates:** NR **Funding source:** NR, but authors from Merck **Interventions:** - Losartan 50 mg daily; therapy intensified at 2-wk intervals for DBP ≥ 90 (see below) (n = 50) - Enalapril 20 mg daily; therapy intensified at 2-wk intervals for DBP ≥ 90 (n = 25) Titration protocol: 1) Double dose of study med 2) Add hctz 25mg daily 3) Add atenolol 50 mg daily and titrate to 100 mg daily *or* add dihydropyridine calcium channel blocker 4) Add other therapy at discretion of investigator **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes (double-dummy) - Providers: Yes - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2- to 7-day baseline washout. No run-in period **Duration of treatment:** 12 wk **Duration of post-treatment followup:** NA	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 75 (2:1 losartan:enalapril) - Began treatment: 75 - Completed treatment: 67 - Withdrawals/losses to followup: 8 **Age:** Mean (SD): 50.9 (11.6) Median: NR Range: 23-74 **Sex (n [%]):** Female: 30 (40%) Male: 45 (60%) **Race/ethnicity (n [%]):** White- 40 (53%) Black- 32 (43%) Hispanic – 2 (3%) Native American – 1 (1%) **Baseline blood pressure:** Trough seated BP measured using a standard mercury sphygmomano-meter after 5 min rest; average of 3 readings taken at 1-min intervals 　　　　Losartan　Enalapril SBP　173.7 ± 14.5　176.5 ± 14.9 DBP　118 ± 3.5　119 ± 3.1 Seated response peak BP also collected (5-8 hr after administration) **Concurrent medications (n [%]):** Antihypertension meds stopped at baseline. No other meds reported. **Comorbidities (n [%]):** NR **Recruitment setting:** 12 US centers (no other info)	**1) Blood pressure:** Seated trough BP: 		Los-pre	Los-12 wk	Enal -pre	Enal -12 wk
SBP	173.7 (14.5)	140.3 (16.1)	176.5 (14.9)	133.8 (14.5)
DBP	118 (3.6)	90.8 (8.7)	119 (3.1)	88.4 (5.1) | All pre-post differences significant at P < 0.05 Diff in SBP between losart and enal (p = 0.037) Diff in DBP between losart and enal (p = 0.051) BP response: By 12 wk, 98% of losartan patients and 100% of enalapril patients had a DBP < 90 or a reduction of DBP ≥ 10 (between-group difference not significant) Subgroup analysis reported for black vs. non-black. "Similar reductions in black compared with non-black patients" SBP: |	Non-black		Black	
	Losart	Enal	Losart	Enal
Pre-	172.5 (15.4)	180.3 (15.3)	175.2 (13.6)	170.9 (12.9)
Post-	141.5 (16.8)	135.4 (14.9)	138.6 (15.8)	131.4 (14.2)
Change	-31.0 (16.2)	-44.9 (16.6)	-36.6 (19.5)	-39.5 (20.0) | DBP: |	Non-black		Black	
	Losart	Enal	Losart	Enal
Pre-	118.2 (3.2)	118.6 (2.5)	118.9 (3.9)	120.3 (3.7)
Post-	91.1 (10.0)	88.2 (4.4)	90.5 (6.9)	88.7 (6.2)
Change	-27.1 (8.9)	-30.4 (4.9)	-28.4 (6.8)	-31.6 (5.0)		**General comments:** - Main limitation is lack of description of numbers screened and eligible **Quality assessment:** Overall rating: Good **Applicability:** - Exclusion criteria limit the applicability to a larger hypertension population - Short time frame - Non-meaningful endpoints beyond BP response and tolerability

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Inclusion criteria: - Sitting trough DBP 115-130 **Exclusion criteria:** - Females of childbearing potential were included only w/ neg preg test w/l 72yrs and monthly thereafter - DM if fasting sugar >180 - Secondary htn - Serious heart, liver, or renal disease - Any other active medical condition or tx that might affect bp or confound results of study - ASA, acetaminophen, nsaids and low dose TCAs had to be OK'd by study monitor	**2) Rate of use of a single antihypertensive agent for BP control:** At week 12: 3/50 in losartan group (6%) 4/25 in enalapril group (16%) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:**	

5) Safety:

	Losartan (n = 50)	Enalapril (n = 25)
Adverse event	35 (70%)	19 (76%)

6/50 pts withdrew from losartan
2/25 pts withdrew from enalapril

6) Specific adverse events:

	Losartan (n = 50)	Enalapril (n = 25)
Headache	22%	20%
Dizziness	14%	12%
Edema	4%	12%
Cough	8%	12%

7) Persistence/adherence: NR

8) Lipid levels: NR

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control: NR

11) LV mass/function: NR

12) Creatinine/GFR: NR

13) Proteinuria: NR

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Ruilope, Jager, and Prichard, 2001
 	
#4640
	Geographical location: 48 centers in France, Germany, Ireland, The Netherlands, Spain, Sweden, and UK
	
	Study dates: NR
	
	Funding source: NR, but contact author employed by Solvay Pharma
	
	Interventions:
	- Eprosartan 600 mg qd (titrated to 800 mg qd after 3 wk if SBP > 140 mm Hg) (n = 168)
	- Enalapril 5 mg qd (titrated to 10, then 20 q 3 wk if SBP > 140 mm Hg) (n = 163)
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: NR
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: Single-blind, placebo run-in 3-4 wks
	
	Duration of treatment: 12 weeks
	
	Duration of post-treatment followup: 7-10 days after treatment period
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: 396
		- Randomized: 334
		- Began treatment: 334
		- Completed treatment: 290
		- Withdrawals/losses to followup: NR; 3 patients had no valid efficacy data and were excluded from analysis; reasons for other discontinuations NR
		- Population analyzed = 331 (eprosartan 168, enalapril 163)
		
		Age:
		Mean (SD): 73
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 181 (54%)
		Male: 153 (46%)
		
		Race/ethnicity (n [%]):
		Caucasian 332 (99%)
		
		Baseline blood pressure (± SEM):
		Trough BP measured 3 times at 2-min intervals after patient seated for at least 5 min using mercury or mercury-calibrated sphygmomano-meter; mean of 3 readings used
		
		        Eprosartan Enalapril
		Sit SBP 176 ± 0.9 175 ± 0.9
		Sit DBP 98 ± 0.4 98 ± 0.4
		
		Concurrent medications (n [%]):
		Any medication:
		Eprosartan: 69%
		Enalapril: 75.5%
		
		Other antihypertensive medication:
		Eprosartan: 8.8%
		Enalapril: 6.7%
			1) Blood pressure:
			Mean post-treatment BP values NR
			
			Mean changes from baseline (at 12 wk):
			          Eprosartan Enalapril P-value
			Sit SBP -18.0 -17.4 0.76
			Sit DBP -9.4 -9.6 0.84
			
			Response rates (Sit SBP < 140 or 140-150 with decrease of ≥ 20 mm Hg from baseline; Sit DBP < 90 or 90-100 with decrease of ≥ 10 mm Hg from baseline); last available BP reading used:
			        Eprosartan Enalapril
			SBP 68/168 (41%) 63/163 (39%)
			DBP 108/68 (64%) 111/163 (68%)
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Other antihypertensive medication taken during trial:
			Eprosartan: 8.8%
			Enalapril: 6.7%
			
			3) Mortality:
			2 deaths, one in each group; neither was considered related to study medication
			
			4) Morbidity: NR
			
			5) Safety:
			              Eprosartan Enalapril
			≥ 1 AE 61 (35.7%) 83 (50.9%)
			Susp/prob. AE 11 (6.4%) 24 (14.7%)
			
			6) Specific adverse events:
			                Eprosartan Enalapril
			Headache 7 (4.1%) 10 (6.1%)
			Fatigue 5 (2.9%) 7 (4.3%)
			Diarrhea 5 (2.9%) 3 (1.8%)
			Injury 4 (2.3%) 2 (1.2%)
			Abdominal pain 3 (1.8%) 4 (2.5%)
			Dizziness 3 (1.8%) 5 (3.1%)
			Infection viral 2 (1.2%) 5 (3.1%)
			Coughing 1 (0.6%) 10 (6.1%)
			UTI 0 (0%) 5 (3.1%)
				General comments:
				None
				
				Quality assessment:
				Overall rating: Good
				
				Comments:
				Enalapril dose not comparable to eprosartan.
				
				Applicability:
				- Multinational, but virtually all Caucasian subjects

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Comorbidities (n [%]): NR	**7) Persistence/adherence:** NR	
		Recruitment setting: Not described	**8) Lipid levels:** NR	
		Inclusion criteria: - Age ≥ 65 years - Essential HTN - Sitting SBP ≥ 160 mmHg and DBP 90-114 mmHg - Newly diagnosed or requiring change in treatment due to poor efficacy or tolerability	**9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR	
		Exclusion criteria: - Secondary HTN - Advanced hypertensive retinopathy - Sitting SBP > 210 mm Hg - MI or CVA < 90 days - CHF, angina - Poorly controlled diabetes - Significant renal or hepatic disease - Significant ventricular tachyarrhythmias -Severe disease (e.g., cancer) which could preclude participation or survival - Alcohol or drug abuse - Recent use of investigational drug - Concurrent use of MAOIs, tricyclics, phenothiazine derivatives, any medication know to affect BP, or sympathomimetic amines	**13) Proteinuria:** NR	
Saito, Asayama, Ohkubo, et al., 2004 **#1860**	**Geographical location:** Japan (nationwide) **Study dates:** 2002 - Mar 2003 **Funding source:** Non-profit foundation, device manufacturers **Interventions:** CCB (n = 239) ACEI (n = 214)	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: 1736 - Randomized: 1086 - Began treatment: NR - Completed treatment: 653 - Withdrawals/losses to followup: 433 had not completed ≥ 6 mo followup **Age:** Mean (SD): NR	**1) Blood pressure:** Home values at 6 mo, measured using automated device: SBP DBP CCB 134 ± 12 82 ± 10 ACEI 136 ± 15 80 ± 10 ARB 134 ± 13 80 ± 9 **2) Rate of use of a single antihypertensive agent for BP control:** At 6 months:	**General comments:** - BP data from home monitoring, may not be comparable to clinic-based seated measurements - Rates of discontinuation and switching driven by protocol, rather than usual care, may be more reliable **Quality assessment:** Overall rating: Fair

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	ARB (n = 200) **Study design:** RCT, parallel-group **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: Yes **Was allocation concealment adequate?:** Yes **Baseline/run-in period:** None **Duration of treatment:** 6 mo **Duration of post-treatment followup:** NA	Median: NR Range: NR **Sex (n [%]):** Female: NR Male: NR **Race/ethnicity (n [%]):** NR (presumably 100% Japanese) **Baseline blood pressure:** Home BP measured using automated device (Omron HEM-747IC-N) SBP DBP CCB 149 ± 14 90 ± 10 ACEI 150 ± 14 89 ± 11 ARB 149 ± 13 89 ± 10 **Concurrent medications (n [%]):** 0 [0%] **Comorbidities (n [%]):** NR **Recruitment setting:** Primary care practice **Inclusion criteria:** - Previously untreated patients ≥ 40 years of age - Home BP values ≥ 135/85 mmHg **Exclusion criteria:** NR	CCB: 34% (82/239) ACEI: 24% (51/214) ARB: 30% (60/200) **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** At 6 months, switches determined by BP values and computerized treatment algorithm: | Drug	Continued	Switched	D/c'd
---	---	---	---
ARB	89%	9%	2%
ACEI	71%	28%	1%
CCB	89%	8%	3% | **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	Comments: - Complicated treatment/switching algorithm - Drug intervention nested within what seems to primarily by a health services intervention - See above, under General comments **Applicability:** - Japanese ethnic population may not be generalizable to U.S.
Sato, Tabata, Hayashi, et al., 2003 **#2640**	**Geographical location:** Ibaraki, Japan **Study dates:** NR **Funding source:** NR **Interventions:** Cross sectional cohort of patients treated with: - Trandolapril (n = 18)	**Number of patients:** 49 (cross-sectional cohort) **Age:** Mean (SD): 63.3 Median: NR Range: NR **Sex (n [%]):** Female: 23 (47%) Male: 26 (53%)	**1) Blood pressure:** NR separately for hypertensive patients **2) Rate of use of a single antihypertensive agent for BP control:** NR separately for hypertensive patients **3) Mortality:** NR **4) Morbidity:** NR	**General comments:** - 15/49 subjects (30.6%) were normotensive; limited results reported separately for hypertensive subjects **Quality assessment:** Overall rating: Poor Comments: - Results not separated by hypertension status

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	- Enalapril (n = 5) or
	- Candesartan (n = 26)
	
	If BP not controlled (< 130/85 mm Hg), then calcium antagonist, α1-blocker, and central-acting α2-stimulant added successively
	
	Study design: Cross-sectional cohort study
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: NA
	
	Baseline/run-in period: NA
	
	Duration of treatment: NA (patients were treated previously with ACEI or ARB for 11 ± 3 months)
	
	Duration of post-treatment followup: NA
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Seated BP measured using a mercury sphygmomanometer after 15-min rest (average of 3 readings)
		Note: 15/49 patients (30.6%) normotensive
		
		Mean baseline BP values:
		        ACEI ARB
		SBP 141 ± 13 142 ± 16
		DBP 78 ± 11 79 ± 9
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): See Inclusion criteria
		
		Recruitment setting: Single hospital
		
		Inclusion criteria:
		- Clinical diagnosis of diabetic nephropathy stage 2 or 3A (defined by presence of either micro-albuminuria with urinary albumin excretion [UAE] 30-300 mg/g creatinine [stage 2] or overt proteinuria [UAE > 300 mg/g creatinine] with a glomerular filtration rate > 60 mL/min [stage 3A])
		
		Exclusion criteria: None specified
			5) Safety: NR
			
			6) Specific adverse events:
			ACEI: cough 2 patients
			No other clinical AEs observed
			
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			NR separately for hypertensive patients
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control:
			NR separately for hypertensive patients
			
			11) LV mass/function:
			NR (LVMI not reported by treatment/hypertension status)
			
			12) Creatinine/GFR:
			NR separately for hypertensive patients
			
			13) Proteinuria:
			Mean changes in urinary albumin excretion (± SEM, mg/g creatinine), hypertensive patients only:
			       ACEI (n = 16) ARB (n = 18)
			Before 417 ± 162 455 ± 166
			After 92 ± 37 99 ± 52
				- Cross-sectional without establishment of an inception cohort
				
				Applicability:
				- Limited to a single hospital in Japan
				- All patients had diabetic nephropathy stage 2 or 3A

Schieffer, Bunte, Witte, et al., 2004 **#12330**	**Geographical location:** Hanover and Hamburg, Germany **Study dates:** NR **Funding source:** Sanofi-Synthelabo **Interventions:**	**Number of patients:** - Screened for inclusion: 60 - Eligible for inclusion: - Randomized: 48 - Began treatment: 48 - Completed treatment: 47 - Withdrawals/losses to followup: 1 (enalapril; symptomatic hypotension);	**1) Blood pressure:** At 3 months (method of assessment NR): Enalapril Irbesartan SBP: 133 ± 19* 133 ± 22* DBP: 83 ± 9** 80 ± 12** * p < 0.01 vs. baseline ** p < 0.05 vs. baseline	**General comments:** None **Quality assessment:** Overall rating: Poor Comments: - Not clear all patients were

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Enalapril 2 x 10 mg/day (gp A, ENAL) (n = 27) - Irbesartan 2 x150 mg/day (gp B, IRB) (n = 21) **Study design:** RCT, parallel-group **Blinding:** - Patients: Yes - Providers: Yes - Assessors of outcomes: NR **Was allocation concealment adequate?:** Yes (randomization list) **Baseline/run-in period:** NA **Duration of treatment:** 3 months **Duration of post-treatment followup:** NA	a further 11 patients were excluded from the analysis due to protocol violations **Age:** Mean (SD): 57.1 (weighted average) Median: NR Range: NR **Sex (n [%]):** Female: 12 Male: 36 **Race/ethnicity (n [%]):** NR **Baseline blood pressure:** Enalapril Irbesartan SBP: 147 ± 35 143 ± 23 DBP: 88 ± 16 84 ± 16 Method of assessment NR **Concurrent medications (n [%]):** 1 patient in each group received oral diabetes medication **Comorbidities (n [%]):** 4 patients receiving irbesartan and 6 receiving enalapril had diabetes **Recruitment setting:** NR (university hospital?) **Inclusion criteria:** - 6-8 weeks after coronary angioplasty - No symptoms of angina or heart failure **Exclusion criteria:** - Receiving ACE, ARB, HMG-CoA reductase inhibitor, NSAID (100 mg aspirin allowed) - CRF - LDL ser levels >150mg/dL	**2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** Reported to be no difference between groups (no numerical data reported) **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	hypertensive - No run-in period - LV results not quantified **Applicability:** - Race of patients not described

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Hypotension (SBP < 90mm)		

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Schram, van Ittersum, Spoelstra-de Man, et al., 2005
 	
#990
	Geographical location: 6 sites in The Netherlands
	
	Study dates: July 1998-Oct 2001
	
	Funding source: AstraZeneca
	
	Interventions:
	- HCTZ 12.5 mg (n = 24)
	- Candesartan 8 mg (n = 24)
	- Lisinopril 10 mg (n = 22)
	
	Dose titration/co-interventions:
	Target BP = seated BP < 130/85 or SBP decrease > 10% with DBP < 85. If target BP not achieved, then following added consecutively:
	- HCTZ 12.5 mg
	- Doubling of study medication
	- Felodipine 5 mg
	- Metoprolol 50 mg
	- Doxazosin 2 mg
	- Felodipine 5 mg
	- Metoprolol 50 mg
	- Doxazosin 2 mg
	- Felodipine 5 mg
	- Metoprolol 100 mg
	- Doxazosin 4 mg
	
	Study design:
	RCT, parallel-group
	
	Blinding:
	- Patients: Yes (double-dummy)
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 1-mo run-in (patients treated with diet only); if on ACEIs, these were withdrawn for 3
		Number of patients:
		- Screened for inclusion: NR
		- Eligible for inclusion: NR
		- Randomized: 70
		- Began treatment: 70
		- Completed treatment: 60
		- Withdrawals/losses to followup: 10 (9 due to AEs, 1 for unspecified reasons)
		
		Age (candesartan and lisinopril groups):
		Mean (SD): 61.0
		Median: NR
		Range: NR
		
		Sex (candesartan and lisinopril groups; n [%]):
		Female: 27/46 (59%)
		Male: 19/46 (41%)
		
		Race/ethnicity (n [%]):
		100% Caucasian
		
		Baseline blood pressure:
		Seated BP measured after 5 min of seated rest; mean of 3 consecutive measurements)
		
		      Candesartan Lisinopril
		      (n = 24) (n = 22)
		SBP 151± 14 149 ± 9
		DBP 94 ± 10 93 ± 7
		
		Concurrent medications (n [%]):
		NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: Outpatient clinics, newspaper advertisements
		
		Inclusion criteria:
			1) Blood pressure:
			Mean seated BP at 12 mo:
			      Candesartan Lisinopril
			      (n = 24) (n = 22)
			SBP 133 ± 15 132 ± 12
			DBP 81 ± 11 80 ± 7
			p = NS for between-group differences
			
			Percentage of patients achieving target BP (seated BP < 130/85 or SBP decrease > 10% with DBP < 85) after titration phase:
			Candesartan: 67%
			Lisinopril: 68%
			
			2) Rate of use of a single antihypertensive agent for BP control: NR
			
			3) Mortality: None
			
			4) Morbidity: NR
			
			5) Safety:
			Withdrawals due to AEs:
			Candesartan: 3/24 (12.5%)
			Lisinopril: 1/22 (4.5%)
			
			AEs leading to withdrawal:
			Candesartan: Palpitations 1; dizziness 1; microalbuminuria 1
			Lisinopril: Rise in creatinine 1
			
			6) Specific adverse events:
			NR except AEs leading to withdrawal (see immediately above)
			
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			No change (data not shown)
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate
				General comments:
				- Comparatively complicated treatment protocol with multiple co-interventions ("aggressive antihypertensive therapy")
				- Pre-study titration phase lasted until target BP achieved or until treatment options exhausted (4-6 mo)
				
				Quality assessment:
				Overall rating: Good
				
				Applicability:
				- No mention of site selection; not clear if all sites were hospital-based clinics
				- All patients had type 2 diabetes
				- 100% Caucasian study population

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	months prior to the run-in period **Duration of treatment:** 4- to 6-mo BP titration period (continued until target BP achieved or until above treatment protocol exhausted), 12-mo study period **Duration of post-treatment followup:** NA	- Type II diabetes mellitus for ≥ 6 mo - Age 35 to 70 yr - Caucasian ethnicity - Urinary albumin excretion < 100 mg/24 hr **Exclusion criteria:** - Pregnancy or planned pregnancy - History of MI, angina, coronary artery bypass surgery, angioplasty, stroke, CHF, malignancy, or other serious illness - Serum creatinine > 140 µmol/L - BMI > 35 kg/m^2 - Alcohol and/or drug abuse - Participation in other clinical trials	**metabolism/diabetes control:** No change in HbA1c (data not shown) **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** Urinary albumin excretion decreased significantly at 12 mo vs. baseline in both groups, with no significant difference between groups (data shown only graphically [Figure 3])	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Shand, 2000 **#5660** *and* **Shand and Lynn, 2000** **#12380**	**Geographical location:** Christchurch, New Zealand **Study dates:** NR **Funding source:** Merck Sharp and Dohme **Interventions:** - Losartan 50-100 mg daily (n = 15) - Enalapril 2.5-10 mg daily (n = 14) Dose titration/co-interventions: Both drugs titrated at discretion of treating MD/investigator **Study design:** RCT, parallel-group **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 14-day washout of previous antihypertensive	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 29 - Began treatment: 29 - Completed treatment: 27 - Withdrawals/losses to followup: 2 withdrawals **Age:** Mean (SD): 45 (13) Median: NR Range: NR **Sex (n [%]):** Female: 14 (48%) Male: 15 (52%) **Race/ethnicity (n [%]): NR** **Baseline blood pressure:** Seated BP measured using a standard mercury sphygmomano-meter; median of 3 readings Losartan Enalapril SBP 153 ± 18 141 ± 14 DBP 100 ± 13 96 ± 13	**1) Blood pressure:** Mean seated BP (SD): |	Losart Pre-	Losart 120 days	Enal Pre-	Enal 120 days
SBP	153 (18)	138 (16)	141 (14)	134 (10)
DBP	100 (13)	88 (8)	96 (13)	87 (10)	 P < 0.01 for losartan SBP and DBP pre-/post- P < 0.01 for enalapril DBP pre-/post- (not SBP) **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** Generally not reported. 1 patient withdrew from enalapril arm due to cough. No other AEs reported. **6) Specific adverse events:** NR except AEs leading to withdrawal (see immediately above)	**General comments:** - One patient in the losartan group was excluded from analysis due to ineffective BP control **Quality assessment:** Overall rating: Poor Comments: - Ill-defined protocol - Not blinded - Missing information - Large BP differences in treatment groups at baseline (suggesting failure of randomization) **Applicability:** - Source of participants and recruitment not described - No information on AEs - All patients had renal parenchymal disease

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	meds; no other run-in
	
	Duration of treatment: 120 days
	
	Duration of post-treatment followup: NA
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
		
		Recruitment setting: NR
		
		Inclusion criteria:
		- Hypertension
		- Renal parenchymal disease
		- Stable renal function
		
		Exclusion criteria:
		- Patients on diuretics at baseline
		- Require > 1 med for BP control at baseline
			7) **Persistence/adherence:** NR
			
			8) **Lipid levels:** NR
			
			9) **Progression to type 2 diabetes:** NR
			
			10) **Markers of carbohydrate metabolism/diabetes control:** NR
			
			11) **LV mass/function:** NR
			
			12) **Creatinine/GFR:**
			Mean creatinine clearance (mL/sec 1.73 m^2):
			
			           Losartan Enalapril
			Baseline 1.88 (0.32) 1.82 (0.21)
			120 days 1.90 (0.32) 1.69 (0.21)
			
			Mean plasma creatinine (mmol/L):
			           Losartan Enalapril
			Baseline 0.11 (0.05) 0.11 (0.04)
			120 days 0.11 (0.06) 0.11 (0.05)
			
			13) **Proteinuria:** NR	

Shibasaki, Masaki, Nishiue, et al., 2002 **#4460**	**Geographical location:** Osaka, Japan **Study dates:** Nov 1998 – April 2000 **Funding source:** Ministry of Education, Science, Sports, and Culture - Japan **Interventions:** Number of patients randomized to each treatment group NR - Losartan 50 mg daily (n = 10 completed) - Amlodipine 5 mg daily (n = 10 completed) - Enalapril 5 mg daily (n = 10 completed) No dose titration or co-interventions	**Number of patients:** - Screened for inclusion: 45 - Eligible for inclusion: 38 - Randomized: 38 - Began treatment: 38 - Completed treatment: 30 - Withdrawals/losses to followup: 8 **Age:** Mean (SD): 55 (3) Median: NR Range: 21-80 **Sex (n [%]):** Female: 11 (37%) Male: 19 (63%) **Race/ethnicity (n [%]):** NR - presume all native Japanese	1) **Blood pressure:** Mean BP, supine and pre-dialysis (seated values, supine SBP and DBP not reported); number analyzed is 10 per group: |	Losartan	Enalapril	Amlodi-pine
---	---	---	---
Baseline	101.5 (4)	101.2 (3.3)	99.3 (2.2)
6 mo	90.8 (2.5)	90.1 (0.9)	88.3 (1.7) | P < 0.05 for all pre-post differences. No p-values reported for between-group differences. 2) **Rate of use of a single antihypertensive agent for BP control:** NR 3) **Mortality:** 1 death (treatment group not	**General comments:** See below **Quality assessment:** Overall rating: Fair Comments: - Small study - Single center - Number of patients randomized to various treatment groups NR - See comments immediately below, under Applicability **Applicability:** - Probably does not reflect equivalent doses of enalapril and losartan, biasing results in favor or losartan - Reports only mean arterial pressure (not SBP, DBP), so difficult to compare

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

	Study design: RCT, parallel-group
	
	Blinding:
	- Patients: Yes
	- Providers: Yes
	- Assessors of outcomes: Yes
	
	Was allocation concealment adequate?: NR
	
	Baseline/run-in period: 2 wk (intervention not described)
	
	Duration of treatment: 6 mo
	
	Duration of post-treatment followup: NA
		Baseline blood pressure:
		Supine pre-dialysis (only mean BP reported); measured using mercury sphygmomanometer
		
		Baseline mean BP (SD) reported for n = 30 completers:
		Losartan: 101.5 (4)
		Enalapril: 101.2 (3.3)
		Amlodipine: 99.3 (2.2)
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]):
		Diabetes:
		   Total - 12/30 (40%)
		   Each group had 4/10 (40%)
		
		Recruitment setting: Single dialysis center in Osaka, Japan
		
		Inclusion criteria:
		- Uremia referred for dialysis
		- On maintenance dialysis for at least 1 mo
		- Maintained stable post-dialysis weight
		- SBP > 150 or DBP > 90
		
		Exclusion criteria:
		- History of ischemic heart disease
		- History of CVA
		- Inadequate echocardiogram for LV mass
		- Atrial fibrillation
		- Recurrent CHF
		- Significant valvular heart disease
		- Nephritic syndrome
		- History of neoplasia
			specified)
			
			4) Morbidity: 1 MI (treatment group not specified)
			
			5) Safety:
			7 patients withdrawn from study and not included in analysis:
			- 1 had heart attack
			- 1 switched from hemo to peritoneal dialysis
			- 1 had myocarditis
			- 1 had death from pulmonary bleeding
			- 3 transferred to other hospitals
			
			No information on initial treatment arm for above withdrawals
			
			6) Specific adverse events:
			NR except AEs leading to withdrawal (see immediately above)
			
			7) Persistence/adherence: NR
			
			8) Lipid levels: NR
			
			9) Progression to type 2 diabetes: NR
			
			10) Markers of carbohydrate metabolism/diabetes control: NR
			
			11) LV mass/function:
			Mean (SD) Left Ventricular Mass Index (g/m^2):
				to other studies
				- Unique dialysis population; may not generalize to non-dialysis hypertensive patients

	Losartan	Enalapril	Amlodi-pine
Baseline	154.5 (9.9)	155.6 (14.3)	156.6 (7.3)
6 mo	114.6 (5.8)	135.3 (10.4)	137.2 (4.1)
Change	-24.7 (3.2)	-11.2 (4.1)	-10.5 (5.2)

P < 0.05 for all pre-post for losart and enalapril, but not amlodipine
P< 0.05 for difference in losartan group compared to enalapril or amlodipine

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			They also report measurements of interventricular septum, posterior wall, end-diastolic volume index, collapsibility index of IVC and LV ejection fraction	

12) Creatinine/GFR:
Mean (SD) serum Cr (mg/mL):

	Losartan	Enalapril	Amlodi-pine
Baseline	9.0 (0.4)	9.9 (0.7)	8.7 (0.5)
6 mo	9.2 (0.5)	10.2 (0.5)	9.4 (0.9)

13) Proteinuria: NR

Tikkanen, Omvik, and Jensen, 1995

#7170

and

Nielsen, Dollerup, Nielsen, et al., 1997

#12180

Geographical location: 32 centers in Finland, Denmark, Iceland, and Norway

Study dates: NR

Funding source: NR

Interventions:
- Losartan 50 mg (n = 202)
- Enalapril 20 mg (n = 205)

No dose titration or co-interventions

Study design:
RCT, parallel-group

Blinding:
- Patients: Yes
- Providers: Yes
- Assessors of outcomes: Yes

Was allocation concealment adequate?: NR

Baseline/run-in period: 2-wk placebo run-in

Number of patients:
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 407
- Began treatment: 399
- Completed treatment: 382
- Withdrawals/losses to followup: 25

Age:
Cannot determine mean age; distribution for total sample:

Age	N	%
< 35	19	4.7
35-44	70	17.2
45-54	152	37.3
55-64	110	27.0
> 64	56	13.8

Sex (n [%]):
Female: 151 (37.1%)
Male: 256 (62.9%)

Race/ethnicity (n [%]): 100% white

Baseline blood pressure:
Trough seated BP measured using a standard mercury sphygmomano-meter after 10 min supine rest;

1) Blood pressure:
N = 399 total for "all patients treated" analysis

Mean (SD) seated trough SBP:

	Losartan (n = 200)	Enalapril (n = 199)
Baseline	157.5 (17.1)	158.8 (16.5)
12 wk	146.9 (18.3)	146.0 (16.9)
Change	-10.6 (13)	-12.9 (12.9)

$p < 0.01$ for within-group pre-/post- changes
$p < 0.05$ enalapril vs. losartan

Mean (SD) seated trough DBP:

	Losartan (n = 200)	Enalapril (n = 199)
Baseline	103.1 (6.0)	103.7 (6.1)
12 wk	94.7 (9.0)	93.0 (7.9)
Change	-8.4 (7.1)	-10.6 (7.2)

$p < 0.01$ for within-group pre-/post- changes
$p < 0.05$ enalapril vs. losartan

Also reported is a separate "per protocol" analysis that excluded patients who did not have BP measured at the appropriate trough time

Also reported is the distribution of treatment response (defined as "excellent, good, fair, or poor"). These results also favored enalapril (p <

General comments:
None

Quality assessment:
Overall rating: Fair

Comments:
- No description of recruiting strategy, allocation, or number of screened patients

Applicability:
- Racially homogeneous population (100% white) with very few comorbidities – does not represent general hypertension population
- There were many protocol deviations in the timing of trough BP measurement resulting in a separate analysis (that was likely post-hoc)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Duration of treatment: 12 wk	average of 3 readings taken at 1-min intervals	0.05).	

Duration of post-treatment followup: NA

	Losartan	Enalapril
SBP	157.5 ±17.1	158.8 ± 16.5
DBP	103.1 ± 6.0	103.7 ± 6.1

Concurrent medications (n [%]): Patients discontinued other antihypertensive meds

Comorbidities (n [%]): Not listed, but include category of "secondary diagnoses" (not defined)

Secondary Diagnoses – "Yes":
  Losartan: n = 123 (60.9%)
  Enalapril: n = 126 (61.5%)
  Total: n = 249 (61.2%)

Recruitment setting: Outpatient primary care clinics

Inclusion criteria:
- Age 20-75
- Sitting DBP 95-120 after 2 wk of placebo

Exclusion criteria:
- Previous therapy of > 2 antihypertensive meds
- Secondary hypertension
- Renal impairment (Cr >150 μmol/L)
- Proteinuria > 1+ on dipstick
- CVA, TIA, or HTN encephalopathy in last 1 yr
- MI or angina pectoris in last 6 months
- Pregnant or nursing women
- Women of child bearing potential
- Current use of NSAIDs or corticosteroids or drugs known to affect BP
- Uncontrolled DM (fasting BS > 11 mmol/L)
- Obesity (arm circumference >41)
- Serum potassium < 3.5 or > 5.5

2) Rate of use of a single antihypertensive agent for BP control: NR

3) Mortality: NR

4) Morbidity: NR

5) Safety:

	Losart, n (%)	Enal, n (%)	p-value
Total AEs	65 (32.2%)	93 (45.4%)	< 0.01
Possibly drug-related AEs	23 (11.4%)	52 (25.4%)	< 0.01
Withdrawals due to AEs	6 (3%)	14 (6.8%)	NS
Withdrawals due to drug-related AEs	3 (1.5%)	12 (5.9%)	< 0.05

6) Specific adverse events:
Headache, edema, rash/itching mentioned as AEs, but not quantified.

	Losart	Enal	p-value
Dry cough at 12 wk	1%	12.2%	< 0.01

7) Persistence/adherence: NR

8) Lipid levels:

	Losartan (mean change %)	Enalapril (mean change %)
Cholesterol level	1.8	-0.2
HDL cholesterol	2.1	1.5
Triglycerides	-3.0	2.3

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Abnormal liver function test (twice upper limit of normal) - Hgb level < 100g/dL - "Other clinically important disease that might interfere with participation" - Previous adverse reaction or lack of treatment response to ACEI	**9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:**	

10) Markers of carbohydrate metabolism/diabetes control:

	Losartan (mean change %)	Enalapril (mean change %)
Glucose level	-0.8	0

11) LV mass/function: NR

12) Creatinine/GFR:

	Losartan (mean change %)	Enalapril (mean change %)
Creatinine level	-0.1	1.7

13) Proteinuria:
Reported for subgroup of patients only (n = 93 Danish and Finnish patients)

Urinary albumin/creatinine ratio (geometric mean x/- antilog SD) in total subgroup:

	Losartan (n = 46)	Enalapril (n = 47)
Baseline	1.14 x/-2.48	0.95 x/-2.45
12 wks	0.81 x/-2.45	0.73 x/-2.0

Differences are significant pre-/post- ($p < 0.05$), but not between treatments.

Urinary albumin/creatinine ratio (geometric mean x/- antilog SD) in microalbuminuric patients (n = 23):

	Losartan (n = 12)	Enalapril (n = 11)
Baseline	4.16 x/- 1.73	3.62 x/- 1.69
12 wks	1.77 x/- 3.94	1.52 x/- 2.21

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Differences are significant pre-/posts (p < 0.05), but not between treatments.	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Townsend, Haggert, Liss, et al., 1995 **#7200**	**Geographical location:** Philadelphia, PA (31 centers) **Study dates:** NR **Funding source:** NR (one author from Merck) **Interventions:** - Losartan: 50 mg once daily switched after 8 weeks, if necessary, to 50 mg losartan plus 12.5 mg HCTZ (n = 132) - Enalapril: 5 mg once daily switched after 4 weeks, if necessary, to 10 mg enalapril and then to 10 mg enalapril and plus 25 mg HCTZ after 8 weeks (n = 136) Titration at each step was required if the SDP remained ≥ 90 mm. Early entry was possible if mean SDBP of 110-115 was evident at baseline and confirmed and confirmed at a repeat visit within 3 days Patients stratified by SDBP. Mild hypertension = mean SDBP 95-104 Moderate =105-115 mm Study medication: Once a day between 6.30-9.30am. On the morning of clinic visits no medication until bp was measured: all measurements at end of 24-hr dosing interval **Study design:** RCT, parallel-group	**Number of patients:** - Screened for inclusion: - Eligible for inclusion: - Randomized: 268 - Began treatment: NR - Completed treatment: NR - Withdrawals/losses to followup: 31, 21 due to AEs, 10 due to protocol violations **Age:** Mean (SD): 54.5, 79.5% < 65 yr Median: NR Range: NR **Sex (n [%]):** Female: 136 (51%) Male: 132 (49%) **Race/ethnicity (n [%]):** Black: 65 (25%) White: 148 (63%) Hispanic: 26 (10%) Oriental: 5 (2%) Native American: 1 (0.5%) Other: 3 (0.5%) **Baseline blood pressure:** At each visit sitting SBP at trough at end of dosing interval and before administration of daily dose. BP measurements after 5 min of rest, in sitting position using a standard mercury sphygmomanometer. Readings repeated to obtain 3 consecutive readings within 1 min interval that did not vary by more than 5 mm from the calculated average of last 3 readings. Primary endpoint was change in mean sitting DBP from baseline to	**1) Blood pressure:** At 12 wk, patients in the losartan group had a mean SBP reduction of 10.3 mm Hg vs. 9.8 mm Hg for enalapril (p = 0.31). 68% of patients taking losartan and 60% of patients taking enalapril reached goal BP (sitting DBP < 90 mm Hg or reduction ≥ 10 mm Hg in sitting DBP vs. baseline; p = 0.16). No other quantitative data reported for overall group results. Subgroup results:	**General comments:** - Study setting not described ("centers") **Quality assessment:** Overall rating: Fair Comments: - No quantitative data reported for overall group results **Applicability:** - Sites not described

Subgroup results:

	Losart	Enal	p
Black (n)	(33)	(32)	
Wk 4	-6.5	-3.3	0.02
Wk 8	-6.8	-5.2	0.06
Wk 12	-10.0	-8.0	0.02
Non-black (n)	(99)	(104)	
Wk 4	-8.4	-7.0	0.10
Wk 8	-9.6	-9.2	0.47
Wk 12	-10.4	-10.4	0.51
≥ 65 yr	(25)	(30)	
Wk 4	-9.0	-6.4	0.06
Wk 8	-9.6	-8.4	0.17
Wk 12	-12.7	-10.1	0.03
< 65 yr	(107)	(68)	
Wk 4	-7.6	-4.9	0.19
Wk 8	-8.7	-8.6	0.06
Wk 12	-9.8	-8.6	0.75

2) Rate of use of a single antihypertensive agent for BP control:
Of 132 losartan patients, 62 (47%) received 50 mg losartan alone, 70 (53%) received 50 mg losartan + 12.5 mg HCTZ by end of study. Of 130 enalapril patients: 33 (24%) received 5 mg enalapril, 39(29%) were titrated to and continued taking 10 mg enalapril, and 64(47%) received 10

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: - Patients: Yes - Providers: NR - Assessors of outcomes: Yes Each patient got an active and a placebo of the alternative treatment using a double blind double dummy design **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 4 week placebo run-in (2 placebo tablets each day in the morning, 1 matching losartan and 1 matching enalapril) **Duration of treatment:** 12 weeks **Duration of post-treatment followup:** NA	end of study Baseline SiDBP: Losartan: 101 ± 5 Enalapril: 100 ± 4 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** NR **Inclusion criteria:** Mean SDBP ≥ 95 and ≤ 115 mm, and did not vary by more than 7 mm between measurements **Exclusion criteria:** - Previously recd. ACE or ARBs - Sensitivity or intolerance to either drug - History of angioedema, heart failure, sec hypertension, malignant hypertension, hypertensive encephalopathy, hypertensive retinopathy, potentially life-threatening arrythmias, decompensated valvular disease, MI, angioplasty, recent coronary bypass surgery, cerebrovascular accident - Pregnant or breast-feeding women	mg enalapril + 25 mg HCTZ by end of study. Between-group differences were not statistically significant. **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** No lab test AEs were serious, no ECG AEs were serious 66% of enalapril patients had 1 or more AE 55% of losartan patients had 1 or more AE 35/132 losartan patients (27%) and 36/136 enalapril patients (26%) had a drug-related AE; no patient had a serious drug-related AE No statistically significant difference in the number of patients who withdrew due to an AE (9 losartan vs. 12 enalapril) **6) Specific adverse events:** Most common AEs (losartan, enalapril): Headache: 10%, 15% Cough: 7%, 12% URI: 8%, 10% Dizziness: 5%, 7% Asthenia: 6%, 2% Drug-related AEs (losartan, enalapril): Cough: 4%, 10% Headache: 4%, 4% Dizziness: 2%, 3% Asthenia/fatigue: 27%, 26% **7) Persistence/adherence:** NR **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			11) LV mass/function: NR	
			12) Creatinine/GFR: NR	
			13) Proteinuria: NR	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Uchiyama-Tanaka, Mori, Kishimoto, et al., 2005 **#1120**	**Geographical location:** Osaka, Japan **Study dates:** NR **Funding source:** NR **Interventions:** - Quinapril 10 mg (n = 25) - Losartan 50 mg (n = 18) Dose titration and co-interventions: If BP not controlled at 2 mo, then given combination of 2 study drugs (i.e., quinapril 10 mg + losartan 50 mg) **Study design:** RCT, parallel-group **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: NR **Was allocation concealment adequate?:** NR **Baseline/run-in period:** None **Duration of treatment:** 1 yr **Duration of post-treatment followup:** NA	**Number of patients:** - Screened for inclusion: 58 - Eligible for inclusion: NR - Randomized: 57 - Began treatment: 57 - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** Mean (SD): 61 ± 9 Median: NR Range: NR **Sex (n [%]):** Female: 32 (56%) Male: 25 (44%) **Race/ethnicity (n [%]):** NR, but presumably 100% Asian **Baseline blood pressure:** Trough seated BP measured 3 times at 2-min intervals with patient resting using an automatic sphygmomanometer; average of 2 "most stable" readings used Baseline values (mean ± SD): 　　　　　Quinapril　Losartan 　　　　　alone　　　alone 　　　　　(n = 25)　(n = 18) SBP　　156 ± 14　156 ± 12 DBP　　92 ± 9　　92 ± 10 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]; n = 43 monotherapy responders):**	**1) Blood pressure:** Quinapril vs. losartan results reported only for patients who achieved response on monotherapy Mean BP (± SD) at 1 yr (monotherapy responders only): 　　　　Quinapril　Losartan 　　　　alone　　　alone 　　　　(n = 25)　(n = 18) SBP　136 ± 7　　135 ± 6 DBP　78 ± 7　　76 ± 8 No significant difference between groups (p-value NR) **2) Rate of use of a single antihypertensive agent for BP control:** 14/57 (25%) took combination quinapril and losartan due to inadequate BP control at 2 mo. Remainder (43/57 = 75%) stayed on monotherapy. **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** NR **8) Lipid levels:** 　　　　Quinapril　Lisinopril 　　　　mono-　　　mono- 　　　　therapy　　therapy 　　　　(n = 25)　(n = 18) LDL　134 (43)　121 (27)	**General comments:** - Quinapril vs. losartan results reported only for patients who achieved response on monotherapy - Open-label study allowing for bias in assessment **Quality assessment:** Overall rating: Fair Comments: - Recruitment and randomization not clearly described - Open-label study allowing for bias in assessment of outcomes - No data on safety/AEs or withdrawals **Applicability:** - Study location in single Japanese medical center - No reporting on safety/AEs/withdrawals - Quinapril vs. losartan results reported only for patients who achieved response on monotherapy

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results			Comments/ quality/applicability
		History of smoking: 17 (39.5%) History of diabetes: 11 (26%) History of hyperlipidemia: (37%) **Recruitment setting:** Outpatients attending renal and hypertension center at the university medical center **Inclusion criteria:** - Untreated hypertension - Diagnosed at the renal and htn center - Mild-to-moderate essential hypertension accord to Japanese Society of Hypertension guidelines **Exclusion criteria:** - Signs, symptoms, or history of cardiac or renal disease, cerebrovascular accident, or any major disease - Required anti-platelet or anti-coagulation medications	baseline LDL 1 yr HDL baseline HDL 1 yr TG baseline TG 1 yr	126 (27) 56 (19) 59 (20) 147 (56) 150 (69)	117 (31) 49 (13) 52 (16) 156 (73) 169 (55)	

None of the changes was statistically significant but no p-values reported

Note: Patients taking antihyperlipidemia were *not* excluded, so cannot necessarily attribute lipid changes to study drugs

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control:

	Quinapril monotherapy (n = 25)	Lisinopril monotherapy (n = 18)
HgA1c baseline	5.5 (1.2)	5.4 (1.1)
HgA1c 1 yr	5.4 (1.0)	5.3 (1.5)

None of the changes was statistically significant but no p-values reported

Note: Patients taking antidiabetes drugs were *not* excluded

11) LV mass/function: NR

12) Creatinine/GFR:

	Quinapril monotherapy (n = 25)	Lisinopril monotherapy (n = 18)
Cr baseline	0.6 (0.2)	0.7 (0.3)
Cr 1 yr	0.7 (0.3)	0.7 (0.2)

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Cr reported in mg/dL	
			None of the changes was statistically significant but no p-values reported	
			13) Proteinuria: NR	

Verdecchia, Schillaci, Reboldi, et al., 2000
 	
#5560
	Geographical location: Perugia, Italy
	
	Study dates: NR
	
	Funding source: Supported in part by grants from the associzone umbra cuore e lapertensione, perugia, italy
	
	Interventions:
	- Losartan 50 mg daily (n = 22)
	- Enalapril 20mg daily (n = 66)
	
	Dose titration/cointerventions:
	In both groups, HCTZ 25 mg daily added if needed (SBP ≥ 140 or DBP > 90)
	
	Study design: Case-control selected from observational registry (n = 701)
	
	Blinding:
	- Patients: No
	- Providers: No
	- Assessors of outcomes: No
	
	Was allocation concealment adequate?: No randomization
	
	Baseline/run-in period: NA
	
	Duration of treatment: Average of 3.3 yr
	
	Duration of post-treatment followup: NA
		Number of patients:
		- Screened for inclusion: 701 (from cohort)
		- Eligible for inclusion: NR
		- Randomized: NA
		- Began treatment: 108
		- Completed treatment: 88
		- Withdrawals/losses to followup: 20 (14 due to AEs, 6 for unspecified reasons)
		
		Age:
		Mean (SD): NR
		Median: NR
		Range: NR
		
		Sex (n [%]):
		Female: 50%
		Male: 50%
		
		Race/ethnicity (n [%]): NR
		
		Baseline blood pressure:
		Seated trough office BP assessed using a standard mercury sphygmanometer; mean of 3 measurements taken after subject rested for 10 min
		
		       Losartan Enalapril
		SBP 155 ± 14 155 ± 15
		DBP 100 ± 9 99 ± 9
		
		Concurrent medications (n [%]): NR
		
		Comorbidities (n [%]): NR
			1) Blood pressure:
			Mean trough seated BP on treatment (avg. 3.3 yr):
			        Losartan Enalapril
			SBP 140 ± 14 140 ± 18
			DBP 90 ± 8 87 ± 7
			All pre-/post- differences p < 0.01
			Between-group p-values NR
			
			Also report 24-hr ABPM data
			
			2) Rate of use of a single antihypertensive agent for BP control:
			Number of patients (%) not taking adjunctive HCTZ:
			Losartan: 12 (55%)
			Enalapril: 32 (48%)
			
			3) Mortality: NR
			
			4) Morbidity: NR
			
			5) Safety:
			Withdrawals due to AEs:
			Losartan: 2 (headache, gastric distress)
			Enalapril: 12 (all cough)
			
			6) Specific adverse events: NR
			
			7) Persistence/adherence: NR
			
			8) Lipid levels:
			Mean total cholesterol (mmol/L):
			        Baseline Followup p-value
			Losartan 5.09 ± 0.79 5.23 ± 0.86 NS
			Enalapril 5.51 ± 0.93 5.92 ± 0.92 NS
			
			Mean HDL cholesterol (mmol/L):
				General comments:
				- Baseline characteristics of patients NR
				
				Quality assessment:
				Overall rating: Poor
				
				Comments:
				- No baseline characteristics reported
				- No detail about extent of followup (only give average of 3.3 yr)
				
				Applicability:
				- No baseline patient characteristics described or compared
				- Little detail about selection of case-controls, reasons for exclusion from eligible patients
				- Duration of therapy not defined at all

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Recruitment setting: - from PIUMA (Progetto Ipertensione Umbria Monitoaggio Ambulatoriale) study [ref 4, 14 in paper] **Inclusion criteria:** - Office SBP ≥ 140 and/or DBP ≥ 90 on ≥ 3 visits - ≥1 valid BP measurement within 24h before enrollment **Exclusion criteria:** - Previous antihypertensive therapy or drugs withdrawn from ≥ 4 wk - Evidence of CHF, CAD, significant valvular defects - Secondary causes of HTN - "Other concomitant important disease"		

	Baseline	Followup	p-value
Losartan	1.26 ± 0.30	1.30 ± 0.21	NS
Enalapril	1.24 ± 0.28	1.28 ± 0.32	NS

Mean LDL cholesterol (mmol/L):

	Baseline	Followup	p-value
Losartan	3.42 ± 0.79	3.32 ± 0.82	NS
Enalapril	3.59 ± 0.85	3.77 ± 0.86	NS

Mean triglycerides (mmol/L):

	Baseline	Followup	p-value
Losartan	1.23 ± 0.49	1.34 ± 0.56	NS
Enalapril	1.47 ± 0.78	1.78 ± 0.86	NS

9) Progression to type 2 diabetes: NR

10) Markers of carbohydrate metabolism/diabetes control:
Mean glucose (mmol/L):

	Baseline	Followup	p-value
Losartan	5.36 ± 0.65	5.31 ± 0.61	NS
Enalapril	5.56 ± 0.88	5.61 ± 0.90	NS

11) LV mass/function:
LV mass (g/BSA [m^2]):

	Baseline	Followup	p-value
Losartan	98 ± 18	87 ± 19	<0.001
Enalapril	98 ± 20	89 ± 20	<0.001

Similar results with LV mass in g/height

Also report multiple other echo measurements including - IVS thickness, LV internal diam, PW thickness, endocardial shortening fraction, midwall shortening fraction, peak E/A ratio

12) Creatinine/GFR:
Mean creatinine (mmol/L):

	Baseline	Followup	p-value
Losartan	85.7 ± 10.4	83.9 ± 12.9	NS
Enalapril	82.8 ± 14.7	93.2 ± 75.6	NS

Note - SD for enalapril on f/u must be a typo

13) Proteinuria: NR

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Williams, Gosse, Lowe, et al., 2006 **#340**	**Geographical location:** 75 centers Austria, France, Germany, Netherlands, South Africa, Spain, Switzerland, and United Kingdom **Study dates:** NR **Funding source:** NR **Interventions:** - Telmisartan 40 mg initial dose and forced titration to 80 mg after 2 wk (n = 397) - Ramipril 5 mg for 8 wk and then force titrated to ramipril 10 mg for the last 6 wk (n = 404) **Study design:** RCT, parallel-group **Blinding:** - Patients: No - Providers: No - Assessors of outcomes: Yes **Was allocation concealment adequate?:** NR **Baseline/run-in period:** 2- to 4-wk single-blind placebo run-in phase in which prior antihypertensives were discontinued **Duration of treatment:** 14 wk **Duration of post-treatment followup:** NR	**Number of patients:** - Screened for inclusion: 1593 - Eligible for inclusion: 801 - Randomized: 801 - Began treatment: 801 - Completed treatment: 714 - Withdrawals/losses to followup: 57, 37 due to AEs, 10 due to lack of efficacy, 10 withdrew consent (note: reported numbers do not total correctly) **Age:** Mean (SD): 53.6 (10.6) Median: NR Range: NR **Sex (n [%]):** Female: 322 (41.2%) Male: 479 (59.8) **Race/ethnicity (n [%]):** White 621 (77.5%) Black 14 (1.7%) Mongoloid 7 (0.9%) Missing 159 (19.9%) **Baseline blood pressure:** Seated trough BP measured in triplicate using a manual sphygmomanometer according to ASH guidelines Telmisartan Ramipril SPB 158.5 ± 11.9 158.3 ± 12.5 DBP 100.1 ± 4.9 100.1 ± 4.9 **Concurrent medications (n [%]):** NR **Comorbidities (n [%]):** NR **Recruitment setting:** Clinic setting **Inclusion criteria:**	**1) Blood pressure:** Changes in trough seated BP from baseline to 14 wk: Reductions were greater with telmisartan 80 mg than with ramipril 10 mg by 4.6 mm Hg for SBP (p < 0.0001) and by 2.2 mm Hg for DBP (p = 0.0002). Pre-/post-treatment mean values NR. Seated DBP response (DBP < 90 mm Hg or reduction from baseline of ≥ 10 mm Hg): Telmisartan: 61.9% Ramipril: 54.8% (p = 0.03) Seated SBP response (SBP < 140 mm Hg or reduction from baseline of ≥ 10 mm Hg): Telmisartan: 76.2% Ramipril: 66.9% (p = 0.004) Also report BP in last 6 hours of 24 hours of ABPM **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** There were no deaths during the study. **4) Morbidity:** NR **5) Safety:** Any AE: Telmisartan: 153/397 (38.5%) Ramipril: 162/404 (40.1%) Severe AEs: Telmisartan: 13 (3.3%) Ramipril: 17 (4.2%) Drug-related AEs: Telmisartan: 6.5% Ramipril: 10.1% Drug-related serious AEs: 0	**General comments:** - Titrations at different times so that telmisartan is titrated up and to higher relative dose than ramipril - No discussion outside of forced titration of BP checks during study and if any additional agents or if SBP very high what was done **Quality assessment:** Overall rating: Fair Comments: - No clear concealment of randomization - Not blinded - Titrated drugs at different times **Applicability:** Excludes so many patients that patients with heart disease, or patients with many comorbidities would be excluded from the trial

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Mean seated DBP of 95-109 mm Hg measured using a manual sphygmomanometer (mean of 3 measurements taken 2 min apart) - 24-hr ABP of DBP ≥ 85 mm Hg after run-in period **Exclusion criteria:** - Known or suspected history of coronary disease, stroke, congestive heart failure, or recent acute cardiovascular event, secondary hypertension, poorly controlled insulin-dependant diabetes mellitus, or chronic kidney disease - Premenopausal women not using adequate contraception - Night shift workers	**6) Specific adverse events:** Drug-related AEs with incidence greater than 1% (fatigue, dizziness, HA, and cough) occurred in 14 (3.5%) telmisartan vs. 23 (5.7%) ramipril patients Cough: 2 (0.5%) telmisartan vs. 23 (5.7%) ramipril **7) Persistence/adherence:** Compliance with treatment was high (> 98.8%) in both groups – recognize this is in 714/801 patients that completed study **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	
Wogen, Kreilick, Livornese, et al., 2003 **#12890**	**Geographical location:** U.S. ("geographically diverse" claims database) **Study dates:** Aug 1998 – Jul 2000 **Funding source:** Novartis Pharmaceuticals, Inc. **Interventions:** Lisinopril (n = 40,238) Valsartan (n = 29,669) Amlodipine (n = 73,148) **Study design:** Retrospective cohort study	**Number of patients:** - Screened for inclusion: 14.6 million - Eligible for inclusion: 142,945 - Randomized: NA - Began treatment: 142,945 - Completed treatment: NA - Withdrawals/losses to followup: NA **Age:** Mean (SD): 63.1 (14.0) Median: NR Range: NR **Sex (n [%]):** Female: 53% Male: 47%	**1) Blood pressure:** NR **2) Rate of use of a single antihypertensive agent for BP control:** NR **3) Mortality:** NR **4) Morbidity:** NR **5) Safety:** NR **6) Specific adverse events:** NR **7) Persistence/adherence:** Discontinuation was defined as a 60+ day period without a new prescription; persistence was defined as the absence of discontinuation.	**General comments:** None **Quality assessment:** Overall rating: Fair Comments: - Non-random allocation to drugs - Differences noted in comorbidity between valsartan-treated patients and those on other antihypertensive drugs - Funded by pharmaceutical company **Applicability:** - Study period soon after introduction of ARBs; early use may not reflect current use patters

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Blinding: - Patients: No - Providers: No - Assessors of outcomes: No **Was allocation concealment adequate?:** NA **Baseline/run-in period:** NA **Duration of treatment:** NA **Duration of post-treatment followup:** 1 yr	**Race/ethnicity (n [%]):** NR; database stated to be "demographically diverse" **Baseline blood pressure:** NR **Concurrent medications (n [%]):** Concurrent cardiovascular meds: Diuretics: 35% Antihyperlipidemics: 32% Beta-blockers: 25.5% Antiplatelets: 14% Nitrates: 15% Digitalis: 9% Diuretic combination: 8% Valsartan patients significantly less likely to be prescribed these meds than patients in other two groups. **Comorbidities (n [%]):** Mean Chronic Disease Score (± SD) was 10.15 ± 6.00 for the entire cohort and was essentially comparable for all groups A significantly smaller proportion of valsartan patients was classified as having a "severe" chronic disease burden (35% vs. 31% for both lisinopril and amlodipine; $p < 0.0001$) **Recruitment setting:** Administrative pharmacy claims database from a large pharmacy benefits manager. Described as a "demographically and geographically diverse database that contains 3 years of longitudinal pharmacy claims data representing the payer mix in the U.S. health care market, including drug-insured lives from health care insurance carriers, managed care organizations, employers, and retirement and government plans."	Discontinuation was examined directly and also in a Cox model that controlled for age, sex, chronic disease burden, and use of other antihypertensive agents. The results of this modeling were similar to the unadjusted results. Compliance was not measured directly, but instead was estimated as the total days' supply of all prescriptions divided by the length of therapy. Predictors of non-compliance included older age, female sex, high chronic disease scores, use of lipid medications, use of beta-blockers, and use of nitrates. 1-yr persistence Compliance Lisinopril 50% 86.3% Valsartan 63% 88.5% Amlodipine 53% 86.7% **8) Lipid levels:** NR **9) Progression to type 2 diabetes:** NR **10) Markers of carbohydrate metabolism/diabetes control:** NR **11) LV mass/function:** NR **12) Creatinine/GFR:** NR **13) Proteinuria:** NR	

Evidence Table. Direct comparator studies of ACEIs vs. ARBs (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Inclusion criteria: - Continuously benefit-eligible for both mail-order and community pharmacy prescriptions between 1 Aug 1997 and 31 Jul 2000 - Initial prescription for one of 3 study drugs between 1 Aug 1998 and 31 Jul 1999 - New to therapy within the drug class (patients who received a prescription for a drug from the same class in the preceding 12 mo were excluded) **Exclusion criteria:** None specified		

Appendix F: Applicability Criteria

Instructions to abstractors/assessors: Do not assign an overall applicability score. Instead, list the most important (up to 3) limitations affecting applicability, if any, based on the following list.

Setting of the study

(1) In which country (or countries) was the study conducted?

(2) In what health care system (or systems) was the study conducted?

(3) Were patients recruited from the primary, secondary, or tertiary care settings?

(4) How were study centers selected for participation?

(5) How were study clinicians selected for participation?

Selection of participants

(6) How were participants diagnosed and identified for eligibility screening before random allocation?

(7) What were the study eligibility criteria?

(8) What were the study exclusion criteria?

(9) Did the study require a run-in period with the control or placebo intervention?

(10) Did the study require a run-in period with the active intervention?

(11) Did the study selectively recruit participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition?

(12) Did the study report the ratio of randomly allocated participants to nonallocated participants (who were eligible)?

(13) Did the study report the proportion of eligible participants who declined random allocation?

Characteristics of study participants

(14) Did the study report participants' baseline characteristics?

(15) Did the study report participants' race?

(16) Did the study report participants' underlying pathology?

(17) Did the study report participants' stage in the natural history of the disease?

(18) Did the study report participants' severity of disease?

(19) Did the study report participants' comorbid conditions?

(20) Did the study report participants' absolute risk of a poor outcome in the control arm?

Differences between the study protocol and routine clinical practice

(21) Were the study interventions (active arm) similar to interventions used in routine clinical practice?

(22) Was the timing of the intervention similar to the timing in routine clinical practice?

(23) Was the study's control arm appropriate and relevant in relation to routine clinical practice?

(24) Were the study's cointerventions—which were not randomly allocated—adequate to reflect routine clinical practice?

(25) Were any interventions prohibited by the study that are routinely used in clinical practice?

(26) Have there been diagnostic or therapeutic advances used in routine practice since the study was conducted?

Outcome measures and followup

(27) If applicable, did the study use a clinically relevant surrogate outcome?

(28) If applicable, did the study use a scale that is clinically relevant, valid, and reproducible?

(29) If applicable, was the intervention beneficial on the most relevant components of the composite outcome?

(30) Which clinician measured the outcome (e.g., treating physician or surgeon)?

(31) Did the study use patient-centered outcomes?

(32) How frequently were participants followed in the study?

(33) Was the duration of participant followup adequate?

Adverse effects of treatment

(34) How completely did the study report the occurrence of relevant adverse effects?

(35) Did the study report the rates of treatment discontinuations?

(36) Were the study centers and/or clinicians selected on the basis of their skill or experience?

(37) Did the study exclude participants at elevated risk of intervention complications?

(38) Did the study exclude participants who suffered adverse effects during the run-in period?

(39) Did the study monitor participants intensively for early signs of adverse effects?

Appendix G: List of Excluded Direct Comparator Studies

All studies listed below were either identified at the abstract screening stage as having treatment duration/length of followup less than 12 weeks or were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Akinboboye OO, Chou RL, Bergmann SR. Augmentation of myocardial blood flow in hypertensive heart disease by angiotensin antagonists: a comparison of lisinopril and losartan. J Am Coll Cardiol 2002;40(4):703-9. *Exclude: N < 20.*

Alcocer L, Fernandez-Bonetti P, Campos E, et al. Clinical efficacy and safety of telmisartan 80 mg once daily compared with enalapril 20 mg once daily in patients with mild-to-moderate hypertension: results of a multicentre study. Int J Clin Pract Suppl 2004;(145):23-8. *Exclude: Followup < 12 wk.*

Almazov VA, Shlyakhto EV, Konrady AO, et al. Correction of hypertensive cardiac remodelling: comparison of different antihypertensive therapies. Med Sci Monit 2000;6(2):309-13. *Exclude: N < 20.*

Altiparmak MR, Trablus S, Apaydin S, et al. Is losartan as effective as enalapril on posttransplant persistent proteinuria? Transplant Proc 2001;33(7-8):3368-9. *Exclude: Not essential hypertension.*

Andersen S, Tarnow L, Rossing P, et al. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000;57(2):601-6. *Exclude: Followup < 12 wk.*

Azizi M, Linhart A, Alexander J, et al. Pilot study of combined blockade of the renin-angiotensin system in essential hypertensive patients. J Hypertens 2000;18(8):1139-47. *Exclude: Followup < 12 wk.*

Bakris G, Sica D, Ram V, et al. A comparative trial of controlled-onset, extended-release verapamil, enalapril, and losartan on blood pressure and heart rate changes. Am J Hypertens 2002;15(1 Pt 1):53-7. *Exclude: Followup < 12 wk.*

Bavanandan S, Morad Z, Ismail O, et al. A comparison of valsartan and perindopril in the treatment of essential hypertension in the Malaysian population. Med J Malaysia 2005;60(2):158-62. *Exclude: Followup < 12 wk.*

Benz J, Oshrain C, Henry D, et al. Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. J Clin Pharmacol 1997;37(2):101-7. *Exclude: Followup < 12 wk.*

Botero R, Matiz H, Maria E, et al. Efficacy and safety of valsartan compared with enalapril at different altitudes. Int J Cardiol 2000;72(3):247-54. *Exclude: Followup < 12 wk.*

Brown NJ, Kumar S, Painter CA, et al. ACE inhibition versus angiotensin type 1 receptor antagonism: differential effects on PAI-1 over time. Hypertension 2002;40(6):859-65. *Exclude: Followup < 12 wk.*

Byyny RL, Merrill DD, Bradstreet TE, et al. An inpatient trial of the safety and efficacy of losartan compared with placebo and enalapril in patients with essential hypertension. Cardiovasc Drugs Ther 1996;10(3):313-9. *Exclude: Followup < 12 wk.*

Cha YJ, Pearson VE. Angioedema due to losartan. Ann Pharmacother 1999;33(9):936-8. *Exclude: Followup < 12 wk.*

Chan P, Tomlinson B, Huang TY, et al. Double-blind comparison of losartan, lisinopril, and metolazone in elderly hypertensive patients with previous angiotensin-converting enzyme inhibitor-induced cough. J Clin Pharmacol 1997;37(3):253-7. *Exclude: Followup < 12 wk.*

Chanudet X, De Champvallins M. Antihypertensive efficacy and tolerability of low-dose perindopril/indapamide combination compared with losartan in the treatment of essential hypertension. Int J Clin Pract 2001;55(4):233-9. *Exclude: Not ACEI vs. ARB.*

Chen JH, Cheng JJ, Chen CY, et al. Comparison of the efficacy and tolerability of telmisartan 40 mg vs. enalapril 10 mg in the treatment of mild-to-moderate hypertension: a multicentre, double-blind study in Taiwanese patients. Int J Clin Pract Suppl 2004;(145):29-34. *Exclude: Followup < 12 wk.*

Chen K, Chiou CF, Plauschinat CA, et al. Patient satisfaction with antihypertensive therapy. J Hum Hypertens 2005;19(10):793-9. *Exclude: Followup < 12 wk.*

Cheung R, Lewanczuk RZ, Rodger NW, et al. The effect of valsartan and captopril on lipid parameters in patients with type II diabetes mellitus and nephropathy. Int J Clin Pract 1999;53(8):584-92. *Exclude: No separate results for subgroup with hypertension.*

Chiou KR, Chen CH, Ding PY, et al. Randomized, double-blind comparison of irbesartan and enalapril for treatment of mild to moderate hypertension. Chung Hua I Hsueh Tsa Chih 2000;63(5):368-76. *Exclude: Followup < 12 wk.*

Chowta KN, Chowta MN, Bhat P, et al. An open comparative clinical trial to assess the efficacy and safety of losartan versus enalapril in mild to moderate hypertension. J Assoc Physicians India 2002;50:1236-9. *Exclude: Followup < 12 wk.*

Critchley JA, Gilchrist N, Ikeda L, et al. A randomized, double-masked comparison of the antihypertensive efficacy and safety of combination therapy with losartan and hydrochlorothiazide versus captopril and hydrochlorothiazide in elderly and younger patients. Curr Ther Res Clin Exp 1996;57(5):392-407. *Exclude: Could not obtain copy.*

Cuocolo A, Storto G, Izzo R, et al. Effects of valsartan on left ventricular diastolic function in patients with mild or moderate essential hypertension: comparison with enalapril. J Hypertens 1999;17(12 Pt 1):1759-66. *Exclude: Followup < 12 wk.*

de la Sierra A, Gil-Extremera B, Calvo C, et al. Comparison of the antihypertensive effects of the fixed dose combination enalapril 10 mg/nitrendipine 20 mg vs losartan 50 mg/hydrochlorothiazide 12.5 mg, assessed by 24-h ambulatory blood pressure monitoring, in essential hypertensive patients. J Hum Hypertens 2004;18(3):215-22. *Exclude: Followup < 12 wk.*

Delles C, Jacobi J, John S, et al. Effects of enalapril and eprosartan on the renal vascular nitric oxide system in human essential hypertension. Kidney Int 2002;61(4):1462-8. *Exclude: Followup < 12 wk.*

Delles C, Schneider MP, John S, et al. Angiotensin converting enzyme inhibition and angiotensin II AT1-receptor blockade reduce the levels of asymmetrical N(G), N(G)-dimethylarginine in human essential hypertension. Am J Hypertens 2002;15(7 Pt 1):590-3. *Exclude: Followup < 12 wk.*

Diamond JA, Gharavi A, Roychoudhury D, et al. Effect of long-term eprosartan versus enalapril antihypertensive therapy on left ventricular mass and coronary flow reserve in stage I-II hypertension. Eprosartan Study Group. Curr Med Res Opin 1999;15(1):1-8. *Exclude: Could not obtain copy.*

Donmez G, Derici U, Erbas D, et al. The effects of losartan and enalapril therapies on the levels of nitric oxide, malondialdehyde, and glutathione in patients with essential hypertension. Jpn J Physiol 2002;52(5):435-40. *Exclude: Followup < 12 wk.*

el-Agroudy AE, Hassan NA, Foda MA, et al. Effect of angiotensin II receptor blocker on plasma levels of TGF-beta 1 and interstitial fibrosis in hypertensive kidney transplant patients. Am J Nephrol 2003;23(5):300-6. *Exclude: Not essential hypertension.*

Erdem Y, Usalan C, Haznedaroglu IC, et al. Effects of angiotensin converting enzyme and angiotensin II receptor inhibition on impaired fibrinolysis in systemic hypertension. Am J Hypertens 1999;12(11 Pt 1):1071-6. *Exclude: No outcomes of interest.*

Erley CM, Bader B, Scheu M, et al. Renal hemodynamics in essential hypertensives treated with losartan. Clin Nephrol 1995;43 Suppl 1:S8-11. *Exclude: Followup < 12 wk.*

Fagard R, Lijnen P, Pardaens K, et al. A randomised, placebo-controlled, double-blind, crossover study of losartan and enalapril in patients with essential hypertension. J Hum Hypertens 2001;15(3):161-7. *Exclude: Followup < 12 wk.*

Fogari R, Zoppi A, Carretta R, et al. Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. J Hypertens 2002;20(5):1007-14. *Exclude: Followup < 12 wk.*

Fogari R, Zoppi A, Corradi L, et al. Comparative effects of lisinopril and losartan on insulin sensitivity in the treatment of non diabetic hypertensive patients. Br J Clin Pharmacol 1998;46(5):467-71. *Exclude: Followup < 12 wk.*

Fogari R, Zoppi A, Lazzari P, et al. ACE inhibition but not angiotensin II antagonism reduces plasma fibrinogen and insulin resistance in overweight hypertensive patients. J Cardiovasc Pharmacol 1998;32(4):616-20. *Exclude: Followup < 12 wk.*

Fox JC, Leight K, Sutradhar SC, et al. The JNC 7 approach compared to conventional treatment in diabetic patients with hypertension: a double-blind trial of initial monotherapy vs. combination therapy. J Clin Hypertens (Greenwich) 2004;6(8):437-42; quiz 443-4. *Exclude: Followup < 12 wk.*

Franchi F, Lazzeri C, Foschi M, et al. Cardiac autonomic tone during trandolapril-irbesartan low-dose combined therapy in hypertension: a pilot project. J Hum Hypertens 2002;16(8):597-604. *Exclude: Followup < 12 wk.*

Gainer JV, Morrow JD, Loveland A, et al. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med 1998;339(18):1285-92. *Exclude: Followup < 12 wk.*

Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? Kidney Int 1994;45(3):861-7. *Exclude: Followup < 12 wk.*

Goldberg MR, Bradstreet TE, McWilliams EJ, et al. Biochemical effects of losartan, a nonpeptide angiotensin II receptor antagonist, on the renin-angiotensin-aldosterone system in hypertensive patients. Hypertension 1995;25(1):37-46. *Exclude: Followup < 12 wk.*

Gradman AH, Arcuri KE, Goldberg AI, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension 1995;25(6):1345-50. *Exclude: Followup < 12 wk.*

Guasti L, Petrozzino MR, Mainardi LT, et al. Autonomic function and baroreflex sensitivity during angiotensin-converting enzyme inhibition or angiotensin II AT-1 receptor blockade in essential hypertensive patients. Acta Cardiol 2001;56(5):289-95. *Exclude: Followup < 12 wk.*

Guasti L, Zanotta D, Diolisi A, et al. Changes in pain perception during treatment with angiotensin converting enzyme-inhibitors and angiotensin II type 1 receptor blockade. J Hypertens 2002;20(3):485-91. *Exclude: Followup < 12 wk.*

Hannedouche T, Chanard J, Baumelou B, et al. Evaluation of the safety and efficacy of telmisartan and enalapril, with the potential addition of frusemide, in moderate-renal failure patients with mild-to-moderate hypertension. J Renin Angiotensin Aldosterone Syst 2001;2(4):246-54. *Exclude: Followup < 12 wk.*

Hasler C, Nussberger J, Maillard M, et al. Sustained 24-hour blockade of the renin-angiotensin system: a high dose of a long-acting blocker is as effective as a lower dose combined with an angiotensin-converting enzyme inhibitor. Clin Pharmacol Ther 2005;78(5):501-7. *Exclude: Followup < 12 wk.*

Hedner T, Oparil S, Rasmussen K, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. Am J Hypertens 1999;12(4 Pt 1):414-7. *Exclude: Followup < 12 wk.*

Himmelmann A, Keinanen-Kiukaanniemi S, Wester A, et al. The effect duration of candesartan cilexetil once daily, in comparison with enalapril once daily, in patients with mild to moderate hypertension. Blood Press 2001;10(1):43-51. *Exclude: Followup < 12 wk.*

Holwerda NJ, Fogari R, Angeli P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. J Hypertens 1996;14(9):1147-51. *Exclude: Followup < 12 wk.*

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