Antihypertensives: Landmark & Recent Trials

Prepared by: **Brent Jensen** BSP for www.rxfiles.ca , Jan, 2003

TRIAL / Regimen n= #pts, **length**, Publication	Study baseline **demographics**/ **Results** (over study period)	**Abstract** of entire trial	**Comments**
AASK [1] Ramipril ALTACE 2.5-10mg od Vs Metoprolol LOPRESSOR 50-200mg od Vs Amlodipine NORVASC 5-10mg od n=1,094 **3-6.4yr**, JAMA 2002	**African Americans**, BP ~150/96, Mean 55yr (18-70yr), **hypertensive nephrosclerosis**, GFR 20-65 ml/min/1.73sq.m Usual BP grp→ BP 141/85 n=554 Lower BP grp→BP 128/78 n=540 ~BP 150/96→ 135/82 ramipril n=436 135/81 metoprolol, n=441 133/81 amlodipine n=217 **1°** % Risk Reduction of ↓GFR ≥ 50%, ESRD, or death: Ramipril vs metoprolol ↓ 22%, Ramipril vs amlodipine ↓ 38%	Hypertension is a leading cause of end-stage renal disease (ESRD) in the United States, with no known treatment to prevent progressive declines leading to ESRD. To compare the effects of 2 levels of blood pressure (BP) control & 3 antihypertensive drug classes on glomerular filtration rate (GFR) decline in hypertension. Randomized 3 x 2 factorial trial with enrollment from February 1995 to September 1998. A total of 1094 African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2)) were recruited from 21 clinical centers throughout the United States & followed up for 3 to 6.4 years. Participants were randomly assigned to 1 of 2 mean arterial pressure goals, 102 to 107 mm Hg (usual; n = 554) or 92 mm Hg or less (lower; n = 540), & to initial treatment with either a beta-blocker (metoprolol 50-200 mg/d; n = 441), an angiotensin-converting enzyme inhibitor (ramipril 2.5-10 mg/d; n = 436) or a dihydropyridine calcium channel blocker, (amlodipine 5-10 mg/d; n = 217). Open-label agents were added to achieve the assigned BP goals. Rate of change in GFR (GFR slope); clinical composite outcome of reduction in GFR by 50% or more (or > or =25 mL/min per 1.73 m2) from baseline, ESRD, or death. Three primary treatment comparisons were specified: lower vs usual BP goal; ramipril vs metoprolol; & amlodipine vs metoprolol. Achieved BP averaged (SD) 128/78 (12/8) mm Hg in the lower BP group & 141/85 (12/7) mm Hg in the usual BP group. The mean (SE) GFR slope from baseline through 4 years did not differ significantly between the lower BP group (-2.21 [0.17] mL/min per 1.73 m2 per year) & the usual BP group (-1.95 [0.17] mL/min per 1.73 m2 per year; P =.24), & the lower BP goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower BP group = 2%; 95% confidence interval [CI], -22% to 21%; P =.85). None of the drug group comparisons showed consistent significant differences in the GFR slope. However, compared with the metoprolol & amlodipine groups, the ramipril group manifested risk reductions in the clinical composite outcome of 22% (95% CI, 1%-38%; P =.04) & 38% (95% CI, 14%-56%; P =.004), respectively. There was no significant difference in the clinical composite outcome between the amlodipine & metoprolol groups. **CONCLUSIONS:** No additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower BP goal. Angiotensin-converting enzyme inhibitors appear to be more effective than beta-blockers or dihydropyridine calcium channel blockers in slowing GFR decline.	**Ramipril slows** GFR decline, ↓ ESRD or death **more** than metoprolol or amlodipine. **Metoprolol** may improve renal outcomes & did ↓ ESRD or death vs amlodipine, esp. in pts with ↑ proteinuria (>300mg/d). **Amlodipine** arm **halted** based on safety monitoring board. **No** additional **benefit** of slowing progression of hypertensive nephrosclerosis was observed with the **lower BP goal** (**128/78** vs **141/85**), but still some additional ↓ in proteinuria.
ALLHAT [2,3] Step1: Doxazosin CARDURA 2-8mg/d n=9,067 3.3yr Vs Amlodipine NORVASC 2.5-10mg od n=9,048 Vs Lisinopril ZESTRIL 10-40mg od n=9,054 **Vs** **Chlorthalidone** 12.5-25mg od n=15,255 Open label: Step 2: Reserpine 0.05-0.2mg/d, Clonidine 0.1-0.3mg bid, Atenolol 25-100mg/d, Step 3: Hydralazine 25-100mg bid n=**33,357** →42,418 incl. doxazosin arm **4.9yr**, JAMA 2002 **ALLHAT LLT** [4] Pravastatin PRAVACHOL 40mg hs vs usual standard care (non-blinded) n=10,365 **4.8yr**, JAMA 2002	↑**BP**(146/84) & **1 other risk factor** (prev MI,stroke,LVH,diabetes,smoke,↓HDL,hx CVD) ≥ 55yr [Mean 67yr;(55-79yr) 93%], Scr 88 ummol/l, 47% women, 35% black,19% hispanic,**36% diabetes.** ↑BP 146/84→133.9/75.4 chlorthalidone 134.7/74.6 amlodipine, 135.9/75.4 lisinopril GFR 78 ml/min/1.73 m² @baseline Chlorthalidone vs amlodipine vs lisinopril: **6yr** rate per 100 persons **1°** : ↔ Fatal CHD & nonfatal MI 11.5 vs 11.3 vs 11.4; NS HF 7.7vs**10.2**vs8.7% Coronary revasc. 9.2vs10vs10.2% Angina hosp./tx 12.1vs12.6vs13.6% CHD 19.9vs19.9vs20.8% fatal CHD, non fatal MI,coronary revascularization angina with hosp. stroke 5.6vs5.4vs6.3% CVD 30.9vs32vs33.3% fatal CHD, non fatal MI, coronary revascularization, angina with & without hospitalization, stroke, heart failure & peripheral arterial dx ESRD 1.8vs2.1v2% GFR 70vs75.1vs70.7 ml/min/1.73 m² @ 4yr Death all 17.3vs16.8vs17.2%; NS amlodipine vs chlorthalidone 6yr rate/100persons ↑ HF 10.2vs7.7%; NNT=40 lisinopril vs chlorthalidone 6yr rate/100persons ↑HF esp. ↑ in blacks 8.7vs7.7%;NNT=100 ↑stroke esp.↑ blacks 6.3vs5.6%;NNT=143 ↑combined CVD dx esp.↑ in blacks 33.3vs30.9%; NNT=42 **Pravastatin** sub-study: 6yr rate/100persons Mean 66yr,LDL 3.8 mmol/l,chol 5.8 mmol/l, CHD~14%, Diabetes 35%. **1°** : death all cause 14.9vs15.3%; NS ↓ Fatal CHD & nonfatal MI 9.3vs10.4%; NS ↓ stroke 5.3vs5.8%; NS	Hypertension is associated with a significantly increased risk of morbidity & mortality. Only diuretics & beta-blockers have been shown to reduce this risk in long-term clinical trials. Whether newer antihypertensive agents reduce the incidence of cardiovascular disease (CVD) is unknown. To compare the effect of **doxazosin**, an alpha-blocker, with chlorthalidone, a diuretic, on incidence of CVD in patients with hypertension as part of a study of 4 types of antihypertensive drugs: chlorthalidone, doxazosin, amlodipine, & lisinopril. Randomized, double-blind, active-controlled clinical trial, the Antihypertensive & Lipid-Lowering Treatment to Prevent Heart Attack Trial, initiated in February 1994. In January 2000, after an interim analysis, an independent data review committee recommended discontinuing the doxazosin treatment arm based on comparisons with chlorthalidone. Therefore, outcomes data presented herein reflect follow-up through December 1999. A total of 625 centers in the United States & Canada. A total of 24,335 patients (aged > or = 55 years) with hypertension & at least 1 other coronary heart disease (CHD) risk factor who received either doxazosin or chlorthalidone. Participants were randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n=15,268), or doxazosin, 2 to 8 mg/d (n=9067), for a planned follow-up of 4 to 8 years. The primary outcome measure was fatal CHD or nonfatal myocardial infarction (MI), analyzed by intent to treat; secondary outcome measures included all-cause mortality, stroke, & combined CVD (CHD death, nonfatal MI, stroke, angina, coronary revascularization, congestive heart failure [CHF], & peripheral arterial disease); compared by the chlorthalidone group vs the doxazosin group. Median follow-up was 3.3 years. A total of 365 patients in the doxazosin group & 608 in the chlorthalidone group had fatal CHD or nonfatal MI, with no difference in risk between the groups (relative risk [RR], 1.03; 95% confidence interval [CI], 0.90-1.17; P=.71). Total mortality did not differ between the doxazosin & chlorthalidone arms (4-year rates, 9.62% & 9.08%, respectively; RR, 1.03; 95% CI, 0.90-1.15; P=.56.) The doxazosin arm, compared with the chlorthalidone arm, had a higher risk of stroke (RR, 1.19; 95% CI, 1.01-1.40; P=.04) & combined CVD (4-year rates, 25.45% vs 21.76%; RR, 1.25; 95% CI, 1.17-1.33; P<.001). Considered separately, CHF risk was doubled (4-year rates, 8.13% vs 4.45%; RR, 2.04; 95% CI, 1.79-2.32; P<.001); RRs for angina, coronary revascularization, & peripheral arterial disease were 1.16 (P<.001), 1.15 (P=.05), & 1.07 (P=.50), respectively. **CONCLUSIONS:** Our data indicate that compared with doxazosin, chlorthalidone yields essentially equal risk of CHD death/nonfatal MI but significantly reduces the risk of combined CVD events, particularly CHF, in high-risk hypertensive patients. Antihypertensive therapy is well established to reduce hypertension-related morbidity & mortality, but the optimal first-step therapy is unknown. Objective To determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs **treatment with a diuretic**. The Antihypertensive & Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active-controlled clinical trial conducted from February 1994 through March 2002. A total of 33 357 participants aged 55 years or older with hypertension & at least 1 other CHD risk factor from 623 North American centers. Randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n = 15 255); amlodipine, 2.5 to 10 mg/d (n = 9048); or lisinopril, 10 to 40 mg/d (n = 9054) for planned follow-up of approximately 4 to 8 years. The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), & combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure [HF], & peripheral arterial disease). Mean follow-up was 4.9 years. The primary outcome occurred in 2956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI, 0.90-1.07) for amlodipine (6-year rate, 11.3%) & 0.99 (95% CI, 0.91-1.08) for lisinopril (6-year rate, 11.4%). Likewise, all-cause mortality did not differ between groups. Five-year systolic blood pressures were significantly higher in the amlodipine (0.8 mm Hg, *P* = .03) & lisinopril (2 mm Hg, *P*<.001) groups compared with chlorthalidone, & 5-year diastolic blood pressure was significantly lower with amlodipine (0.8 mm Hg, *P*<.001). For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25-1.52). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05-1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02-1.30); & HF (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07-1.31). **CONCLUSIONS:** Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD & are less expensive. They should be preferred for first-step antihypertensive therapy. Studies have demonstrated that statins administered to individuals with risk factors for coronary heart disease (CHD) reduce CHD events. However, many of these studies were too small to assess all-cause mortality or outcomes in important subgroups. To determine whether **pravastatin** compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor. Multicenter (513 primarily community-based North American clinical centers), randomized, nonblinded trial conducted from 1994 through March 2002 in a subset of participants from the Antihypertensive & Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Ambulatory persons (n = 10 355), aged 55 years or older, with low-density lipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL if known CHD) & triglycerides lower than 350 mg/dL, were randomized to pravastatin (n = 5170) or to usual care (n = 5185). Baseline mean total cholesterol was 224 mg/dL; LDL-C, 146 mg/dL; high-density lipoprotein cholesterol, 48 mg/dL; & triglycerides, 152 mg/dL. Mean age was 66 years, 49% were women, 38% black & 23% Hispanic, 14% had a history of CHD, & 35% had type 2 diabetes. Intervention Pravastatin, 40 mg/d, vs usual care. The primary outcome was all-cause mortality, with follow-up for up to 8 years. Secondary outcomes included nonfatal myocardial infarction or fatal CHD (CHD events) combined, cause-specific mortality, & cancer. Results Mean follow-up was 4.8 years. During the trial, 32% of usual care participants with & 29% without CHD started taking lipid-lowering drugs. At year 4, total cholesterol levels were reduced by 17% with pravastatin vs 8% with usual care; among the random sample who had LDL-C levels assessed, levels were reduced by 28% with pravastatin vs 11% with usual care. All-cause mortality was similar for the 2 groups (relative risk [RR], 0.99; 95% confidence interval [CI], 0.89-1.11; *P* = .88), with 6-year mortality rates of 14.9% for pravastatin vs 15.3% with usual care. CHD event rates were not significantly different between the groups (RR, 0.91; 95% CI, 0.79-1.04; *P* = .16), with 6-year CHD event rates of 9.3% for pravastatin & 10.4% for usual care. **CONCLUSIONS:** Pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension & moderately elevated LDL-C. The results may be due to the modest differential in total cholesterol (9.6%) & LDL-C (16.7%) between pravastatin & usual care compared with prior statin trials supporting cardiovascular disease prevention.	~BP 140/90 achieved in about 2/3 of high risk hypertensive pts by the 5th year of trial by using an average of **TWO** BP meds. **Doxazosin** α blocker: arm **discontinued**, since essentially equal risk of CHD death/nonfatal MI, but sig. ↑ **risk** of combined CVD events, particularly **HF** & **stroke**. **Chlorthalidone** (thiazide diuretic): well tolerated, as effective & least expensive treatment, more effective at ↓ heart failure than amlodipine, & more effective at ↓ heart failure, strokes & other complications of hypertension than lisinopril (but mainly an advantage in black subgroup). As effective in preventing fatal CHD & nonfatal MI as comparators. Observed: ↑ Cholesterol,↑ hypokalemia 8 vs 4 % on KCL supplements & ↑ new diabetes 11.6 vs 9.8 vs 8.1%, but still overall ↓ cardiovascular outcomes the most. **Amlodipine** (dihydropyridine): ↑ **heart failure** vs chlorthalidone, but previous concerns of calcium channel blockers such as ↑ MI, GI bleeds & cancer not seen in this trial. **Lisinopril** (ACE inhibitor): ↑ **stroke & combined CV complications** (both esp. in **black** subgroup) **& heart failure** vs chlorthalidone. But BP was higher esp. in blacks & in ≥ 65yr, BP control was less & more add on BP meds (often a beta blocker) used. Angioedema: **0.4** vs 0.1% vs 0.1%, but ↑ to **0.7% in blacks**. **Pravastatin** 77.4% on statin @6yr was as good as standard therapy, but placebo 28.5% on cholesterol meds, 26% on statin@6yr pts receiving cholesterol therapy diminished the expected benefit in this non blinded trial. The total cholesterol difference was only 9.6% 17.2vs 7.6% , & the LDL difference was only 16.7% 27.7 vs 11% @ 4yrs. Such a large placebo cholesterol lowering effect has not been seen in other major statin trials. ALT was > 3x normal in 0.4% of pravastatin patients. In treated hypertensive pts, with baseline CHD 14%, diabetes 35%, LDL 3.8 mmole/l , a ↓ LDL of ~16% made no clinically significant difference.
CALM [5] Candesartan ATACAND 16mg od Vs Lisinopril ZESTRIL 20mg od Vs Combo candesartan & lisinopril n=199 **24weeks**, BMJ 2000	**Type 2 diabetes**, ↑**BP** (163/96) & **microalbuminuria**, Mean 60yr (30-75): Cand vs lisi vs combo: ↓ SBP 14, 17, 25mm Hg ↓ DBP 10, 11, 16mm Hg ↓ Urinary alb:Scr ratio 24, 39, 50%	To assess & compare the effects of candesartan or lisinopril, or both, on blood pressure & urinary albumin excretion in patients with microalbuminuria, hypertension, & type 2 diabetes. DESIGN: Prospective, randomised, parallel group, double blind study with four week placebo run in period & 12 weeks' monotherapy with candesartan or lisinopril followed by 12 weeks' monotherapy or combination treatment. Tertiary hospitals & primary care centres in four countries (37 centres). 199 patients aged 30-75 years. Candesartan 16 mg once daily, lisinopril 20 mg once daily. Blood pressure & urinary albumin:creatinine ratio. At 12 weeks mean (95% confidence interval) reductions in diastolic blood pressure were 9.5 mm Hg (7.7 mm Hg to 11.2 mm Hg, P<0.001) & 9.7 mm Hg (7.9 mm Hg to 11.5 mm Hg, P<0.001), respectively, & in urinary albumin:creatinine ratio were 30% (15% to 42%, P<0.001) & 46% (35% to 56%, P<0.001) for candesartan & lisinopril, respectively. At 24 weeks the mean reduction in diastolic blood pressure with combination treatment (16.3 mm Hg, 13.6 mm Hg to 18.9 mm Hg, P<0. 001) was significantly greater than that with candesartan (10.4 mm Hg, 7.7 mm Hg to 13.1 mm Hg, P<0.001) or lisinopril (mean 10.7 mm Hg, 8.0 mm Hg to 13.5 mm Hg, P<0.001). Furthermore, the reduction in urinary albumin:creatinine ratio with combination treatment (50%, 36% to 61%, P<0.001) was greater than with candesartan (24%, 0% to 43%, P=0.05) & lisinopril (39%, 20% to 54%, P<0.001). All treatments were generally well tolerated. **CONCLUSIONS:** Candesartan 16 mg once daily is as effective as lisinopril 20 mg once daily in reducing blood pressure & microalbuminuria in hypertensive pts with type 2 diabetes.Combo treatment is well tolerated & more effective in reducing blood pressure.	Monotherapy with **lisinopril** especially & candesartan ↓ BP & **microalbuminuria**; **combination** of **each** may be more effective to ↓BP & to some extent albuminuria. (In the **RESOLVD** trial [6] Circualtion 1999; N=768; 43 wks in HF pts candesartan 4,8,16mg od alone was as effective, safe, & tolerable as enalapril 10mg bid . Combination of candesartan & enalapril was more beneficial for preventing left ventricular remodeling than either agent alone.) {**COOPERATE** [7]: trandolapril 3mg od & losartan 100mg od ↓ primary endpoint of double Scr & ESRD.}

CAPPP [8] Captopril CAPOTEN 50-100mg po od/bid Vs Conventional tx (eg. atenolol/metoprolol 50-100mg od/HCT 25mg od) n=10,985 **6.1yr**, Lancet 1999	In **DBP>100** (BP 162/100 captopril, BP 160/98 conventional), Mean 53yr (25-66), Diabetes 5% 5.6% captopril vs 4.8% conv. Ischemic Dx 64% capt. vs 81% conv. **1°** : ↑ All MI, stroke & other CV deaths 6.6vs6.1%; NS ↓CV mortality Fatal MI & stroke,CV & sudden 1.4vs1.7%; NS ↑ stroke 3.4vs2.7%; NNT=143	Angiotensin-converting-enzyme (ACE) inhibitors have been used for more than a decade to treat high blood pressure, despite the lack of data from randomised intervention trials to show that such treatment affects cardiovascular morbidity & mortality. The Captopril Prevention Project (CAPPP) is a randomised intervention trial to compare the effects of ACE inhibition & conventional therapy on cardiovascular morbidity & mortality in patients with hypertension. CAPPP was a prospective, randomised, open trial with blinded endpoint evaluation. 10,985 patients were enrolled at 536 health centres in Sweden & Finland. Patients 25-66 years with a measured diastolic blood pressure of 100 mm Hg or more on two occasions were randomly assigned captopril or conventional antihypertensive treatment (diuretics, beta-blockers). Analysis was by intention-to-treat. The primary endpoint was a composite of fatal & non-fatal myocardial infarction, stroke, & other cardiovascular deaths. Of 5492 assigned captopril & 5493 assigned conventional therapy, 14 & 13, respectively, were lost to follow-up. Primary endpoint events occurred in 363 patients in the captopril group (11.1 per 1000 patient-years) & 335 in the conventional-treatment group (10.2 per 1000 patient-years; relative risk 1.05 [95% CI 0.90-1.22], p=0-52). **RESULTS**: Cardiovascular mortality was lower with captopril than with conventional treatment (76 vs 95 events; relative risk 0.77 [0.57-1-04], p=0.092), the rate of fatal & non-fatal myocardial infarction was similar (162 vs 161), but fatal & non-fatal stroke was more common with captopril (189 vs 148; 1.25 [1-01-1-55]. p=0.044). Captopril & conventional treatment did not differ in efficacy in preventing cardiovascular morbidity & mortality. The difference in stroke risk is probably due to the lower levels of blood pressure obtained initially in previously treated patients randomised to conventional therapy.	Captopril & conventional arms were equal in preventing CV morbidity & mortality; however **less strokes in the conventional** arm. In patients with **diabetes, captopril** had **less** cardiac & fatal **events** than the beta-blocker arm. In this trial the two arms had baseline randomization flaws.
ELITE II [9] Losartan COZAAR 50mg od Vs Captopril CAPOTEN 50mg tid n=3,152 **1.5yr**, Lancet 2000 (original **ELITE** study n=**722**)	**Heart Failure** II-IV EF <40%(Mean 31%), Mean 71yr(≥60yrs), BP 134/78. **1°** death all cause 17.7vs15.9%; NS ↑ Sudden death 8.2vs6.4%; NS	The ELITE study showed an association between the angiotensin II antagonist losartan & an unexpected survival benefit in elderly heart-failure patients, compared with captopril, an angiotensin-converting-enzyme (ACE) inhibitor. We did the ELITE II Losartan Heart Failure Survival Study to confirm whether losartan is superior to captopril in improving survival & is better tolerated. We undertook a double-blind, randomised, controlled trial of 3,152 patients aged 60 years or older with New York Heart Association class II-IV heart failure & ejection fraction of 40% or less. Patients, stratified for beta-blocker use, were randomly assigned losartan (n=1,578) titrated to 50 mg once daily or captopril (n=1,574) titrated to 50 mg three times daily. The primary & secondary endpoints were all-cause mortality, & sudden death or resuscitated arrest. We assessed safety & tolerability. Analysis was by intention to treat. Median follow-up was 555 days. **RESULTS**: There were no significant differences in all-cause mortality (11.7 vs 10.4% average annual mortality rate) or sudden death or resuscitated arrests (9.0 vs 7.3%) between the two treatment groups (hazard ratios 1.13 [95.7% CI 0.95-1.35], p=0.16 & 1.25 [95% CI 0.98-1.60], p=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse effects (9.7 vs 14.7%, p<0.001), including cough (0.3 vs 2.7%).	**Losartan 50mg od not superior to captopril in HF**, but less losartan discontinued due to side effects 9.7 vs 14.7%. (Concomitant treatment: β-blockers 22% & on ASA 59%.) Other ACE trials with **important benefits in CHF/MI** include: **CONSENSUS** enalapril 20mg bid [10], **SOLVD** enalapril 10mg bid [11] which ↓ mortality 35.2 vs 39.7%, over 3.5yr; NNT=23), **AIRE** ramipril 5mg bid [12] & **ATLAS** lisinopril 12.5-35mg od [13].
FACET [14] Fosinopril MONOPRIL 20mg od Vs Amlodipine NORVASC 10mg hs n=380 **2.5yr**, Diabetes Care'98	↑**BP** & **Type 2** diabetes, Mean 63yr ↑ BP ~170/95→157/88 fosinopril 153/86 amlodipine **1°** : ↓ acute MI, stroke, hospitalized angina 7.4vs14.1%; NNT=15 ↓ MI 5.3vs6.8%; NS Death all cause 2.1vs2.6% NS	ACE inhibitors & calcium antagonists may favorably affect serum lipids & glucose metabolism. The primary aim of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) was to compare the effects of fosinopril & amlodipine on serum lipids & diabetes control in NIDDM patients with hypertension. Prospectively defined cardiovascular events were assessed as secondary outcomes. Inclusion criteria included a diagnosis of NIDDM & hypertension (systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg). Exclusion criteria included a history of coronary heart disease or stroke, serum creatinine > 1.5 mg/dl, albuminuria > 40 micrograms/min, & use of lipid-lowering drugs, aspirin, or antihypertensive agents other than beta-blockers or diuretics. A total of 380 hypertensive diabetics were randomly assigned to open-label fosinopril (20 mg/day) or amlodipine (10 mg/day) & followed for up to 3.5 years. If blood pressure was not controlled, the other study drug was added. Both treatments were effective in lowering blood pressure. At the end of follow-up, between the two groups there was no significant difference in total serum cholesterol, HDL cholesterol, HbA1c, fasting serum glucose, or plasma insulin. The patients receiving fosinopril had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina than those receiving amlodipine (14/189 vs. 27/191; hazards ratio = 0.49, 95% CI = 0.26-0.95). **CONCLUSIONS**: Fosinopril & amlodipine had similar effects on biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major vascular events, compared with the patients randomized to amlodipine.	**Fosinopril** significantly ↓ **major vascular events** vs amlodipine, despite amlodipine ↓ BP 4/2mm Hg more than fosinopril. **Note**: Trial was non blinded & 1/3 of pts were receiving both drugs.
HOPE [15,16,17] Ramipril ALTACE 10mg po hs Vs **Placebo** N=9,297 **4.5yr**, NEJM 2000	**High risk** (CAD 80%, peripheral vascular dx 44%, diabetes 38%, stroke/TIA 11%) & **1 other risk** (eg. HTN 47%) **factor**. Mean 66yr(≥ 55),LVH ~8%, not ↓ EF or heart failure. BP 139/79→136/76 ramipril 139/77 plac. **1°** ↓ MI, stroke, CV death 14vs17.8%; NNT=27 ↓MI 9.9vs12.3%; NNT=42 ↓HF 9vs11.5%; NNT=40 ↓stroke 3.4vs4.9%; NNT=67 ↓CV death 6.1vs8.1%; NNT=50 **↓death all 10.4 vs 12.2%; NNT=56** ↓new diabetes 3.6vs5.4%;NNT=56 ↓diabetes complications 6.4vs7.6%; NNT=84 **Diabetes** substudy: n=3577,Lancet'00 ~BP142/80→140/77 ramipril 142/77 plac **1°** ↓ MI, stroke, CV death 15.3vs19.8%; NNT=23 ↓MI 10.2vs12.9%; NNT=37 ↓stroke 4.2vs6.1%; NNT=53 ↓ CV death 6.2vs9.7%; NNT=29 **↓ death all 10.8vs14%; NNT=32** ↓nephropathy overt 6.8vs8.5%; NNT=59	Treatment with ramipril reduced the rates of death from **cardiovascular causes** (6.1 percent, as compared with 8.1 percent in the placebo group; relative risk, 0.74; P<0.001), myocardial infarction (9.9 percent vs. 12.3 percent; relative risk, 0.80; P<0.001), stroke (3.4 percent vs. 4.9 percent; relative risk, 0.68; P<0.001), death from any cause (10.4 percent vs. 12.2 percent; relative risk, 0.84; P=0.005), revascularization procedures (16.0 percent vs. 18.3 percent; relative risk, 0.85; P=0.002), cardiac arrest (0.8 percent vs. 1.3 percent; relative risk, 0.63; P=0.03), heart failure (9.0 percent vs. 11.5 percent; relative risk, 0.77; P<0.001), & complications related to diabetes (6.4 percent vs. 7.6 percent; relative risk, 0.84; P=0.03). **CONCLUSIONS**: Ramipril significantly reduces the rates of death, myocardial infarction, & stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure. Diabetes mellitus is a strong risk factor for cardiovascular & renal disease. We investigated whether the angiotensin-converting-enzyme (ACE) inhibitor ramipril can lower these risks in patients with **diabetes**. 3577 people with diabetes included in the Heart Outcomes Prevention Evaluation study, aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, & who were not taking ACE inhibitors, were randomly assigned ramipril (10 mg/day) or placebo, & vitamin E or placebo, according to a two-by-two factorial design. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy. The study was stopped 6 months early (after 4.5 years) by the independent data safety & monitoring board because of a consistent benefit of ramipril compared with placebo. Ramipril lowered the risk of the combined primary outcome by 25% (95% CI 12-36, p=0.0004), myocardial infarction by 22% (6-36), stroke by 33% (10-50), cardiovascular death by 37% (21-51), total mortality by 24% (8-37), revascularisation by 17% (2-30), & overt nephropathy by 24% (3-40, p=0.027). After adjustment for the changes in systolic (2.4 mm Hg) & diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (12-36, p=0.0004). **INTERPRETATION**: Ramipril was beneficial for cardiovascular events & overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in blood pressure. This treatment represents a vasculoprotective & renoprotective effect for people with diabetes. To determine the effect of the angiotensin converting enzyme inhibitor ramipril on the secondary **prevention of stroke**. Randomised controlled trial with 2x2 factorial design. 267 hospitals in 19 countries. 9297 patients with vascular disease or diabetes plus an additional risk factor, followed for 4.5 years as part of the HOPE study. Stroke (confirmed by computed tomography or magnetic resonance imaging when available), transient ischaemic attack, & cognitive function. Blood pressure was recorded at entry to the study, after 2 years, & at the end of the study. RESULTS: Reduction in blood pressure was modest (3.8 mm Hg systolic & 2.8 mm Hg diastolic). The relative risk of any stroke was reduced by 32% (156 v 226) in the ramipril group compared with the placebo group, & the relative risk of fatal stroke was reduced by 61% (17 v 44). Benefits were consistent across baseline blood pressures, drugs used, & subgroups defined by the presence or absence of previous stroke, coronary artery disease, peripheral arterial disease, diabetes, or hypertension. Significantly fewer patients on ramipril had cognitive or functional impairment. **CONCLUSIONS**: Ramipril reduces the incidence of stroke in patients at high risk, despite a modest reduction in blood pressure.	**Ramipril** significantly **reduces** the **rates of death**, MI & stroke when compared to **placebo** in (especially hypertensive [18]) **high-risk pts** who were not known to have a low ejection fraction or heart failure. Benefits greater in **diabetes**. **BP reduction may be greater than the "modest" initially reported**. **Ramipril** given @ **hs**→ BP measured in morning 10-18 hrs later. (Ambulatory BP in 38 peripheral arterial dx pts at 1yr had night time BP ↓ by **17/8** mm Hg vs morning office reading of ↓ 8/2 mm Hg. Morning office BP's for entire trial was a ↓ of only 3/2 mm Hg) [19]. Baseline: **diuretics** 15%, β blockers 39%,ASA 76% & lipid meds 29%.
HOT [20] BP→target 3 separate DBP gps **Felodipine RENEDIL** 5→10mg od, +/-ACE, +/- Beta-blocker, +/-diuretic Aspirin 75mg od vs **placebo** N=18,790 **3.8yr**, Lancet 1998	↑**BP** 170/105→to **3 DBP gps**: ≤ 90 gp →144/85; ≤ 85 gp→141/83; ≤80 gp→140/81 8% diabetes, Mean 61.5yr (50-80): **1°** ↔MI, stroke, CV death 3.7 vs 3.7 vs 3.5%; NS Death all cause 3 vs 3.1 vs **3.3**%; NS diabetes ↓ 1° MI, stroke, CV death ≤ 90gp vs ≤80gp: 9vs4.4;NNT=22 **Aspirin study**: **1°** : ↓ MI, stroke, CV death 3.3vs3.9%; NNT=**167** ↓ MI 0.9vs1.4%; NNT=200 ↔stroke 1.6vs1.6%; NS ↑ Major non fatal bleed 1.4vs0.7%;NNH=**143**	Despite treatment, there is often a higher incidence of cardiovascular complications in patients with hypertension than in normotensive individuals. Inadequate reduction of their blood pressure is a likely cause, but the optimum target blood pressure is not known. The impact of acetylsalicylic acid (aspirin) has never been investigated in patients with hypertension. We aimed to assess the optimum target diastolic blood pressure & the potential benefit of a low dose of acetylsalicylic acid in the treatment of hypertension. 18790 patients, from 26 countries, aged 50-80 years (mean 61.5 years) with hypertension & diastolic blood pressure between 100 mm Hg & 115 mm Hg (mean 105 mm Hg) were randomly assigned a target diastolic blood pressure. 6264 patients were allocated to the target pressure < or =90 mm Hg, 6264 to < or =85 mm Hg, & 6262 to < or =80 mm Hg. Felodipine was given as baseline therapy with the addition of other agents, according to a five-step regimen. In addition, 9399 patients were randomly assigned 75 mg/day acetylsalicylic acid (Bamycor, Astra) & 9391 patients were assigned placebo. Diastolic blood pressure was reduced by 20.3 mm Hg, 22.3 mm Hg, & 24.3 mm Hg, in the < or =90 mm Hg, < or =85 mm Hg, & < or =80 mm Hg target groups, respectively. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mm Hg; the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg. Further reduction below these blood pressures was safe. In patients with diabetes mellitus there was a 51% reduction in major cardiovascular events in target group < or =80 mm Hg compared with target group < or =90 mm Hg (p for trend=0.005). Acetylsalicylic acid reduced major cardiovascular events by 15% (p=0.03) & all myocardial infarction by 36% (p=0.002), with no effect on stroke. There were seven fatal bleeds in the acetylsalicylic acid group & eight in the placebo group, & 129 versus 70 non-fatal major bleeds in the two groups, respectively (p<0.001). **INTERPRETATION**: Intensive lowering of blood pressure in patients with hypertension was associated with a low rate of cardiovascular events. The HOT Study shows the benefits of lowering the diastolic blood pressure down to 82.6 mm Hg. Acetylsalicylic acid significantly reduced major cardiovascular events with the greatest benefit seen in all myocardial infarction. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major bleeds were twice as common.	Lowest MI, stroke & CV death was @ BP 139/**82.6** mm Hg. Lowest CV mortality @ 139/**86.5** mm Hg. Authors state "**Most** of these **benefit**s achieved at a ~BP of **140/90**, and only a small further benefit obtained by lowering BP any further." Pts with **diabetes** n=1501 had a **major ↓ in MI,stroke, & CV death** @ **DBP ≤80** vs DBP ≤90 mm HG, thus supporting aggressive BP lowering for patients with diabetes. **ASA**: ↓ MI, stroke, & CV death (no effect on stroke), but at a cost of ↑ non fatal major bleeds. In this study 78% pts were on felodipine,41% on ACE, & 28% on beta-blockers.

IDNT [21] Irbesartan AVAPRO 75→**300mg** od Vs Amlodipine NORVASC 2.5→**10mg** od Vs **Placebo** Other BP meds: Open label diuretics, α or β blockers & centrally acting (Non-study BP meds in irbesartan & amlodipine gps average was 3 vs 3.3 in placebo gp) n=1,715 **2.6yr**, NEJM 2001	**Type 2 diabetes** & **Nephropathy**, Mean ~59yr (30-70yr) BP: 160/87→140/77 irbesartan vs 159/87→141/77 amlodipine vs 158/87→144/80 placebo **Protein excretion** ≥ 900mg/d (Median 2.9 g/d), Urinary Albumin excretion (Median 1.9g/d), Scr 88-265 umol/l. Irbesartan vs placebo: **1°** : ↓ double Scr, onset end-stage renal dx, death 32.6vs39%; NNT= 16 ↓Double Scr 16.9vs23.7%;NNT=15 ↓ Onset end stage renal dx 14.2vs17.8%; NS Death all cause 15vs16.3%; NS ↓ Proteinuria 1.1 g/24hr vs 0.3 ↓ GFR rate 5.5vs6.5 ml/min/1.73 m²/yr	It is unknown whether either the angiotensin-II-receptor blocker irbesartan or the calcium-channel blocker amlodipine slows the progression of nephropathy in patients with type 2 diabetes independently of its capacity to lower the systemic blood pressure. We randomly assigned 1715 hypertensive patients with nephropathy due to type 2 diabetes to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mm Hg or less in all groups. We compared the groups with regard to the time to the primary composite end point of a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death from any cause. We also compared them with regard to the time to a secondary, cardiovascular composite end point. RESULTS: The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the primary composite end point that was 20 percent lower than that in the placebo group (P=0.02) & 23 percent lower than that in the amlodipine group (P=0.006). The risk of a doubling of the serum creatinine concentration was 33 percent lower in the irbesartan group than in the placebo group (P=0.003) & 37 percent lower in the irbesartan group than in the amlodipine group (P<0.001). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23 percent lower than that in both other groups (P=0.07 for both comparisons). These differences were not explained by differences in the blood pressures that were achieved. The serum creatinine concentration increased 24 percent more slowly in the irbesartan group than in the placebo group (P=0.008) & 21 percent more slowly than in the amlodipine group (P=0.02). There were no significant differences in the rates of death from any cause or in the cardiovascular composite end point. **CONCLUSIONS**: The angiotensin-II-receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes.	**Irbesartan** is effective in **delaying** the progression of **nephropathy** due to type 2 diabetes (amlodipine no better than placebo), despite a BP that was similar in both groups. Hyperkalemia requiring discontinuation in **1.9** vs 0.4% the irbesartan vs placebo groups. **Unfortunately** in **IDNT & IRMA II & RENAAL** the **ARB not compared to ACEI** -the **previous gold standard.**
INSIGHT [22] Nifedipine ADALAT 30-60mg GITS od Vs HCT **25**mg/amiloride 2.5mg (1-**2** tabs od) Adding atenolol 25-50mg or Enalapril 5-10mg od n=6,321 ~**3.5yr**, Lancet 2000	↑**BP & 1 additional risk factor**, Mean 65yr (55-80), ↑chol 52%,ISH 24%, diabetes20%, ↑ BP 173/99→138/82 both groups **1°** : ↑ CV death; HF ,stroke & MI 6.3vs5.8%; NS ↑ MI 3vs2.7%; NS ↑ HF 0.8vs0.3%; NNT=200 ↓ stroke All 2.1vs2.3%; NS Death all cause 9.7vs9.6%; NS	The efficacy of antihypertensive drugs newer than diuretics & beta-blockers has not been established. We compared the effects of the calcium-channel blocker nifedipine od with the diuretic combination co-amilozide on cardiovascular mortality & morbidity in high-risk patients with hypertension. We did a prospective, randomised, double-blind trial in Europe & Israel in 6321 patients aged 55-80 years with hypertension (blood pressure > or = 150/95 mm Hg, or > or = 160 mm Hg systolic). Patients had at least one additional cardiovascular risk factor. We randomly assigned patients nifedipine 30 mg in a long-acting gastrointestinal-transport-system (GITS) formulation (n=3157), or co-amilozide (hydrochlorothiazide 25 mg [corrected] plus amiloride 2.5 mg; n=3164). Dose titration was by dose doubling, & addition of atenolol 25-50 mg or enalapril 5-10 mg. The primary outcome was cardiovascular death, myocardial infarction, heart failure, or stroke. Analysis was done by intention to treat. Primary outcomes occurred in 200 (6.3%) patients in the nifedipine group & in 182 (5.8%) in the co-amilozide group (18.2 vs 16.5 events per 1000 patient-years; relative risk 1.10 [95% CI 0.91-1.34], p=0.35). Overall mean blood pressure fell from 173/99 mm Hg (SD 14/8) to 138/82 mm Hg (12/7). **RESULTS**: There was an 8% excess of withdrawals from the nifedipine group because of peripheral oedema (725 vs 518, p<0.0001), but serious adverse events were more frequent in the co-amilozide group (880 vs 796, p=0.02). Deaths were mainly non-vascular (nifedipine 176 vs co-amilozide 172; p=0.81). 80% of the primary events occurred in patients receiving randomised treatment (157 nifedipine, 147 co-amilozide, difference 0.33% [-0.7 to 1.4]). Nifedipine once daily & co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications. The choice of drug can be decided by tolerability & blood-pressure response rather than long-term safety or efficacy.	Nifedipine & co-amilozide (=1/2 tab of Moduret) **equal** in preventing CV death, stroke & all MI. **Less fatal MI & heart failure** in the **diuretic arm**. Nifedipine stopped early in 8% of pts because of ↑ peripheral edema, but overall severe adverse events more in mid-high dosed co-amilozide 28 vs 25%. Heart rate ↓ slightly in both gps.
IRMA II [23] Irbesartan AVAPRO 150mg od Vs AVAPRO 300mg od Vs **Placebo** {nondihydropyridine CCB 27%, diuretic 25%, β-blocker 19%, other 15%} n=590 **2yr**, NEJM 2001	↑**BP**,**Type 2 diabetes** & **normal** GFR, Scr<133umol/l & microalbuminuria, Mean ~58yr (30-70yr): BP 153/91→141/83 irbesartan 300mg vs 153/90→143/83 irbesartan 150mg vs 153/90→144/83 placebo Diabetic nephropathy onset urinary albumin excretion >200ug/min & ↑ baseline ≥ 30% 5.2 irb 300mg vs9.7 irb 150mg vs14.9% placebo	Microalbuminuria & hypertension are risk factors for diabetic nephropathy. Blockade of the renin-angiotensin system slows the progression to diabetic nephropathy in patients with type 1 diabetes, but similar data are lacking for hypertensive patients with type 2 diabetes. We evaluated the renoprotective effect of the angiotensin-II-receptor antagonist irbesartan in hypertensive patients with type 2 diabetes & microalbuminuria. A total of 590 hypertensive patients with type 2 diabetes & microalbuminuria were enrolled in this multinational, randomized, double-blind, placebo-controlled study of irbesartan, at a dose of either 150 mg daily or 300 mg daily, & were followed for two years. The primary outcome was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate that was greater than 200 microg per minute & at least 30 percent higher than the base-line level. RESULTS: The base-line characteristics in the three groups were similar. Ten of the 194 patients in the 300-mg group (5.2 percent) & 19 of the 195 patients in the 150-mg group (9.7 percent) reached the primary end point, as compared with 30 of the 201 patients in the placebo group (14.9 percent) (hazard ratios, 0.30 [95 percent confidence interval, 0.14 to 0.61; P< 0.001] & 0.61 [95 percent confidence interval, 0.34 to 1.08; P=0.081 for the two irbesartan groups, respectively). The average blood pressure during the course of the study was 144/83 mm Hg in the placebo group, 143/83 mm Hg in the 150-mg group, & 141/83 mm Hg in the 300-mg group (P=0.004 for the comparison of systolic blood pressure between the placebo group & the combined irbesartan groups). Serious adverse events were less frequent among the patients treated with irbesartan (P=0.02). **CONCLUSIONS**: Irbesartan is renoprotective independently of its blood-pressure-lowering effect in patients with type 2 diabetes & microalbuminuria.	**Irbesartan delays progression to nephropathy** in **Type 2 diabetes patients with microalbuminuria**. The effect was **dose related** with 300mg od having the greatest effect. **Unfortunately** in **IDNT & IRMA II & RENAAL** the **ARB not compared to ACEI** -the **previous gold standard.**
LIFE [24, 25, 26] Losartan COZAAR 50-100mg od +/-HCT 12.5-25mg od Vs Atenolol TENORMIN 50-100mg od +/-HCT 12.5-25mg od n=9,193 **4.8yr**, Lancet 2002	↑ **BP** 174/98→144/81 losar. 145/81 aten. & **left ventricular hypertrophy.** Vascular dx 25%, CHD 16%, diabetes 13%, stroke/TIA 8%,ISH 13%.Mean 67yr(55-80). **1°** : ↓ CV events death,MI,stroke 11vs12.8%; NNT=56 **↓ CV death** 4.4vs5.1%; NS **↑ MI** 4.3vs4.1%; NS ↓ stroke All 5vs6.7%; NNT=59 ↓new diabetes 6vs8%; NNT=50 Death all cause 8.3vs9.4%; NS **Diabetes substudy**: BP 177/96→146/79 losar. 148/79 aten. N=1,195 (13%); over 4.7yr. A. fibrillation losartan 5%, atenolol 8%. **1°** : ↓ CV events death,MI,stroke 17.6vs22.8%; NNT=20 ↓ MI 7vs8.2%; NS ↓ stroke 8.7vs10.7%; **NS** ↓ CV death 6.5vs10%; NNT=29 **↓ death all 10.8vs17.1%; NNT=16** **ISH substudy**: n=1,326 over 4.7yr BP 174/83→~146/74 Diabetes losartan 15.6%, atenolol 19.8% A. fibrillation losartan 4.2%, atenolol 5.9% **1°**: ↓ CV events death,MI,stroke 11.4vs15.6%; **NS** ↓ MI 4.7vs5.4%; NS ↓stroke 4.8vs8.4%; NNT=28 ↓ new diabetes 5.7vs9%; NNT=31 ↓ CV death 4.1vs7.8%; NNT=27 **↓ death all 10vs14%; NNT=25**	Blood pressure reduction achieved with beta-blockers & diuretics is the best recorded intervention to date for prevention of cardiovascular morbidity & death in patients with hypertension. **Left ventricular hypertrophy** (LVH) is a strong independent indicator of risk of cardiovascular morbidity & death. We aimed to establish whether selective blocking of angiotensin II improves LVH beyond reducing blood pressure &, consequently, reduces cardiovascular morbidity & death. We did a double-masked, randomised, parallel-group trial in 9193 participants aged 55-80 years with essential hypertension (sitting blood pressure 160-200/95-115 mm Hg) & LVH ascertained by electrocardiography (ECG). We assigned participants once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years & until 1040 patients had a primary cardiovascular event (death, myocardial infarction, or stroke). We used Cox regression analysis to compare regimens. Blood pressure fell by 30.2/16.6 (SD 18.5/10.1) & 29.1/16.8 mm Hg (19.2/10.1) in the losartan & atenolol groups, respectively. The primary composite endpoint occurred in 508 losartan (23.8 per 1000 patient-years) & 588 atenolol patients (27.9 per 1000 patient-years; relative risk 0.87, 95% CI 0.77-0.98, p=0.021). 204 losartan & 234 atenolol patients died from cardiovascular disease (0.89, 0.73-1.07, p=0.206); 232 & 309, respectively, had fatal or non-fatal stroke (0.75, 0.63-0.89, p=0.001); & myocardial infarction (non-fatal & fatal) occurred in 198 & 188, respectively (1.07, 0.88-1.31, p=0.491). New-onset diabetes was less frequent with losartan. **INTERPRETATION**: Losartan prevents more cardiovascular morbidity & death than atenolol for a similar reduction in blood pressure & is better tolerated. Losartan seems to confer benefits beyond reduction in blood pressure The most suitable antihypertensive drug to reduce the risk of cardiovascular disease in patients with hypertension & **diabetes** is unclear. In prespecified analyses, we compared the effects of losartan & atenolol on cardiovascular morbidity & mortality in diabetic patients. As part of the LIFE study, in a double-masked, randomised, parallel-group trial, we assigned a group of 1195 patients with diabetes, hypertension, & signs of left-ventricular hypertrophy (LVH) on electrocardiograms losartan-based or atenolol-based treatment. Mean age of patients was 67 years (SD 7) & mean blood pressure 177/96 mm Hg (14/10) after placebo run-in. We followed up patients for at least 4 years (mean 4.7 years [1.1]). We used Cox regression analysis with baseline Framingham risk score & electrocardiogram-LVH as covariates to compare the effects of the drugs on the primary composite endpoint of cardiovascular morbidity & mortality (cardiovascular death, stroke, or myocardial infarction). Mean blood pressure fell to 146/79 mm Hg (17/11) in losartan patients & 148/79 mm Hg (19/11) in atenolol patients. The primary endpoint occurred in 103 patients assigned losartan (n=586) & 139 assigned atenolol (n=609); relative risk 0.76 (95% CI 0.58-.98), p=0.31. 38 & 61 patients in the losartan & atenolol groups, respectively, died from cardiovascular disease; 0.63 (0.42-0.95), p=0.028. Mortality from all causes was 63 & 104 in losartan & atenolol groups, respectively; 0.61 (0.45-0.84), p=0.002. **INTERPRETATION**: Losartan was more effective than atenolol in reducing cardiovascular morbidity & mortality as well as mortality from all causes in patients with hypertension, diabetes, & LVH. Losartan seems to have benefits beyond blood pressure reduction Drug intervention in placebo-controlled trials has been beneficial in **isolated systolic hypertension**. To test the hypothesis that losartan improves outcome better than atenolol in patients with isolated systolic hypertension & electrocardiographically documented left ventricular hypertrophy (ECG-LVH). Double-blind, randomized, parallel-group study conducted in 1995-2001. A total of 1326 men & women aged 55 through 80 years (mean, 70 years) with systolic blood pressure of 160 to 200 mm Hg & diastolic blood pressure of less than 90 mm Hg (mean, 174/83 mm Hg) & ECG-LVH, recruited from 945 outpatient settings in the Nordic countries, the United Kingdom, & the United States. Patients were randomly assigned to receive once-daily losartan (n = 660) or atenolol (n = 666) with hydrochlorothiazide as the second agent in both arms, for a mean of 4.7 years. Composite end point of cardiovascular death, stroke, or myocardial infarction. RESULTS: Blood pressure was reduced by 28/9 & 28/9 mm Hg in the losartan & atenolol arms. The main outcome was reduced by 25% with losartan compared with atenolol, 25.1 vs 35.4 events per 1000 patient-years (relative risk [RR], 0.75; 95% confidence interval [CI], 0.56-1.01; P =.06, adjusted for risk & degree of ECG-LVH; unadjusted RR, 0.71; 95% CI, 0.53-0.95; P =.02). Patients receiving losartan had reductions in the following without a difference in the incidence of myocardial infarction: cardiovascular mortality (8.7 vs 16.9 events per 1000 patient-years; RR, 0.54; 95% CI, 0.34-0.87; P =.01), nonfatal & fatal stroke (10.6 vs 18.9 events per 1000 patient-years; RR, 0.60; 95% CI, 0.38-0.92; P =.02), new-onset diabetes (12.6 vs 20.1 events per 1000 patient-years; RR, 0.62; 95% CI, 0.40-0.97; P =.04), & total mortality (21.2 vs 30.2 events per 1000 patient-years; RR, 0.72; 95% CI, 0.53-1.00; P =.046). Losartan decreased ECG-LVH more than atenolol (P<.001) & was better tolerated. **CONCLUSIONS**: These data suggest that losartan is superior to atenolol for treatment of patients with isolated systolic hypertension & ECG-LVH.	**Losartan** was more effective than atenolol in preventing **stroke** in hypertensive patients with **left ventricular hypertrophy** (**no** difference in **CV mortality** or **MI** or **stroke in blacks** 5.8% of pts). Losartan: more hypotension 2.6 vs 1.6% but well tolerated since 13 vs 18% with atenolol gp discontinued due to adverse events. **Hydrochlorothiazide** used in 44% of losartan & 38% of atenolol pts. In patients with **diabetes, losartan ↓**'s overall **CV death & total mortality,** but not MI or stroke in pts with LVH & ↑BP. Atenolol group was at higher baseline risk. Fewer than 40% of all patients attained a SBP <140 (Mean BP ~**147/79**). Pts with **ISH** & **LVH, losartan** did not reduce overall CV events, but did **↓ stroke, CV & total mortality**. The atenolol group was at higher baseline risk. Survival curves for the primary endpoint separate early. **Unfortunately** in **LIFE** the **ARB not compared to diuretics.**

NORDIL [27] Diltiazem CARDIZEM 180-360mg od +ACEI,diuretic,α blocker as required Vs Diuretic +/- Beta-blocker +ACEI,α blocker as required n=10,881 **4.5yr**, Lancet 2000	**DBP >100**, Mean 60yr (50-74), Diabetes ~7%, ↑ BP 173/106→ to 155/89 diltiazem, 152/89 BB & diuretic **1°** : ↔ CV events death,MI,stroke 7.4vs7.3%; NS ↑ MI 3.4vs2.9%; NS ↔HF 0.1vs0.1%; NS ↓stroke 2.9vs3.6%; NNT=143 ↑ CV death 2.4vs2.1%; NS Death all cause 4.3vs4.2%; NS	Calcium antagonists are a first-line treatment for hypertension. The effectiveness of diltiazem, a non-dihydropyridine calcium antagonist, in reducing cardiovascular morbidity or mortality is unclear. We compared the effects of diltiazem with that of diuretics, beta-blockers, or both on cardiovascular morbidity & mortality in hypertensive patients. In a prospective, randomised, open, blinded endpoint study, we enrolled 10,881 patients, aged 50-74 years, at health centres in Norway & Sweden, who had diastolic blood pressure of 100 mm Hg or more. We randomly assigned patients diltiazem, or diuretics, beta-blockers, or both. The combined primary endpoint was fatal & non-fatal stroke, myocardial infarction, & other cardiovascular death. Analysis was done by intention to treat. Systolic & diastolic blood pressure were lowered effectively in the diltiazem & diuretic & beta-blocker groups (reduction 20.3/18.7 vs 23.3/18.7 mm Hg; difference in systolic reduction p<0.001). A primary endpoint occurred in 403 patients in the diltiazem group & in 400 in the diuretic & beta-blocker group (16.6 vs 16.2 events per 1000 patient-years; relative risk 1.00 [95% CI 0.87-1.15], p=0.97). Fatal & non-fatal stroke occurred in 159 patients in the diltiazem group & in 196 in the diuretic & beta-blocker group (6.4 vs 7.9 events per 1000 patient-years; 0.80 [0.65-0.99], p=0.04) & fatal & non-fatal myocardial infarction in 183 & 157 patients (7.4 vs 6.3 events per 1000 patient-years; 1.16 [0.94-1.44], p=0.17). **INTERPRETATION**: Diltiazem was as effective as treatment based on diuretics, beta-blockers, or both in preventing the combined primary endpoint of all stroke, myocardial infarction, & other cardiovascular death.	**Diltiazem ↓ stroke**, but not MI or CV death, compared to diuretic & β-blockers although treated **BP's were high**. [In the **PRAISE** trial n=1,153 pts with HF; 1.2yr; NEJM 1996 [28] **amlodipine** did not ↑ CV morbidity or mortality in pts with severe heart failure, & with nonischemic dilated cardiomyopathy may ↑ survival. In the **PREVENT** n=825 pts with CAD; 3yr; Ciruclation 2000 [29] trial **amlodipine** had no demonstrable effect on angiographic progression of CAD or the risk of major CV events, but was assoc. with ↓ hospitalizations for unstable angina & revascularization.]
OPTIMAAL [30] Losartan COZAAR 12.5→50mg od Vs Captopril CAPOTEN 6.25x1→12.5→50mg tid n=5,477, **2.7yr**, Lancet 2002	High risk pts **post MI**, ~BP 123/71 Mean 67yr (≥50yr): **1°** : death all cause 18.2vs16.4%; NS ↑ CV death 15.3vs13.3%;NNT=50	ACE inhibitors attenuate the detrimental effects of angiotensin II, & improve survival & reduce morbidity in patients with acute myocardial infarction & evidence of heart failure or left-ventricular dysfunction. Selective antagonism of the angiotensin type 1 receptor represents an alternative approach to inhibition of the renin-angiotensin system. We did a multicentre, randomised trial to test the hypothesis that the angiotensin II antagonist losartan would be superior or non-inferior to the ACE inhibitor captopril in decreasing all-cause mortality in high-risk patients after acute myocardial infarction. 5477 patients 50 years of age or older (mean age 67.4 years [SD 9.8]), with confirmed acute myocardial infarction & heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction, were recruited from 329 centres in seven European countries. Patients were randomly assigned & titrated to a target dose of losartan (50 mg once daily) or captopril (50 mg three times daily) as tolerated. The primary endpoint was all-cause mortality. Analysis was by intention to treat. There were 946 deaths during a mean follow-up of 2.7 (0.9) years: 499 (18%) in the losartan group & 447 (16%) in the captopril group (relative risk 1.13 [95% CI 0.99-1.28], p=0.07). The results for the secondary & tertiary endpoints were as follows: sudden cardiac death or resuscitated cardiac arrest 239 (9%) versus 203 (7%), 1.19 (0.98-1.43), p=0.07, & fatal or non-fatal reinfarction 384 (14%) versus 379 (14%), 1.03 (0.89-1.18), p=0.72. The all-cause hospital admission rates were 1806 (66%) versus 1774 (65%), 1.03 (0.97-1.10), p=0.37. Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (458 [17%] vs 624 [23%], 0.70 [0.62-0.79], p<0.0001). **INTERPRETATION**: Since we saw a non-significant difference in total mortality in favour of captopril, ACE inhibitors should remain first-choice treatment in patients after complicated acute myocardial infarction. Losartan cannot be generally recommended in this population. However, it was better tolerated than captopril, & was associated with significantly fewer discontinuations. Although the role of losartan in patients intolerant of ACE inhibition is not clearly defined, it can be considered in such patients.	**Captopril** ≤50mg TID **↓ CV death** more **than losartan** 50mg od in **post MI patients**. Medication discontinued due to adverse reactions: 7% for losartan vs 14% with captopril.
PROGRESS [31] Perindopril COVERSYL 4mg +/- indapamide LOZIDE 2.5mg od Vs **Placebo** n=6,105 **3.9yr**, Lancet 2001 (58% active pts on indapamide)	Non BP 136/79 & ↑BP 159/94 gps, **hx stroke/TIA** within 5yr,Mean 64yr ↓BP 9/4active (5/3 perin,12/5 perin&indap) **1°** : ↓ stroke 10.1 active vs13.8% placebo; NNT=27 Perind.↓stroke 12.3vs12.9%; NS **Combo** ↓stroke 8.5vs14.4%;NNT=**17** ↑BP gp↓stroke11.1vs16.2%NNT=**20** ☑BP↓stroke 9.1vs11.5%; NNT=42 Death all cause 10vs10.4% NS	Blood pressure is a determinant of the risk of stroke among both hypertensive & non-hypertensive individuals with cerebrovascular disease. However, there is uncertainty about the efficacy & safety of blood-pressure-lowering treatments for many such patients. The perindopril protection against recurrent stroke study (PROGRESS) was designed to determine the effects of a blood-pressure-lowering regimen in hypertensive & non-hypertensive patients with a history of stroke or transient ischaemic attack. 6105 individuals from 172 centres in Asia, Australasia, & Europe were randomly assigned active treatment (n=3051) or placebo (n=3054). Active treatment comprised a flexible regimen based on the angiotensin- converting-enzyme inhibitor perindopril (4 mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. The primary outcome was total stroke (fatal or non-fatal). Analysis was by intention to treat. Over 4 years of follow up, active treatment reduced blood pressure by 9/4 mm Hg. 307 (10%) individuals assigned active treatment suffered a stroke, compared with 420 (14%) assigned placebo (relative risk reduction 28% [95% CI 17-38], p<0.0001). Active treatment also reduced the risk of total major vascular events (26% [16-34]). There were similar reductions in the risk of stroke in hypertensive & non-hypertensive subgroups (all p<0.01). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg & stroke risk by 43% (30-54). Single-drug therapy reduced blood pressure by 5/3 mm Hg & produced no discernable reduction in the risk of stroke. **INTERPRETATION**: This blood-pressure-lowering regimen reduced the risk of stroke among both hypertensive & non-hypertensive individuals with a history of stroke or transient ischaemic attack. Combination therapy with perindopril & indapamide produced larger blood pressure reductions & larger risk reductions than did single drug therapy with perindopril alone. Treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischaemic attack, irrespective of their blood pressure.	Active treatment ↓ stroke in normal & hypertensive pts with previous stroke/TIA. **Perindopril + indapamide** ↓BP 12/5 & significantly **↓ rate of stroke** in normal & hypertensive pts with previous stroke/TIA. Perindopril **alone did not** ↓ stroke. The **hypertensive group benefited most**.
QUIET [32] Quinapril ACCUPRIL 10→20mg od Vs **Placebo** n=1,750, **2.3yr**, Am.J.Cardio 2001	Pt's with **CAD** & preserved LV fx (EF 59%); BP 123/74, angioplasty, Mean 58yr (18-75): **1°** : Time to 1st cardiac event 38.5vs37.7%; NS ↓# of Neworiginally nonintervened angioplasty 9vs13.1%; NNT=25 Death all cause 3.1vs3.1; NS	Angiotensin-converting enzyme inhibitors improve endothelial function, inhibit experimental atherogenesis, & decrease ischemic events. The Quinapril Ischemic Event Trial was designed to test the hypothesis that quinapril 20 mg/d would reduce ischemic events (the occurrence of cardiac death, resuscitated cardiac arrest, nonfatal MI, coronary artery bypass grafting, coronary angioplasty, or hospitalization for angina pectoris) & the angiographic progression of coronary artery disease in patients without systolic left ventricular dysfunction. 1,750 patients were randomized to quinapril 20 mg/d or placebo & followed a mean of 27 +/- 0.3 months. The 38% incidence of ischemic events was similar for both groups (RR 1.04; 95% confidence interval 0.89 to 1.22; p = 0.6). There was also no significant difference in the incidence of patients having angiographic progression of coronary disease (p = 0.71). The rate of development of new coronary lesions was also similar in both groups (p = 0.35). However, there was a difference in the incidence of angioplasty for new (previously unintervened) vessels (p = 0.018). Quinapril was well tolerated in patients after angioplasty with normal left ventricular function. **RESULTS**: Quinapril 20 mg did not significantly affect the overall frequency of clinical outcomes or progression of coronary atherosclerosis. However, absence of the demonstrable effect of quinapril may be due to several limitations in study design.	**Quinapril** was well tolerated in pts after angioplasty/atherectomy with normal LV function, but **no effect** on the overall frequency of clinical outcomes or the angiographic progression of coronary atherosclerosis.
RENAAL [33] Losartan COZAAR 50-100 71% mg od Vs **Placebo** { diuretic 84%, CCB 81%, α-blocker 46%, β-blocker 37% , other 22%} n=1,513 **3.4yr**, NEJM 2001	**Type 2 diabetes** with **Nephropathy**, Mean 60yr (31-70), BP~153/82→140/74losar,142/74placebo Baseline **nephropathy**: a ratio of **urinary albumin**(mg/l) to **urinary creatinine** (g/l) ≥ 300 (or urinary protein excretion ≥0.5g/d) Scr 115-265 umol/l **1°** : ↓ Double Scr, end-stage renal dx, death 43.5vs47.1%;NNT=28 ↓ Double Scr 21.6vs26%;NNT= 23 ↓ End stage renal dx 19.6vs25.5%;NNT= 17 Death all cause 21vs20.3% NS ↓ 1st hospitalization for heart failure 11.9vs16.7%;NNT=21 ↓GFR 4.4vs5.2 ml/min/1.73 m^2 / yr	Diabetic nephropathy is the leading cause of end-stage renal disease. Interruption of the renin-angiotensin system slows the progression of renal disease in patients with type 1 diabetes, but similar data are not available for patients with type 2, the most common form of diabetes. We assessed the role of the angiotensin-II-receptor antagonist losartan in patients with type 2 diabetes & nephropathy. A total of 1513 patients were enrolled in this randomized, double-blind study comparing losartan (50 to 100 mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, alpha-blockers, beta-blockers, & centrally acting agents), for a mean of 3.4 years. The primary outcome was the composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death. Secondary end points included a composite of morbidity & mortality from cardiovascular causes, proteinuria, & the rate of progression of renal disease. A total of 327 patients in the losartan group reached the primary end point, as compared with 359 in the placebo group (risk reduction, 16 percent; P=0.02). Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25 percent; P=0.006) & end-stage renal disease (risk reduction, 28 percent; P=0.002) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity & mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32 percent; P=0.005). The level of proteinuria declined by 35 percent with losartan (P<0.001 for the comparison with placebo). **CONCLUSIONS**: Losartan conferred significant renal benefits in patients with type 2 diabetes & nephropathy, & it was generally well tolerated.	**Losartan** more effective than placebo in **protecting** against the progression of **nephropathy** due to type 2 diabetes, despite BP that was similar in both groups. The authors extrapolate a "**delay of two years** in the need for **dialysis or transplantation"**. **Losartan stopped:** hyperkalemia 1.1 vs 0.5%; & ↑ Scr 1.5 vs 1.2%. In both arms, similar numbers of additional antihypertensives (including dihydropyridines) were used as in the placebo group. **Unfortunately** in **IDNT & IRMA II & RENAAL** the **ARB not compared to ACEI**- the **previous gold standard.**
SHEP [34, 35, 36] Chlorthalidone 12.5→25mg od Then as needed: +/-Atenolol 25-50mg od or reserpine 0.05-0.1mg/d Vs **Placebo** (15% rec'd BP meds during trial) n=4,736, **4.5yr**, JAMA 1991	**ISH**,↑BP 170/77,Mean **72yr**(≥60yr), 12% diabetes, cholesterol 6.1mmol/l: BP 170/77→143/68active,155/72placebo **1°**↓stroke @4.5yr 4.4vs6.7%;NNT=44 ↓ left ventricular failure 2vs4.3%;NNT=44 ↓ CV events death,MI,stroke 8.4vs12.2; NNT=27 ↓CV dx 12.2vs17.5%; NNT=19 death,MI,stroke,CABG,angio.,aneurysm,endarterecto.	To assess the ability of antihypertensive drug treatment to reduce the risk of nonfatal & fatal(total) stroke in isolated systolic hypertension. Multicenter, randomized, double-blind, placebo-controlled. Community-based ambulatory population in tertiary care centers. PARTICIPANTS. 4736 persons (1.06%) from 447,921 screenees aged 60 years & above were randomized (2365 to active treatment, 2371 to placebo). Systolic blood pressure ranged from 160 to 219 mm Hg & diastolic blood pressure was less than 90 mm Hg. Of the participants, 3161 were not receiving antihypertensive medication at initial contact, & 1575 were. The average systolic blood pressure was 170 mm Hg; average diastolic blood pressure, 77 mm Hg. The mean age was 72 years, 57% were women, & 14% were black. Participants were stratified by clinical center & by antihypertensive medication status at initial contact. For step 1 of the trial, dose 1 was chlorthalidone, 12.5 mg/d, or matching placebo; dose 2 was 25 mg/d. For step 2, dose 1 was atenolol, 25 mg/d, or matching placebo; dose 2 was 50 mg/d. Primary. Nonfatal & fatal (total) stroke. Secondary. Cardiovascular & coronary morbidity & mortality, all-cause mortality, & quality of life measures. RESULTS. Average follow-up was 4.5 years. The 5-year average systolic blood pressure was 155 mm Hg for the placebo group & 143 mm Hg for the active treatment group, & the 5-year average diastolic blood pressure was 72 & 68 mm Hg, respectively. The 5-year incidence of total stroke was 5.2 per 100 participants for active treatment & 8.2 per 100 for placebo. The relative risk by proportional hazards regression analysis was 0.64 (P = .0003). For the secondary end point of clinical nonfatal myocardial infarction plus coronary	**Chlorthalidone ↓ stroke & CV events in elderly ISH pts & has greater absolute benefit in patients with diabetes**. When **DBP<65**mm Hg in an analysis by Somes et al, this was associated with an **↑ risk of stroke & CVD.** ~½ pts ONLY on chlorthalidone (12.5mg 30% & 25mg 16% od) Potassium < 3.2mmole occurred in 3.9 vs 0.8% of pts over 4.5yr.

SHEP continued… n=4,736 **4.5yr**, JAMA 1991	Death [all cause] 9vs10.2%; NS **Diabetes substudy**: n=583 (12%) ↓stroke 8.8vs12%; NS ↓CV dx 20.1vs27.7%; NNT=14 death,MI,stroke,CABG,angio.,aneurysm,endarterecto. Death [all cause] 13.8vs16%; NS	death, the relative risk was 0.73. Major cardiovascular events were reduced (relative risk, 0.68). For deaths from all causes, the relative risk was 0.87. **CONCLUSIONS**: In persons aged 60 years & over with isolated systolic hypertension, antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants. Major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000.	
STOP-Hypertension 2 [37] 1. Metoprolol CR 100mg, atenolol 50mg, pindolol 5mg od;+/- HCT/amiloride 25/2.5mg od 2. Felodipine/isradipine 2.5mg od +/- β-blocker 3. Enalapril/lisinopril 10mg od +/-HCT≤25mg od n=6,614, **5yr**, Lancet 1999 (STOP-Hypertension n=1,627)	**Elderly** ↑**BP**(194/98)→159/81 [3 gps], Mean **76yr** (70-84), diabetes 11%: Conventional [gp 1] vs newer [gp 2 & 3]: **1°**:↓ CV events [death, fatal MI & fatal stroke] 10 vs 10%; NS ↓ CV events [death, MI & stroke] 20.1vs20.2%; NS Conventional vs CCB vs ACE: MI 7vs**8.2vs6.3%** [ACE sig better vs CCB] HF 8vs**8.5vs6.8%** [ACE sig better vs CCB] stroke 10.7 vs 9.4 vs 9.8%; NS Death[all] 16.7 vs 16.5 vs 17.2%; NS	The efficacy of new antihypertensive drugs has been questioned. We compared the effects of conventional & newer antihypertensive drugs on cardiovascular mortality & morbidity in elderly patients. We did a prospective, randomised trial in 6614 patients aged 70-84 years with hypertension (blood pressure > or = 180 mm Hg systolic, > or = 105 mm Hg diastolic, or both). Patients were randomly assigned conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily) or newer drugs (enalapril 10 mg or lisinopril 10 mg, or felodipine 2.5 mg or isradipine 2-5 mg daily). We assessed fatal stroke, fatal myocardial infarction, & other fatal cardiovascular disease. Analysis was by intention to treat. Blood pressure was decreased similarly in all treatment groups. The primary combined endpoint of fatal stroke, fatal myocardial infarction, & other fatal cardiovascular disease occurred in 221 of 2213 patients in the conventional drugs group (19.8 events per 1000 patient-years) & in 438 of 4401 in the newer drugs group (19.8 per 1000; relative risk 0.99 [95% CI 0.84-1.16], p=0.89). The combined endpoint of fatal & non-fatal stroke, fatal & non-fatal myocardial infarction, & other cardiovascular mortality occurred in 460 patients taking conventional drugs & in 887 taking newer drugs (0.96 [0.86-1.08], p=0.49). **INTERPRETATION**: Old & new antihypertensive drugs were similar in prevention of cardiovascular mortality or major events. Decrease in blood pressure was of major importance for the prevention of cardiovascular events.	**Conventional & newer drugs** were **similar in CV** mortality & overall major events in this open trial of elderly hypertensives. 1/2 of all patients received more than one BP med. **Of the newer antihypertensives:** **ACE inhibitors had less MI & HF** than the calcium channel blockers.
SYST-EUR [38,39] Nitrendipine [dihydropyridine] 10-20mg bid +/- enalapril 5-20mg hs & HCT 12.5-25mg od Vs **Placebo** (2/3 rec'd BP meds) n=4,695 **2yr** (stopped early) Lancet 1997	**Elderly ISH** ≥60yr(Mean **70yr**), Diabetes 10.5%, ↑BP 174/86→151/79[active]161/84[placebo] **1°**:↓ stroke 2vs3.4%; NNT=72 ↓ Total CV [sudden death, MI, HF] 5.7vs8.1%; NNT=42 Death [all cause] 5.1vs6%;NS	Isolated systolic hypertension occurs in about 15% of people aged 60 years or older. In 1989, the European Working Party on High Blood Pressure in the Elderly investigated whether active treatment could reduce cardiovascular complications of isolated systolic hypertension. Fatal & non-fatal stroke combined was the primary endpoint. All patients (> 60 years) were initially started on masked placebo. At three run-in visits 1 month apart, their average sitting systolic blood pressure was 160-219 mm Hg with a diastolic blood pressure lower than 95 mm Hg. After stratification for centre, sex, & previous cardiovascular complications, 4695 patients were randomly assigned to nitrendipine 10-40 mg daily, with the possible addition of enalapril 5-20 mg daily & hydrochlorothiazide 12.5-25.0 mg daily, or matching placebos. Patients withdrawing from double-blind treatment were still followed up. We compared occurrence of major endpoints by intention to treat. At a median of 2 years' follow-up, sitting systolic & diastolic blood pressures had fallen by 13 mm Hg & 2 mm Hg in the placebo group (n = 2297) & by 23 mm Hg & 7 mm Hg in the active treatment group (n = 2398). The between-group differences were systolic 10.1 mm Hg (95% CI 8.8-11.4) & diastolic, 4.5 mm Hg (3.9-5.1). Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patient-years (42% reduction; p = 0.003). Non-fatal stroke decreased by 44% (p = 0.007). In the active treatment group, all fatal & non-fatal cardiac endpoints, including sudden death, declined by 26% (p = 0.03). Non-fatal cardiac endpoints decreased by 33% (p = 0.03) & all fatal & non-fatal cardiovascular endpoints by 31% (p < 0.001). Cardiovascular mortality was slightly lower on active treatment (-27%, p = 0.07), but all-cause mortality was not influenced (-14%; p = 0.22). **INTERPRETATION:** Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major cardiovascular endpoints.	In **elderly with ISH**, antihypertensive drug treatment **starting with nitrendipine** ↓ rate of CV complications, stroke & possibly dementia [40]. The **benefit was significantly greater** in the **diabetes** arm to ↓ CV mortality & all CV events.
UKPDS [41, 42] **38** [tight control] & **39** [atenolol vs captopril] Captopril 25-50mg BID **or** Atenolol 50-100mg OD vs Furosemide 20-40mg OD-BID Nifedipine SR 10-40mg BID Methyldopa 250-500mg BID Prazosin 1-5mg TID 29% of tight control pts, **required 3 or more BP meds** n=1,148 **8.4yr** BMJ 1998	**Type 2 diabetes**,↑BP ~160/94; Mean 56yr (25-65): **UKPDS 38** tight control tight BP →144/82 [n=758] vs less tight BP→154/87 [n=390] **1°**: ↓ any diabetes endpoint 34.2vs 43.6%; NNT=11 ↓ stroke 5vs8.7%; NNT=27 **1°**: ↓ death related to diabetes 10.8vs15.9%; NNT=20 **1°**: death [all cause] 17.7vs21.3%;NS **UKPDS 39** [captopril vs atenolol] **captopril** [n=400] BP144/83 vs **atenolol** [n=358] BP143/81: **1°**: ↑ any diabetes endpoint 35.3vs33%; NS ↑ stroke 5.3vs4.7%; NS **1°**: death [all cause] 18.8vs16.5%;NS	**UKPDS 38:** To determine whether **tight control of blood pressure** prevents macrovascular & microvascular complications in patients with type 2 diabetes. Randomised controlled trial comparing tight control of blood pressure aiming at a blood pressure of <150/85 mm Hg (with the use of an angiotensin converting enzyme inhibitor captopril or a beta blocker atenolol as main treatment) with less tight control aiming at a blood pressure of <180/105 mm Hg. 20 hospital based clinics in England, Scotland, & Northern Ireland. 1148 hypertensive patients with type 2 diabetes (mean age 56, mean blood pressure at entry 160/94 mm Hg); 758 patients were allocated to tight control of blood pressure & 390 to less tight control with a median follow up of 8.4 years. Predefined clinical end points, fatal & non-fatal, related to diabetes, deaths related to diabetes, & all cause mortality. Surrogate measures of microvascular disease included urinary albumin excretion & retinal photography. Mean blood pressure during follow up was significantly reduced in the group assigned tight blood pressure control (144/82 mm Hg) compared with the group assigned to less tight control (154/87 mm Hg) (P<0.0001). Reductions in risk in the group assigned to tight control compared with that assigned to less tight control were 24% in diabetes related end points (95% confidence interval 8% to 38%) (P=0.0046), 32% in deaths related to diabetes (6% to 51%) (P=0.019), 44% in strokes (11% to 65%) (P=0.013), & 37% in microvascular end points (11% to 56%) (P=0.0092), predominantly owing to a reduced risk of retinal photocoagulation. There was a non-significant reduction in all cause mortality. After nine years of follow up the group assigned to tight blood pressure control also had a 34% reduction in risk in the proportion of patients with deterioration of retinopathy by two steps (99% confidence interval 11% to 50%) (P=0.0004) & a 47% reduced risk (7% to 70%) (P=0.004) of deterioration in visual acuity by three lines of the early treatment of diabetic retinopathy study (ETDRS) chart. After 9 years of follow up 29% of patients in the group assigned to tight control required 3 or more treatments to lower blood pressure to achieve target blood pressures. **CONCLUSIONS**: Tight blood pressure control in patients with hypertension & type 2 diabetes achieves a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy & deterioration in visual acuity. **UKPDS 39:** To determine whether tight control of blood pressure with either a **beta blocker or an angiotensin converting enzyme inhibitor** has a specific advantage or disadvantage in preventing the macrovascular & microvascular complications of type 2 diabetes. Randomised controlled trial comparing an ACEI (captopril) with a beta blocker (atenolol) in patients with type 2 diabetes aiming at a blood pressure of <150/<85 mm Hg. 20 hospital based clinics in England, Scotland, & Northern Ireland. 1148 hypertensive patients with type 2 diabetes (mean age 56 years, mean blood pressure 160/94 mm Hg). Of the 758 patients allocated to tight control of blood pressure, 400 were allocated to captopril & 358 to atenolol. 390 patients were allocated to less tight control of blood pressure. Predefined clinical end points, fatal & non-fatal, related to diabetes, death related to diabetes, & all cause mortality. Surrogate measures of microvascular & macrovascular disease included urinary albumin excretion & retinopathy assessed by retinal photography. Captopril & atenolol were equally effective in reducing blood pressure to a mean of 144/83 mm Hg & 143/81 mm Hg respectively, with a similar proportion of patients (27% & 31%) requiring three or more antihypertensive treatments. More patients in the captopril group than the atenolol group took the allocated treatment: at their last clinic visit, 78% of those allocated captopril & 65% of those allocated atenolol were taking the drug (P<0.0001). Captopril & atenolol were equally effective in reducing the risk of macrovascular end points. Similar proportions of patients in the two groups showed deterioration in retinopathy by two grades after nine years (31% in the captopril group & 37% in the atenolol group) & developed clinical grade albuminuria >=300 mg/l (5% & 9%). The proportion of patients with hypoglycaemic attacks was not different between groups, but mean weight gain in the atenolol group was greater (3.4 kg v 1.6 kg). **CONCLUSIONS**: Blood pressure lowering with captopril or atenolol was similarly effective in reducing the incidence of diabetic complications. This study provided no evidence that either drug has any specific beneficial or deleterious effect, suggesting that blood pressure reduction in itself may be more important than the treatment used	**Tight blood pressure** (~BP 144/82) control in pts with hypertension & **type 2 diabetes** treated with captopril or atenolol achieves a clinically important ↓ diabetes related **morbidity & mortality**. ↓BP with captopril or atenolol was similarly effective in ↓ diabetic complications (BP reduction, preserve renal function & proteinuria & CV complications). No evidence that either drug has any specific beneficial or deleterious effect. **Captopril**: more cough [4 vs 0%]. **Atenolol**: intermittent claudication or cold feet or bronchospasm [10 vs 0%]; ↑weight [3.4 vs 1.6kg] over the 9yrs. **Note: BP control vs Blood glucose control:** Except for metformin in obese type 2 diabetes **tight glucose** control did **not reduce cardiovascular** morbidity & mortality.
Val-HeFT [43, 44] Valsartan DIOVAN 40→160mg bid Vs **Placebo** n=5,010 **1.9yr**, NEJM 2001	**HF** Class II-IV & EF < 40% (Mean 27%); Mean 63yr, diabetes ~25%: **1°**: ↓ Morbidity & mortality 28.8vs32.1%; NNT=31 ↓ hospitalizations for heart failure 13.8vs18.2; NNT=23 **1°**: death [all cause] 19.7vs19.4;NS ACE naïve group n=366 **1°**:↓ Morbidity & mortality 24.9vs42.5%; NNT=6 **1°** death [all cause] 17.3vs27.1;NS	Actions of angiotensin II may contribute to the progression of heart failure despite treatment with currently recommended drugs. We therefore evaluated the long-term effects of the addition of the angiotensin-receptor blocker valsartan to standard therapy for heart failure. A total of 5010 patients with heart failure of New York Heart Association (NYHA) class II, III, or IV were randomly assigned to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality & the combined end point of mortality & morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 hours. Overall mortality was similar in the 2 groups. The incidence of the combined end point, however, was 13.2 percent lower with valsartan than with placebo (relative risk, 0.87; 97.5 percent confidence interval, 0.77 to 0.97; P=0.009), predominantly because of a lower number of patients hospitalized for heart failure; 455 (18.2 percent) in the placebo group & 346 (13.8 percent) in the valsartan group (P<0.001). Treatment with valsartan also resulted in significant improvements in NYHA class, ejection fraction, signs & symptoms of heart failure, & quality of life as compared with placebo (P<0.01). In a post hoc analysis of the combined end point & mortality in subgroups defined according to base-line treatment with angiotensin-converting-enzyme inhibitors or beta-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs. **CONCLUSIONS**: Valsartan significantly reduces the combined end point of mortality & morbidity & improves clinical signs & symptoms in patients with heart failure, when added to prescribed therapy. However, the post hoc observation of an adverse effect on mortality & morbidity in the subgroup receiving valsartan, an ACE inhibitor, & a beta-blocker raises concern about the potential safety of this specific combination.	**Valsartan** ↓ mortality & morbidity predominantly in the 7% of pts with HF **not** treated with ACE inhibitors. Valsartan appears to be an effective therapy in ACE inhibitor-intolerant pts. However, the post hoc observation of **increased mortality** & morbidity in the subgroup receiving valsartan, with **both** an **ACE inhibitor** [93% at baseline], **AND a beta-blocker** [35% at baseline] raises concern. Only 5% of pts were receiving spironolactone.

Rounded→absolute value to **0.1%** **1°**: primary outcome of study **ACEI**=angiotensin converting enzyme inhibitor **ARB**=angiotensin receptor blocker ☑**BP**=normal blood pressure **BP**=blood pressure **CHD**=coronary heart disease **CV**=cardiovascular **DBP**=diastolic blood pressure **Dx**=disease **EF**=ejection fraction **ESRD**=end stage renal disease **GFR**=glomerular filtration rate **HCT**=hydrochlorothiazide **HF**=heart failure **IHD**=ischemic heart dx **ISH**=isolated systolic hypertension **LVH**=left ventricular hypertrophy **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat over average duration of study.

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