Antihypertensives: Landmark & Recent Trials

Study baseline demographics (Results over study period)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study</th>
</tr>
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<tbody>
<tr>
<td><strong>AASK</strong></td>
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<tr>
<td>Ramipril ALTACE</td>
<td></td>
</tr>
<tr>
<td>2.5-10mg od</td>
<td>n=66</td>
</tr>
<tr>
<td>Metoprolol LORPERPRA</td>
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<tr>
<td>50-200mg od</td>
<td>n=88</td>
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<tr>
<td>Amlodipine NORSVC</td>
<td></td>
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<tr>
<td>5-10mg od</td>
<td>n=1,094</td>
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<tr>
<td>Lisinopril ZESTRIL</td>
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<tr>
<td>10-20mg od</td>
<td>n=8,054</td>
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<tr>
<td><strong>ALLHAT</strong></td>
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<tr>
<td>Steer:</td>
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<tr>
<td>Doxazosin CARDURA</td>
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<tr>
<td>(n=7,300)</td>
<td>3.3yr</td>
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<tr>
<td>Amlodipine NORSVC</td>
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<tr>
<td>2.5-10mg od</td>
<td>n=9,048</td>
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<tr>
<td>Lisinopril ZESTRIL</td>
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<tr>
<td>10-20mg od</td>
<td>n=8,054</td>
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<tr>
<td><strong>BPAT</strong></td>
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<tr>
<td>Pravastatin PRAVACHOL</td>
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<tr>
<td>40mg hs vs</td>
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<tr>
<td>non-blind</td>
<td>n=10,365</td>
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<td>Candesartan ATACAND</td>
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<td>Lisinopril ZESTRIL</td>
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<tr>
<td>20mg od</td>
<td>n=250</td>
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**Comments**

- BP 140/90 achieved in about 2/3 of high-risk hypertensives by the 5th year of trial by using an average of TWO BP meds.
- Doxazosin, a blocker, arm discontinued, since essentially equal risk of CHD death/nonfatal MI, but sig. ↑ risk of combined CVD events, particularly HF & stroke.

Chlorhidaladine (thiazide diuretic): well tolerated, as effective & less expensive treatment, more effective at ↓ heart failure than amloidipine, & 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, hypothalamia (<0.4 in ALC supplement) & new diabetes up to 15% vs. 11%, but still overall cardiovascular outcomes are better than any other Rx.

Amlodipine arm halted based on safety monitoring board.

No additional benefit of slow progression of hypertensive nephropathy was observed with the lower BP goal. Angioteensin-converting enzyme inhibitors were more effective than beta-blockers or dihydropyridine calcium blockers in slowing decline.
Angiotensin-converting-enzyme (ACE) inhibitors have been used for more than a decade to treat high blood pressure, despite the lack of data from CAPPP.

**CAPPP**

BP 160/98 conventional), 5.6% captopril vs 4.8% conv.

Ischemic Heart Dx 64% capt. vs 81% conv.

A composite of fatal & non-fatal myocardial infarction, stroke, & other cardiovascular deaths. Of 5492 assigned captopril & 5493 assigned conventional.

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.

**II-IV EF <40%(Mean 31%)**, losartan discontinued due to side effects 9.7 vs 14.7%.

**HOT**

**BP-target 3 separate DBP gps**

Felodipine RENELID 5+10mg od, +/-ACE, +/- Beta-blocker, +/-diuretic

Amlodipine NORVASC 10mg od, Diabetes NORLIP 30mg od

Diabetes 3.7 vs 3.7 vs 3.5% NS

Diabetes death ↑ 1%. MI, stroke, death ≥ 90% vs ≥80%: 9x4.4;N=22

Aspirin study.

Aspirin study.

**Amlodipine**

**Beta-blocker**

In DBP 100 (BP 162/100)

Mean 53yr (25-66), Diabetes 5% (0-8%), Ischemic Heart Dx 6.3%, Stroke 3.7% vs 3.5% NS

↓ MI, stroke, death CV 3.1% vs 3.3%, NS

↓ MI, stroke, death CV ≥90% vs ≥80%: 9x4.4;N=22

Aspirin study.

Aspirin study.

**Diabetes**

Mean 61.5yr (50-80)

↓ MI, stroke, death CV 3.7 vs 3.7 vs 3.5% NS

↓ MI, stroke, death CV 3.1 vs 3.3%, NS

↓ MI, stroke, death CV ≥90% vs ≥80%: 9x4.4;N=22

Aspirin study.

Aspirin study.

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 optimal target blood pressure is not known. The impact of acetylsalicylic acid (aspirin) on the incidence of cardiovascular events in patients with hypertension is still unknown. The potential benefit of a low dose of acetylsalicylic acid in the treatment of hypertension. 18,790 patients, from 26 countries, aged 50-80 years (mean 61.5 years) with hypertension & diastolic blood pressure between 100 mm Hg & 115 mm (mean 105 mm Hg) were randomly assigned a target diastolic blood pressure of 90 mm Hg. 456 patients were allocated to placebo, and 456 patients to 81 mg acetylsalicylic acid daily. Aspirin was given as baseline therapy with the addition of other agents, according to a five-step regimen. In addition, 9,359 patients were randomly assigned 75 mg atorvastatin daily (mean 47.5% of patients), 2.27 mm Hg, in the < or =90 mm Hg group, & 3.22 mm Hg, in the < or =85 mm Hg group, & 3.95 mm Hg, in the < or =80 mm Hg group, respectively. 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% (95% CI: 12-36, p=0.0004). 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.

**CONCLUSIONS**

Ramipril significantly reduces the incidence of stroke in patients at high risk, despite a modest reduction in blood pressure.

Captopril & conventional regimens were equal in preventing CV morbidity & mortality; however less strokes in the conventional.

In patients with diabetes, captopril had less cardiac & fatal events than the beta-blocker arm.

In this trial the two arms had baseline randomisation flaws.
It is unknown whether either the angiotensin-II-receptor blocker irbesartan or the calcium-channel blocker amlodipine slows the progression of diabetes due to type 2 diabetes (amlodipine no better than 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. Amlodipine NORVASC 1.9 vs 0.4% the 2.9 g/d), Urinary Albumin excretion(Median 1.9g/d), Scr 88-265 umol/l.

Placebo
Other BP meds: Open label
Irbesartan vs placebo:
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.

Nifedipine co-amilozide (-12 to 14% of Moduril) 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 were more in mid-high dosed co-amilozide 23 vs 14%. Heart rate ↓ slightly in both gps.

In patients with diabetes, losartan ↓ 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 =14779).

Ps 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.
Calcium antagonists are a first-line treatment for hypertension. The effectiveness of diltiazem, a non-dihydropyridine calcium antagonist, in reducing blood pressure was compared against a diuretic and a beta-blocker. In a trial involving 403 patients, diltiazem reduced systolic blood pressure by 20.3/18.7 mm Hg compared to 23.3/18.7 mm Hg for the diuretic-betablocker group (difference in systolic reduction p<0.001). A primary endpoint, which was the occurrence of CV events (death, MI, stroke) within 5 years, was met in 159 patients in the diltiazem group and in 196 in the diuretic-beta-blocker group (6.4 vs 7.9 events per 1000 patient-years; 0.80 vs 0.83). The secondary endpoints of CV death, MI, stroke also showed no significant difference between the two groups.

ACE inhibitors attenuate the detrimental effects of angiotensin II, improve survival and reduce morbidity in patients with acute myocardial infarction and evidence of heart failure or left ventricular dysfunction. Selective antagonists of the angiotensin type 1 receptor represent 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 60 years [95% CI 58.8, 61.6]), with confirmed acute myocardial infarction & heart failure during the acute phase of a new Q-wave anterior infarction or reinfarction, were recruited from 221 centres in seven European countries. Patients were randomly assigned (1:1) to treatment with captopril (50 mg once daily) or to the ACE inhibitor losartan (50 mg once daily) over a period of 30 days. 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, 3.3] years (417 in the captopril group & 529 in the losartan group). The hazard ratio for all-cause death in the losartan group was 0.89 (95% CI 0.80 to 0.99), p=0.02. The rate of CV death and MI was lower in the losartan group (0.60 vs 0.76 per 1000 patient-years; 0.76 vs 0.87; p<0.001). A primary endpoint was met in 39% of patients in the losartan group compared with 46% in the captopril group (hazard ratio 0.85, 95% CI 0.75 to 0.97; p=0.02). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing treatment (48% vs 52% [0.70 0.92]; p<0.001).

Losartan is more effective than placebo in patients after myocardial infarction or stroke when used instead of an ACE inhibitor. This advantage may persist for up to 10 years. Losartan is well tolerated and produces a consistent blood pressure reduction in patients with a history of stroke or transient ischemic attack. Treatment with these two agents should now be considered for patients with a history of stroke or transient ischemic attack, irrespective of their blood pressure.

Blood pressure is a strong determinant of the risk of stroke among both hypertensive and non-hypertensive individuals with cardiovascular disease. There is also a large body of evidence concerning the safety and effectiveness of antihypertensive treatment for the secondary prevention of stroke.
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.

In persons aged 60 years & over with isolated systolic hypertension, antihypertensive stepped-care drug treatment with low-dose

Diabetes substudy

n=4,736

diabetes 11%:

Mean 56yr (25-65):

+/-

5yr

8.5vs6.8%      NNT=42

↓

3/2 rec’d BP meds

HCT 12.5-25mg od

Tight blood pressure

BP with captopril or atenolol was similarly effective 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. The between-group differences were significant in 10% (0.5 mm Hg; 95% CI 0.0-1.0 mm Hg) & 4.5% (9.3 vs 4.9%). Active treatment reduced the total rate of stroke from 13.9 vs 10.3% per 1000 patient-years (p < 0.001). Non-fatal stroke decreased by 44% (p = 0.003). In the active treatment group, all fatal & non-fatal cardiac endpoints, including sudden death, declined by 29% (p = 0.001). Total & non-fatal cardiac endpoints by 52% (p < 0.001). Total & non-fatal cardiac endpoints by 25% (p = 0.001). Total & non-fatal cardiac endpoints by 24% (p < 0.001). Total & non-fatal cardiac endpoints by 23% (p < 0.001).

In elderly with ISH, antihypertensive drug treatment starting with nitrateding reduces rate of CV complications, stroke & possibly dementia.

The benefit was significantly greater in the diabetes arm ↓ CV mortality & all CV events.

HCT/amiloride 25/2.5mg od

also

1o:

death, MI, stroke, CABG, angio., aneurysm, endarterecto.

The efficacy of new antihypertensive drugs has been questioned. We compared the effects of conventional & newer antihypertensive drugs on mortality & 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 & death from major cardiovascular disease (13.5 vs 22.3 patients per 1000 patient-years; hazard ratio 0.61; 95% confidence interval, 0.48 to 0.77) was reached significantly more slowly in the group assigned to treatment with the active treatment (HCT/amiloride) than in the placebo group (HCT). The between-group difference was significant (9.6% [1.0% to 18.6%]; p = 0.03). Reductions in the rate of fatal stroke & death from other fatal cardiovascular disease were also significant (p = 0.008).

![Image](https://example.com/figure.png)
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). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2988-3007.


