Efficacy of antihypertensive drugs: new evidence from large studies

WHAT WE ALREADY KNEW ABOUT THE EFFICACY OF ANTIHYPERTENSIVE THERAPIES

The **prevention of cardiovascular events** not only depends on the lowering of blood pressure and the control of hypercholesterolaemia, but also on specific biochemical mechanisms for each class of antihypertensive agents.

In comparisons with placebo, the evidence available so far has shown that, besides lowering blood pressure (*Lancet* 2000;356:1955-64)

- √ **thiazide diuretics** and **beta-blockers** reduce all-cause mortality, stroke, heart failure and coronary heart disease;
- √ **ACE-inhibitors** reduce all-cause mortality, stroke and coronary heart disease;
- √ **calcium channel blockers** reduce stroke and—as combined outcomes—cardiovascular disease events and cardiovascular mortality; they do not, however, reduce coronary heart disease, heart failure and all-cause mortality.

IMAGE NOT AVAILABLE

Two recent meta-analyses of randomised controlled studies (*Lancet* 2000;356:1949-54 and 1955-64) have been presented in **Information pack no. 1** (available on www.ceveas.it). The meta-analyses directly compared these classes of drugs and pointed to a substantial similarity of clinical efficacy between diuretics and/or beta-blockers and ACE-inhibitors in first-step antihypertensive therapy; the use of calcium channel blockers, however, was associated with a higher incidence of heart failure, myocardial infarction and coronary heart disease, and a lower incidence of stroke.

INDEX

Comparison of four classes of antihypertensive drugs: the ALLHAT study (*JAMA* 2002;288:2981-97)

CHARACTERISTICS AND OBJECTIVES OF THE STUDY

This was a randomised, double-blind, multicenter study carried out in North America. Its objective was **to determine whether an ACE-inhibitor (lisinopril), a calcium channel blocker (amlodipine) and an alpha-blocker (doxazosin) would be more effective than a thiazide diuretic (chlorthalidone) - as first-choice drugs -** in the prevention of the main cardiovascular disease events in hypertensive patients with at least one other coronary heart disease risk factor. The study involved 42,418 patients; the target blood pressure for each patient was 140/90. One part of the study (which could be the subject of a later in-depth investigation) also assessed the efficacy of lipid-lowering therapy with pravastatin.

Patients included

- 42,418 patients with Stage I (140-159 / 90-99) or Stage II (160-179 / 100-109) hypertension; mean: 146 / 84
- with at least one of the following risk factors: smoking; HDL < 35 mg/dL or other atherosclerotic cardiovascular disease; left ventricular hypertrophy (verified by ECG or echocardiography); type 2 diabetes; previous myocardial infarction or stroke
- patients excluded: those with left ventricular ejection fraction < 35%; those with treated heart failure
- age > 55 years (mean 67); 53% male; 60% white, 35% black, 5% other ethnicities

Comparison of treatments (blind) and dosages

* in cases where target blood pressure was not achieved with the previous dosage

Drug	1st dose	2nd dose*	3rd dose*
Chlorthalidone	12.5 mg/day	12.5 mg/day	25 mg/day
Amlodipine	2.5 mg/day	5 mg/day	10 mg/day
Lisinopril	10 mg/day	20 mg/day	40 mg/day
Doxazosin *(discontinued Jan '00)*	2 mg/day	4 mg/day	8 mg/day

Possible additional therapy decided by doctor (for target blood pressure 140/90)

- Atenolol (from 25 to 100 mg/day)
- Reserpine (from 0.05 to 0.2 mg/day)
- Clonidine (from 0.1 to 0.3 mg twice a day)

2nd step

- Hydralazine (from 25 to 100 mg twice a day)

3rd step

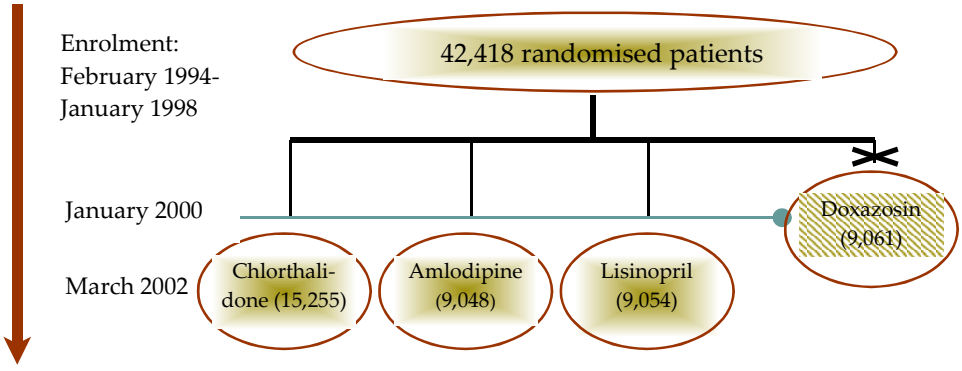
Mean follow-up

4.9 years

Clinical outcomes

- Non-fatal myocardial infarction + fatal coronary heart disease (primary outcome)
- All-cause mortality
- Stroke (fatal and non-fatal)
- Coronary heart disease, revascularisation, hospitalised angina
- Heart failure
- Combined outcomes (the sum of the above outcomes + peripheral arterial disease)

IMAGE NOT AVAILABLE



Results of the ALLHAT study (*JAMA* 2002;288:2981-97)

DIFFERENCES IN CLINICAL OUTCOMES BETWEEN THE STUDIED DRUGS

Incidence of clinical outcomes (expressed as 6-year rate per 100 persons) in chlorthalidone, amlodipine and lisinopril treatment groups (statistically significant differences in red; ns = not significant)

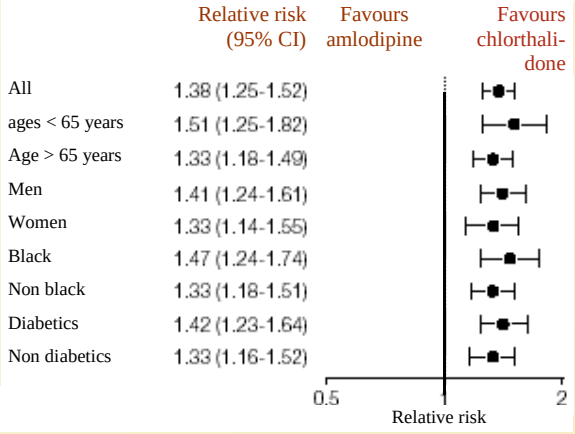
Clinical outcomes	Drug			Differences (%) and NNT*			
	Chlorthalidone (15,255 pat.)	Amlodipine (9,048 pat)	Lisinopril (9,054 pat.)	Chlorthalidone *vs* amlodipine		Chlorthalidone *vs* lisinopril	
				Diff.%	NNT*	Diff.%	NNT*
Fatal and non-fatal myocardial infarction	11.5%	11.3%	11.4%	ns	ns	ns	ns
Total mortality	17.3%	16.8%	17.2%	ns	ns	ns	ns
Stroke	5.6%	5.4%	6.3%	ns	ns	**-0.7%**	**143**
Coronary heart disease, revascularization and angina (hospitalised)	19.9%	19.9%	20.8%	ns	ns	ns	ns
Combined CVD	30.9%	32.0%	33.3%	ns	ns	**-2.4%**	**42**
Heart failure	7.7%	10.2%	8.7%	**-2.5%**	**40**	**-1.0%**	**100**

**NNT= number needed to treat with chlorthalidone (with respect to the other drug) to avoid an outcome*

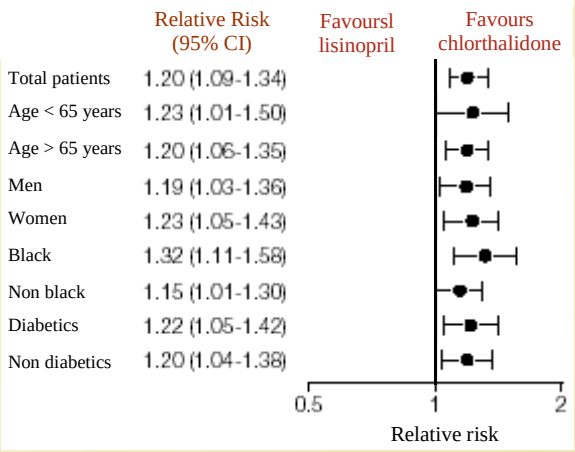
MAIN RESULTS

- ✓ The incidence of fatal and non-fatal myocardial infarction (primary outcome of the study) is similar in patients treated with chlorthalidone, amlodipine and lisinopril.
- ✓ The incidence of **heart failure is lower** in patients treated with **chlorthalidone** compared to those treated with **amlodipine** or **lisinopril.** The lower incidence of heart failure is also evident in various population subgroups and **is attributed to chlorthalidone in diabetics, the elderly (> 65 years) and white patients as well.**
- ✓ The incidence of stroke and cardiovascular heart disease (combined outcome) is lower in patients treated with chlorthalidone compared to those treated with lisinopril. No differences are evident if only white patients are considered.
- ✓ All-cause mortality is similar in patients treated with chlorthalidone, amlodipine or lisinopril.
- ✓ The higher incidence of hyperglycaemia and hypokalaemia in patients treated with chlorthalidone is of modest clinical relevance (see following page) and has not determined differences in clinical outcomes. No differences in the variation of cholesterolaemia were observed among the three groups.
- ✓ The mean reduction in systolic blood pressure is higher in patients treated with chlorthalidone (2 mm Hg *vs* lisinopril; 0.8 mm Hg *vs* amlodipine), while the mean reduction in diastolic blood pressure is higher in patients treated with amlodipine (0.8 mm Hg *vs* chlorthalidone).

*Relative risk of heart failure (95% CI): **amlodipine** treatment groups vs **chlorthalidone** treatment groups*



*Relative risk of heart failure (95% CI): **lisinopril** treatment groups vs **chlorthalidone** treatment groups*



Results of the ALLHAT study (*JAMA* 2002;288:2981-97)

FREQUENCY OF MULTI-DRUG THERAPY AND COMPLIANCE WITH TREATMENT (IN 5 YEARS)

	Chlor (15,255)	Amlo (9,048)	Lisin (9,054)
% patients for whom a 2nd/3rd step of therapy was necessary	40.7	39.5	43.0
% patients who have used other anti-hypertensive drugs	4.9	8.0	12.7
% patients treated with the assigned drug for 5 years	71.2	72.1	61.2
% patients treated with the assigned drug or a drug of the same class for 5 yrs	80.5	80.4	72.6

✓ **The arterial pressure of about half the patients was well-controlled in single-drug therapy**

✓ Taking the long follow-up period into consideration, there was found to be a high level of compliance during the study

METABOLIC EFFECTS OF THE DRUGS STUDIED (IN 4TH YEAR OF TREATMENT)

	Chl (15,255)	Amlo (9,048)	Lisin (9,054)	Chl *vs* amlo	Chl *vs* lisin
				NNH	
***Glycaemia** mean in mg/dL*	126.3	123.7	121.5		
% patients with glycaemia > 126 mg/dL (and var. comp. to baseline)	32.7% (+ 3.8%)	30.5% (+ 1.3%)	28.7% (- 0.7%)	ns	23
***Potassaemia** mean in mEq/L*	4.1	4.4	4.5		
% patients with potassium < 3,5 mEq/L (and var. comp. to baseline)	8.5% (+ 5.1%)	1.9% (- 1.5%)	0.8% (- 1.8%)	16	15

✓ **Hyperglycaemia** (*> 126 mg/dL)*: one more case—in 4 years—every 23 patients treated with chlorthalidone instead of with lisinopril

✓ **Hypokalaemia** *(< 3,5 mEq/L):* one more case—in 4 years—every 15 (16) patients treated with chlorthalidone instead of with lisinopril (or amlodipine)

✓ These metabolic effects DID NOT determine worse clinical outcomes in patients treated with chlorthalidone.

WHY THE DOXAZOSIN TREATMENT GROUP WAS DISCONTINUED (*JAMA* 2000;283:1967-75)

✓ In January 2000, following an interim analysis, the American National Heart, Lung, and Blood Institute (NHLBI) decided to discontinue the doxazosin treatment arm.

✓ The decision was taken after it became evident that **the incidence of hospitalised heart failure in doxazosin treatment groups had doubled and cardiovascular event rate had exceeded 25% (in relative terms) compared to chlorthalidone treatment groups.**

✓ On the basis of those results, the NHLBI further recommended - in an *ad hoc* announcement - that all patients undergoing treatment with alpha-blockers consult their doctor for possible alternative therapy (www.nhlbi.nih.gov/new/press/mar08-00.htm).

✓ Later statistical analyses have shown that **the risk of heart failure** associated with doxazosin treatment is **3.1 times higher** when it is used **in single-drug therapy** and **1.4 times higher** when it is **associated with other antihypertensives.** Moreover, that risk is **independent of the level of arterial pressure achieved** (*Ann Intern Med* 2002;137:313-20).

Incidence of clinical outcomes (expressed as 4-year rate per 100 persons) in chlorthalidone and doxazosin treatment groups - statistically significant values in red

	% events in 4 years		Relative Risk (95% CI) doxazosin *vs* chlorthalidone	Pat. to treat in 4 years with doxazosin instead of chlorthalidone to produce 1 more negative event (NNH)
CLINICAL OUTCOMES	Chlorthalidone (15,268 pt)	Doxazosin (9,067 pt)		
Myocardial infarction*	6.3	6.3	1.03 (0.90-1.17)	
Total mortality	9.1	9.6	1.03 (0.90-1.15)	
Myocardial infarction + cor. revascularization + hospitalized angina	12.0	13.1	1.10 (1.00-1.12)	91
Stroke *	3.6	4.2	1.19 (1.01-1.40)	167
Heart failure*	4.5	8.1	2.04 (1.79-2.32)	28
Coronary revascularization	5.2	6.2	1.15 (1.00-1.32)	100
Angina	10.2	11.5	1.16 (1.05-1.27)	77
Peripheral artery disease	2.9	2.9	1.07 (0.88-1.30)	

* These diagnoses were validated by a predefined panel of clinicians for a sample of hospitalised or deceased patients.

IMAGE NOT AVAILABLE

ALLHAT study: remarks

ALLHAT was the largest study ever carried out to evaluate the efficacy of four classes of drugs as optimal first-step antihypertensive therapy. The study was designed and conducted at the National Institute of Health (a public research institute) in the United States. Contrary to the initial objectives laid out (superiority of a calcium channel blocker, an ACE-inhibitor and an alpha-blocker to a thiazide) the study has demonstrated that:

- ✓ treatment with **low doses of a thiazide-type diuretic (chlorthalidone)** is **more effective** than treatment with a **calcium channel blocker (amlodipine)** or an **ACE-inhibitor (lisinopril)** in **preventing heart failure.** However, no differences were evident in all-cause mortality, myocardial infarction and stroke among the drugs studied (apart from a higher incidence of stroke in black patients treated with lisinopril in comparison to those treated with chlorthalidone)
- ✓ treatment with a **thiazide-type diuretic** is **more effective** than treatment with **alpha-blockers** in reducing the risk of **heart failure** and **stroke**. These differences led to the **discontinuation of the doxazosin treatment group** two years before the termination of the study
- ✓ **the differences related to heart failure remain in the various population subgroups studied (white, diabetic, elderly).**

IMAGE NOT AVAILABLE

WHAT HAS BEEN ADDED TO PREVIOUSLY AVAILABLE EVIDENCE

- ✓ The ALLHAT results, which come from a very large sample, confirm data already available from meta-analyses *(Lancet 2000;356:1949-54 and 1955-64)* on the higher efficacy of thiazides in comparison to calcium channel blockers in the prevention of heart failure.
- ✓ The ALLHAT study does not however confirm the superiority of calcium channel blockers when compared to thiazides in the prevention of stroke (suggested from results carried out on less numerous samples and from meta-analyses).

THE PRESCRIPTION OF SOME CARDIOVASCULAR DRUGS IN THE PROVINCE OF MODENA

	Province of Modena		
	% DDD		% drug exp
	2001	2002	2002
Thiazide diuretics	4.6%	4.3%	1.4%
Calcium channel blockers (dihydro)	23.0%	21.4%	22.7%
ACE-inibitors	25.8%	26.1%	23.7%
ACE-inhibitors + thiazides	11.8%	11.6%	16.1%
Alpha-blockers	2.6%	2.6%	5.0%
Beta-blockers	10.1%	10.3%	7.6%
Sartans	6.1%	7.3%	9.1%
Sartans + thiazides	2.8%	3.9%	6.9%
Other antihypertensives	13.2%	12.5%	7.5%
Total	100,0%	100,0%	100,0%

IMPLICATIONS FOR CLINICAL PRACTICE

On the basis of these results, the American **National Heart, Lung, and Blood Institute concluded that**:

- → given their superiority in preventing one or more cardiovascular events and their **low cost**, **thiazide diuretics** must be used as **first-choice drugs** for most hypertensive patients;
- → in particular, they must be considered as an alternative for patients in therapy with alpha-blockers as their first choice;
- → given that many hypertensive patients request more than one drug for effective control of their blood pressure, thiazide diuretics must be introduced in every treatment regime - unless indicated otherwise.

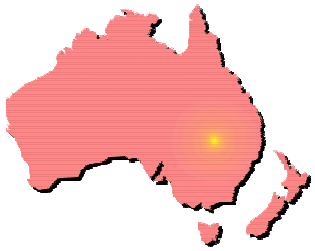
IMAGE NOT AVAILABLE

ACE-inhibitors *vs* diuretics in non-complicated hypertension: the ANBP2 study (Australian National Blood Pressure study group) *NEJM* 2003;348:583-92

CHARACTERISTICS AND OBJECTIVES OF THE STUDY

This was a randomised, multicenter, open-label (doctor and patient knew which therapy was allocated to the patient) study whose objective was to compare **- as first-choice drugs - ACE-inhibitors and diuretics** in the prevention of the main cardiovascular outcomes. The study involved 6,083 hypertensive patients (> 160/90) enrolled from Australian family medical practices.

Patients included	✓ 6,083 hypertensive patients (*>160/90; mean 168 /91*) ✓ selected from 1,594 family medical practices throughout Australia ✓ patients excluded: those with cardiovascular events in the previous 6 months, malignant hypertension or generally bad clinical conditions (life-threatening) ✓ age 65-84 years (mean 72); 49% male; 95% white
Target blood pressure	✓ Systolic: reduction of at least 20 mm Hg to < 160 mm Hg (up to < 140 mm Hg if therapy is tolerated) ✓ Diastolic: reduction of at least 10 mm Hg to < 90 mm Hg (up to < 80 mm Hg if therapy is tolerated)
Comparison of treatments (open-label)	✓ Enalapril or other ACE-inhibitor (agent and dose *chosen by GP)* ✓ Hydrochlorothiazide or other diuretic (agent and dose *chosen by GP*)
Possible additional therapy for target blood pressure	Beta-blockers, calcium-channel antagonists, alpha-blockers
Mean follow-up	4.1 years
Main clinical outcomes	✓ <u>All cardiovascular events + all-cause mortality</u> (primary outcome) ✓ All-cause mortality ✓ Myocardial infarction ✓ Heart failure ✓ Stroke

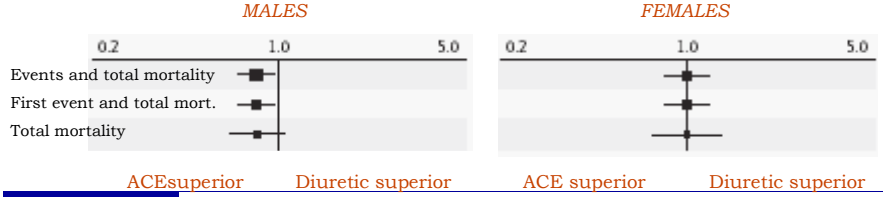


THE DIFFERENCES IN CLINICAL OUTCOMES AMONG THE DRUGS STUDIED

Incidence of clinical outcomes (expressed as one-year rate per 100 patients) in ACE-inhibitor and diuretic treatment groups

Outcome	ACE-inhibitors	Diuretics	Diff %	NNT
All cardiovascular events + all cause mortality (primary outcome)	5.6%	6.0%	-0.4%	250
First cardiovascular event + all cause mortality	4.2%	4.6%	-0.4%	ns
Total mortality	1.6%	1.7%	-0.1%	ns
Myocardial infarction	0.5%	0.7%	-0.2%	500
Heart failure	0.6%	0.6%	-	ns
Stroke	0.9%	0.9%	-	ns

Relative risk of events in ACE-inhibitor vs diuretic treatment groups



- ✓ In the population studied, patients treated with ACE-inhibitors have a lower overall risk of cardiovascular events and death (combined outcome) and a lower risk of myocardial infarction compared to patients treated with diuretics.
- ✓ Differences were observed only among male patients.
- ✓ In general, these results refer to subjects with few risk factors (see following page), a relatively elderly population (mean age 72 years) with semi-serious hypertension (stage II or higher).

ANBP2 and ALLHAT studies: differences and general remarks

COMPARISON OF THE CHARACTERISTICS OF THE ANBP2 AND ALLHAT STUDIES

	ANBP2 (*NEJM* 2003;348:583-92)	ALLHAT (*JAMA* 2002;288:2981-97)
No. of participants	**6,083**	**42,418**
POPULATION STUDIED: ✓ **Risk factors**	✓ 62% previously treated with antihypertensives ✓ 8% coronary heart disease ✓ 7% diabetes mellitus ✓ 7% smokers	✓ 90% previously treated with antihypertensives ✓ 25% coronary heart disease ✓ 36% diabetes mellitus ✓ 22% smokers ✓ The participants had to have at least one of these risk factors (or also: left ventricular hypertrophy; previous stroke; atherosclerotic cardiovascular disease)
✓ **Age**	**65-84** (mean 72)	**> 55** (mean 67)
✓ **Blood pressure levels and target blood pressure**	✓ Included patients with stage II or higher hypertension (**mean 168/91**) ✓ Target blood pressure: at least <160/90 (<140/80 if possible)	✓ Included patients with Stage I or II hypertension (**mean 146/84**) ✓ Target blood pressure: <140/90
✓ **Black patients**	**< 5%**	**35%** (analysis done for subgroups)
"Blindness" in the design of the study	Only in data analysis (doctor and patient knew which therapy was allocated to the patient)	Blind both in drug administration and data analysis
COMPARISON OF DRUGS	✓ **ACE-inhibitors chosen** by doctor (enalapril preferred with flexibility of doses) ✓ **Diuretics chosen** by doctor (hydrochlorothiazide preferred with flexibility of doses)	✓ Chlorthalidone (12.5-25 mg) ✓ Amlodipine (2.5-10 mg) ✓ Lisinopril (10-40 mg) ✓ Doxazosin *(discontinued January 2000:* 2-8 mg*)*
Other antihypertensives to achieve target blood pressure	Beta-blockers, calcium-channel antagonists or alpha-blockers (chosen by doctor)	Atenolol, reserpine or clonidine (chosen by doctor); hydralazine (3rd step)
Blood pressure check (comparison of the differences among drugs)	After 5 years, ACE-inhibitor and diuretic reduce systolic and diastolic in equal measure (by 26/12 mm Hg)	After 5 years, chlorthalidone reduces systolic by 1.8 mm Hg more than lisinopril (12.3 *vs* 10.5 mm Hg). Diastolic is reduced in equal measure by the two drugs (8.6 *vs* 8.7 mm Hg)
Funding for the study	Public and private (company manufacturing enalapril)	Public and private (pharmaceutical suppliers)

THE ANBP2 STUDY - ALLHAT AND PREVIOUS EVIDENCE: REMARKS

- ✓ A meta-analysis on previous randomised studies that compared ACE-inhibitors with diuretics and/or beta-blockers *(Lancet 2000;356:1955-64)* pointed to a substantial similarity among these classes of drugs based on main clinical outcomes.
- ✓ The ANBP2 and ALLHAT studies differ in numbers (6,083 *vs* 42,418 patients) and the type of population studied. The ALLHAT study, in particular, has a much larger sample size than any other study on the efficacy of antihypertensive therapies. It also comprises an extremely representative population (with a wide spectrum of risk factors) and provides data on specific population subgroups (white, diabetic, elderly, etc.)
- ✓ The large number and general characteristics of the populations studied are elements to consider in the interpretation of the differences between the ANBP2 and ALLHAT studies and, more generally, in the choice of antihypertensive therapy.

Sartans *versus* ß-blockers in patients with left ventricular hypertrophy: the LIFE study (*Lancet* 2002;359:995-1003 and 1004-10)[1,2]

CHARACTERISTICS AND OBJECTIVES OF THE STUDY

This was a randomised, double-blind, multicenter study whose objective was to compare the efficacy of an angiotensin-II receptor blocker (**losartan**) and a beta-blocker (**atenolol**) in the prevention of the main cardiovascular outcomes in hypertensive patients with left ventricular hypertrophy.

Patients included	➢ 9,193 hypertensive patients (*160-200 / 95-115; mean 174 / 98* ➢ with *left ventricular hypertrophy* (verified by ECG); ➢ patients excluded: those with secondary hypertension, stroke or myocardial infarction within the previous 6 months, angina, heart failure, left ventricular ejection fraction < 40% ➢ age 55-80 years (mean 67); 46% male
Treatment (dosages)	*Losartan* (*50 mg*), with possibility to increase dose (100 mg) and to add hydrochlorothiazide (12.5-25 mg), according to blood pressure levels
Control group	*Atenolol* (*50 mg*), with possibility to increase dose (100 mg) and to add hydrochlorothiazide (12.5-25 mg), according to blood pressure levels
Mean follow-up	4.8 years
Clinical outcomes	➢ Stroke (fatal/nonfatal) ➢ Myocardial infarction ➢ Cardiovascular mortality ➢ Composite end-point (sum of the above outcomes) ➢ Total mortality

DIFFERENCES IN CLINICAL OUTCOMES BETWEEN THE DRUGS STUDIED

% incidence of clinical outcomes in losartan and atenolol treatment groups in all patients and in two subgroups (diabetics/non diabetics) - statistically significant differences in red

Clinical outcome	**All patients**				**Diabetic patients**				**Non-diabetic patients**			
	Losartan (n=4605)	Atenolol (n=4588)	Diff. %	NNT*	Losartan (n=586)	Atenolol (n=609)	Diff. %	NNT*	Losartan (n=4019)	Atenolol (n=3979)	Diff. %	NNT*
Stroke	5%	7%	-2%	50	9%	11%	ns	ns	5%	6%	-1%	100
Myocardial infarction	4%	4%	ns	ns	7%	8%	ns	ns	4%	3%	ns	ns
Cardiovascular mortality	4%	5%	ns	ns	6%	10%	-4%	25	4%	4%	ns	ns
Composite end-point	11%	13%	-2%	50	18%	23%	-5%	20	10%	11%	ns	ns
Total mortality	8%	9%	ns	ns	11%	17%	-6%	17	8%	8%	ns	ns

**NNT= number needed to treat with losartan (instead of with atenolol) to avoid an outcome*
ns = statistically NOT significant

Sartans *versus* ß-blockers in the LIFE study: remarks on the published results

CORRESPONDENCE

Was the LIFE trial independent?

IMAGE NOT AVAILABLE

Three months after the publication of LIFE, the Lancet published a series of letters that cast doubts on the methodology and results of the study, highlighting a few limits to the applicability of the conclusions.

What was particularly criticised was the promotion of the results through a letter written on University of Gothenburg (the main centre for the study) headed paper and signed by Prof. Bjorn Dalhof, the person in charge of the LIFE study.

The letter, which did not cite the name of the sponsoring company, went on to describe the study as independent of commercial influences. As for Prof. Dalhof, he explained that he had not been informed about being the signatory of the letter in question.

SOME DOUBTS THAT EMERGE FROM *IN-DEPTH* ANALYSIS OF THE STUDY	IMPLICATIONS FOR CLINICAL PRACTICE
✓ **The authors did not present data related to non-diabetic patients.** In this subgroup - much larger than the diabetic subgroup - losartan and atenolol reduce mortality equally.	✓ *In non-diabetic patients with left ventricular hypertrophy, losartan*-based therapy is associated with a lower incidence of diabetes and a lower incidence of stroke in comparison to atenolol-based therapy. However, total mortality is similar in both groups. ✓ *In diabetic patients with left ventricular hypertrophy, losartan*-based therapy is associated with a lower *total mortality* and a lower cardiovascular mortality in comparison to atenolol-based therapy.
✓ **Relatively few patients received only losartan or atenolol** (11% *vs* 12%, respectively).	✓ The results of the study could be difficult to apply to patients in single-drug therapy [5,6].
✓ **Data from the study is the exclusive property of the sponsoring company** which does not consent to carrying out independent analyses and evaluations from the original database[5].	✓ More research should further clarify the role of sartans in hypertensive therapy, and be carried out through independent investigations in which these drugs will also be compared to diuretics and ACE-inhibitors (considered suitable first-choice drugs in patients with left ventricular hypertrophy).

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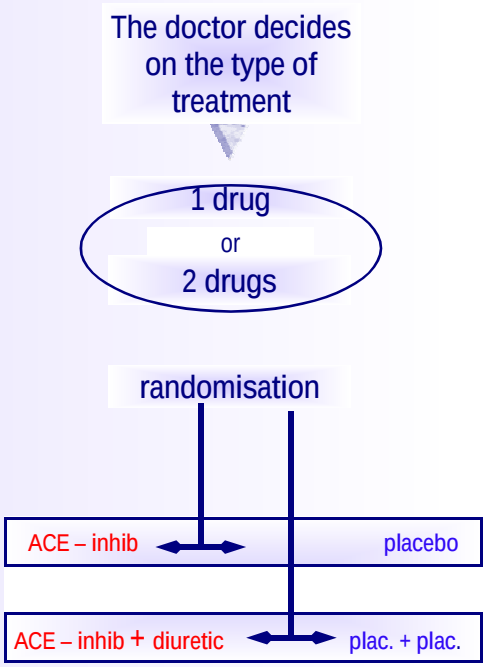
ACE-inhibitors (perindopril) in the prevention of recurrent stroke: the PROGRESS study (*Lancet* 2001;358:1033-41)[1]

CHARACTERISTICS AND OBJECTIVES OF THE STUDY

This was a randomised, double-blind, multicenter study whose **objective** was *to verify the efficacy of a therapeutic strategy based on the use of an ACE-inhibitor (perindopril) - with the addition of a thiazide diuretic (indapamide) if necessary - in the prevention of recurrent stroke in both hypertensive and non-hypertensive subjects*. A placebo was used as a control.

Patients included	➢ 6,105 normal and hypertensive patients with controlled blood pressure ➢ with a history of stroke or TIA within the previous 5 years ➢ without specific indication (eg. heart failure) or contraindications (eg. intolerance) to the use of ACE-inhibitors ➢ mean blood pressure: 147 / 86 ➢ mean age: 64 years; 70% male
Treatment (dosages)	*Perindopril* (*4 mg*), with the addition of *indapamide* (*2.5 mg/day*), in patients for whom the additional treatment was judged necessary according to the physician responsible
Control group	*Placebo* (*or double placebo* in patients for whom the doctor decided on an additional treatment)
Mean follow-up	➢ 3.9 years
Clinical outcomes	➢ Fatal/non-fatal stroke (primary outcome) ➢ Total major vascular events (stroke + myocardial infarction + death due to vascular causes) ➢ Total mortality



METHODOLOGICAL PROBLEMS IN THE PROGRESS STUDY

Some important methodological problems that seriously limit the validity of the study and the applicability of the results, as reported by the authors, have been highlighted in ACP Journal Club 2002;136:51. In particular:

- the PROGRESS study results actually represent a combination of results from two separate studies carried out on patients with different prognostic characteristics and factors. These two studies considered the comparison of perindopril and placebo and the comparison of the perindopril-indapamide combination and placebo respectively;
- the characteristics of the patients included in the study (hypertensives *vs* normal) and the specific characteristics of patients undergoing the combined perindopril and indapamide therapy are not clear;
- no provision was made for a group being treated with indapamide alone. This would have allowed the evaluation of the efficacy of the ACE-inhibitor-diuretic combination treatment compared to treatment with the diuretic alone;
- some of the patients selected at the beginning (14%) were excluded from the study because of intolerance to a perindopril-based treatment (4-week period: 2 mg daily for 2 weeks followed by 4 mg for another 2 weeks) that caused hypotension or other side-effects.

IMAGE NOT AVAILABLE

ACE-inhibitors (perindopril) in the prevention of recurrent stroke: Remarks on the results of the PROGRESS study

THE DIFFERENCES IN THE CLINICAL OUTCOMES BETWEEN THE TREATMENTS STUDIED

% incidence of clinical outcomes in perindopril treatment groups - with or without indapamide - and placebo (statistically significant differences in red)

	Only perindopril (n=1281)	Placebo (n=1280)	Diff. %	NNT*
Stroke	12.3%	12.9%	ns	ns
Major cardiovascular events	17.7%	18.5%	ns	ns
	Perindopril + indapamide (n=1770)	**Double placebo (n=1774)**	**Diff. %**	**NNT***
Stroke	8.5%	14.0%	-5.5%	17
Major cardiovascular events	13.0%	21.0%	-7.0%	14
	Active treatment (n=3051)	**Placebo (n=3054)**	**Diff. %**	**NNT***
Stroke	10.1%	13.8%	3.7%	27
Major cardiovascular events	15.0%	19.8%	4.8%	21

IMAGE NOT AVAILABLE

Sum of the data of the two studies

MAIN RESULTS AND COMMENTS

- ✓ **Treatment with perindopril alone is not more effective than placebo in reducing the incidence of stroke and major cardiovascular events. Effective therapy was demonstrated *only* in the group that used the ACE-inhibitor along with the diuretic.**
- ✓ **The advantage of the perindopril-indapamide combination therapy could depend on the presence of the diuretic rather than on the combination itself. However, it is not possible to evaluate whether treatment with the diuretic alone is effective in itself given the absence of the relevant treatment arm.**
- ✓ **Total mortality is similar in patients randomised to active treatment or to placebo.**

IMPLICATIONS FOR CLINICAL PRACTICE

- ✓ The results of the PROGRESS study are **difficult to apply to clinical practice** in that the specific characteristics of patients undergoing combined therapy with perindopril and indapamide are not clear. To be more precise, the reasons for the doctor opting for the use of the combined therapy were not reported.
- ✓ **Further studies should illustrate:**
  1. **which patients have an advantage in using combination ACE-inhibitor-diuretic therapy (in comparison to single-drug therapy with ACE-inhibitor) for the prevention of recurrent stroke.**
  2. **whether it is possible to obtain a therapeutic advantage simply by using low doses of a thiazide-type diuretic.**

Efficacy of antihypertensive drugs: what the new studies add to our knowledge

- ✓ In first-step treatment of hypertension, **low doses of thiazide diuretics** (chlorthalidone) are more effective (prevention of heart failure) or equally effective (prevention of other cardiovascular events) than calcium channel blockers (amlodipine) and ACE-inhibitors (lisinopril), in a general hypertensive population with at least one risk factor. **The American National Heart, Lung, and Blood Institute states that thiazide diuretics should be used as first-choice drugs for most hypertensive patients.**
- ✓ The ALLHAT study has confirmed the high incidence of heart failure in patients treated with **calcium channel blockers** (amlodipine) compared to those treated with thiazide (*Lancet* 2000;356:1949-54 and 1955-64). However, the efficacy of calcium channel blockers when compared to thiazide diuretics in the prevention of stroke has not been confirmed.
- ✓ Moreover, the ALLHAT study has not confirmed the efficacy of **ACE-inhibitors** when compared to thiazides in the prevention of heart failure, nor the particular benefits of ACE-inhibitors in diabetics or renal-impaired patients. A smaller Australian study (ANBP2 study) has instead shown that ACE-inhibitors are at least as effective (if not more effective in some cases) as thiazide diuretics when compared to thiazide diuretics in a hypertensive population with few risk factors relative to the ALLHAT population.
- ✓ **Alpha-blockers** (doxazosin) are associated with a higher incidence of heart failure and stroke in comparison to thiazide diuretics (chlorthalidone) and should only be used when other drugs have been contraindicated or are unable to control blood pressure adequately (ALLHAT study).
- ✓ The role of **sartans** in antihypertensive therapy needs further investigation. The LIFE study has shown that losartan is superior to atenolol in a hypertensive population with left ventricular hypertrophy.
- ✓ The role of **ACE-inhibitors in the prevention of recurrent stroke** needs further investigation; in the PROGRESS study, only the combination treatment with a diuretic is shown to be effective, but it is not clear which type of patients benefited from that treatment.

IMAGE NOT AVAILABLE

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