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Strong evidence that antihypertensive pharmacologic treatment reduces cardiovascular morbidity and mortality

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The clinical usefulness of lowering elevated blood pressure with pharmacologic treatment is one of the best documented areas of medical therapy: the incidence of stroke, and to a lesser degree coronary heart disease morbidity and mortality, are reduced [1, 2]. In addition to the "classical" 13 intervention trials [1] (16 if the Hypertension in the Elderly Trials are included [3]), frequently and erroneously added up to 14 or 17 respectively, five new large intervention trials in hypertension have been presented recently. These are the Shanghai Trial Of Nifedipine in Elderly Hypertensives (STONE) [4], the Systolic Hypertension in the Elderly trial (Syst-Eur) [5], the Hypertension Optimal Treatment (HOT) study [6], the Captopril Prevention Project (CAPPP) [7] and the Systolic Hypertension in China (Syst-China) study [8].

In addition, a great number of prospective intervention trials with newer antihypertensive agents such as calcium antagonists and angiotensin II receptor antagonists are currently in progress and some of them will be briefly reviewed here. *J Clin Basic Cardiol* 1999; 2: 128–9.

Key words: Antihypertensive treatment, intervention trials, cardiovascular mortality and morbidity

Results of antihypertensive treatment on "hard endpoints"

The first study comparing antihypertensive treatment versus no treatment on cardiovascular morbidity was conducted by Hamilton et al. in the UK more than three decades ago [9]. The US Veterans Administration (VA) Study [10, 11] also deserves a special comment. The VA Study was a double-blind, placebo-controlled, intervention trial in male hypertensives using a triple-combination of reserpine plus hydralazine plus hydrochlorothiazide. The main results, reported in 1967 [10] and 1970 [11], showed impressive reductions in cardiovascular morbidity. The VA findings were instrumental for the rapid acceptance of antihypertensive treatment that followed during the next decade in all industrialized countries. The results of 13 of the major "hard endpoint" intervention studies in hypertension, ie, studies in which cardiovascular mortality and morbidity were the trial endpoints, have later been summarized in a meta-analysis [1]. In brief, a lowering of the diastolic blood pressure by 5–6 mmHg was found to be associated with a 42 % reduction in fatal and non-

fatal strokes and a 14 % reduction in fatal and non-fatal coronary heart disease (CHD) [1].

Even more positive results of antihypertensive treatment were later shown in three major placebo-controlled intervention trials in elderly patients, the Systolic Hypertension in the Elderly Program (SHEP) [12], the Swedish Trial in Old Patients with Hypertension (STOP Hypertension) [13] and the Medical Research Council Trial in Older Adults (MRC) [14] (Table 1).

Two recently published "hard endpoint" intervention trials in which a calcium antagonist was used as the basic therapy deserve a special comment. The Shanghai Trial Of Nifedipine in Elderly hypertensives (STONE) showed a statistically significant reduction in the incidence of stroke [4]. Unfortunately, this Chinese trial used sequential allocation rather than proper randomization, ie, every second patient received active therapy with the calcium antagonist and every other was given placebo. This procedure does not exclude the possibility of bias and detracts from the value of the trial. The Systolic Hypertension in Europe (Syst-Eur) was a properly randomized, double-blind, placebo-controlled trial. Treatment with the calcium antagonist reduced cardiovascular morbidity significantly (Table 2) [5]. The STONE and the Syst-Eur trials are the first to demonstrate that calcium antagonists given to hypertensive patients reduce "hard endpoints" [4, 5]. The recently concluded Syst-China study lends further support to the usefulness of a calcium antagonist-based antihyperten-

Table 1. Summary of the results of the SHEP, STOP-Hypertension and MRC trials in elderly hypertensive patients

	SHEP	STOP	MRC
n	4736	1627	4396
Follow-up (years)	4.5	2.1	5.8
BP Inclusion SBP (mmHg)	160–219	180–230	160–209
DBP (mmHg)	< 90	> 90	< 115
Δ BP (mmHg)	12/4	20/8	12/5
Results (% reduction):			
Deaths, all causes	13 n.s.	43 p < 0.01	3 n.s.
Stroke, all	37 p < 0.001	47 p < 0.01	25 p = 0.04
CHD	25 p < 0.05	13 (MI) n.s.	19 n.s.
CV Events, all	32 p < 0.01	40 p < 0.01	17 p = 0.03
SHEP = Systolic Hypertension in the Elderly Program [12]			
STOP = Swedish Trial in Old Patients with Hypertension [13]			
MRC = Medical Research Council trial in older adults [14]			

Table 2. Summary of the Systolic Hypertension in Europe (Syst-Eur) Study (Revised from Staessen JA et al. 1997 [5])

Design: Double-blind European multinational study in 22 countries
Patients: n = 4695; average age = 70 years
Inclusion criteria: Isolated systolic hypertension: 200–160/<95 mmHg
Intervention: Placebo vs. nitrendipin (+ enalapril)

Results:

All CV endpoints reduced by	31 % p < 0.003
Fatal and non-fatal stroke reduced by	42 % p < 0.001
Fatal and non-fatal Myocardial Infarcts reduced by	30 % n.s.
Cardiovascular mortality reduced by	27 % n.s.
Fatal and non-fatal cancer reduced by	15 % n.s.

Table 3. Summary of the Antihypertensive Lipid Lowering Heart Attack Trial (ALLHAT) (Based on: Davis BR et al. 1996 [20])**Design:**

Double-blind comparison of four antihypertensive therapies: amlodipine, doxazosin, lisinopril and chlorthalidone and open assessment of lipid lowering with pravastatin

Material:

40,000 hypertensive patients in the US, 55 % black

Time schedule:

Recruitment finished early in 1998. Results expected in 2003

sive regimen in the prevention of cardiovascular morbidity and mortality in patients with isolated systolic hypertension [8]. Regretfully the Syst-China suffers from the same fault as the STONE trial, ie, every second patient was given active treatment and every other placebo, a less than ideal form of randomization.

The results of the Syst-Eur trial have already had an impact on the most recent American guidelines for the management of hypertension, issued in November 1997 by the Joint National Committee for the Detection, Prevention and Treatment of Hypertension (JNC VI) [15]. Long-acting dihydropyridine-derived calcium antagonists are now listed as a first-line alternative for the treatment of isolated systolic hypertension in the elderly [15]. This brings the US guidelines closer to those issued by the World Health Organization (WHO) and the International Society of Hypertension (ISH). The latest guidelines from WHO/ISH, issued in 1993, clearly listed calcium antagonists, along with alpha-blockers, angiotensin converting enzyme inhibitors, beta-blockers and diuretics as suitable first-line agents for the management of hypertension [16].

Ongoing intervention trials in hypertension

As mentioned above, numerous intervention trials with "hard endpoints" are currently in progress [17–21] to mention just a few. The largest of these ongoing trials is the Antihypertensive and Lipid Lowering Heart Attack Trial (ALLHAT) [20]. ALLHAT is a US National Institutes of Health (NIH) sponsored study that has included some 40,000 hypertensive patients. This will make it the largest ever intervention trial in hypertension. Under double-blind conditions four different antihypertensive therapies will be compared: the calcium antagonist amlodipine, the alpha-blocker doxazosin, the ACE inhibitor lisinopril and the diuretic chlorthalidone (Table 3) [20]. Using a factorial design the value of lipid-lowering treatment with pravastatin will also be assessed in an open evaluation. A unique feature of ALLHAT was the aim to recruit 55 % black patients [20].

Conclusions

The success of treating hypertension is indisputable. The benefits achieved by lowering elevated arterial pressure, in terms of reducing cardiovascular mortality and morbidity, are well established. Recently published results, in particular from the HOT study, show that the optimal protection against "hard endpoints" is obtained when blood pressure is treated down to a level of 138/83 mmHg and that further reductions below this level are safe.

Within the next few years, results from several ongoing large intervention trials in hypertension will further strengthen the foundations upon which antihypertensive treatment is based.

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