

After the ALLHAT Trial, What Do we Know About Treatment for Hypertension That we Did not Know Before?

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THE MOST IMPORTANT GOAL WITH HYPERTENSION IS TO LOWER BLOOD PRESSURE

The sixth report of the Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure (JNC-VI) states that diuretics or beta-blockers (BB) should be the drugs of choice when initiating treatment of uncomplicated hypertension.¹ In contrast, the report of the World Health Organization and the International Society of Hypertension (WHO-ISH) does not express a preference in the choice of the initial treatment, indicating that all available drugs could constitute a suitable therapeutic alternative.²

The question of great importance is whether the new drugs (calcium antagonists [CA], angiotensin converting enzyme [ACE] inhibitors and angiotensin II receptor antagonists [ARA II]) provide as good or better prognosis for hypertensive patients compared to diuretics and BB.

A range of studies have compared the benefit of antihypertensive treatment with diuretics and/or BB with a strategy based on CA, ACE inhibitor and ARA II. The CAPPP (ACE inhibitor vs BB/diuretics),³ INSIGHT (nifedipine GITS vs hydrochlorothiazide and amiloride),⁴ NORDIL (diltiazem vs BB/diuretics)⁵ and STOP-2 (ACE inhibitor vs dihydropyridine CA vs BB/diuretics)⁶ studies are the main clinical trials that have analyzed the influence of these different therapeutic interventions on prognosis. No significant differences were observed in the primary outcomes, suggesting the most important goal in the treatment of hypertension is to lower blood pressure. The agent used to achieve this goal is of secondary importance. This conclusion has been refined in a number of ways. For

example, because a large proportion of patients registered high blood pressure throughout follow-up in all these studies, it could be concluded that if the patients are hypertensive, the most important goal is to lower their blood pressure. But in high-risk hypertensive patients (diabetics, patients with target organ lesion or clinical cardiovascular disease) with blood pressure values near to normal, a particular therapeutic group might provide greater protection from clinical cardiovascular disease. For such subjects, pharmacological groups that block the renin-angiotensin system could be of particular benefit, as suggested by the results of the HOPE,⁷ MICRO-HOPE,⁸ IDNT,⁹ IRMA II,¹⁰ RENAAL¹¹ and LIFE¹² studies. Of these, only the LIFE study was designed for hypertensive patients, but taken together they still provide a strong justification for this recommendation.

Various meta-analyses have considered the possibility that the hypotensive effect of antihypertensive agents is not the only way by which such agents offer protection against cardiovascular disease.¹³⁻¹⁵ Overall, no significant differences are observed between the newest antihypertensive agents (ACE inhibitors and CA) and the more established ones (diuretics and BB). All analyses emphasized the importance attaining blood pressure treatment goals, given that a larger reduction in the risk of cardiovascular complications was associated with a larger reduction in blood pressure.

Around 20% of the Spanish population over 40 years of age needs anti-hypertensive treatment. Therefore, it is of great importance for clinical practice and health economics and policy to know whether a therapeutic strategy based on diuretics or BB offers at least the same if not greater protection against cardiovascular disease compared to the newest pharmacological groups.

MAIN CHARACTERISTICS AND RESULTS FROM THE ALLHAT STUDY

The recent publication of the final results from the ALLHAT study (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),

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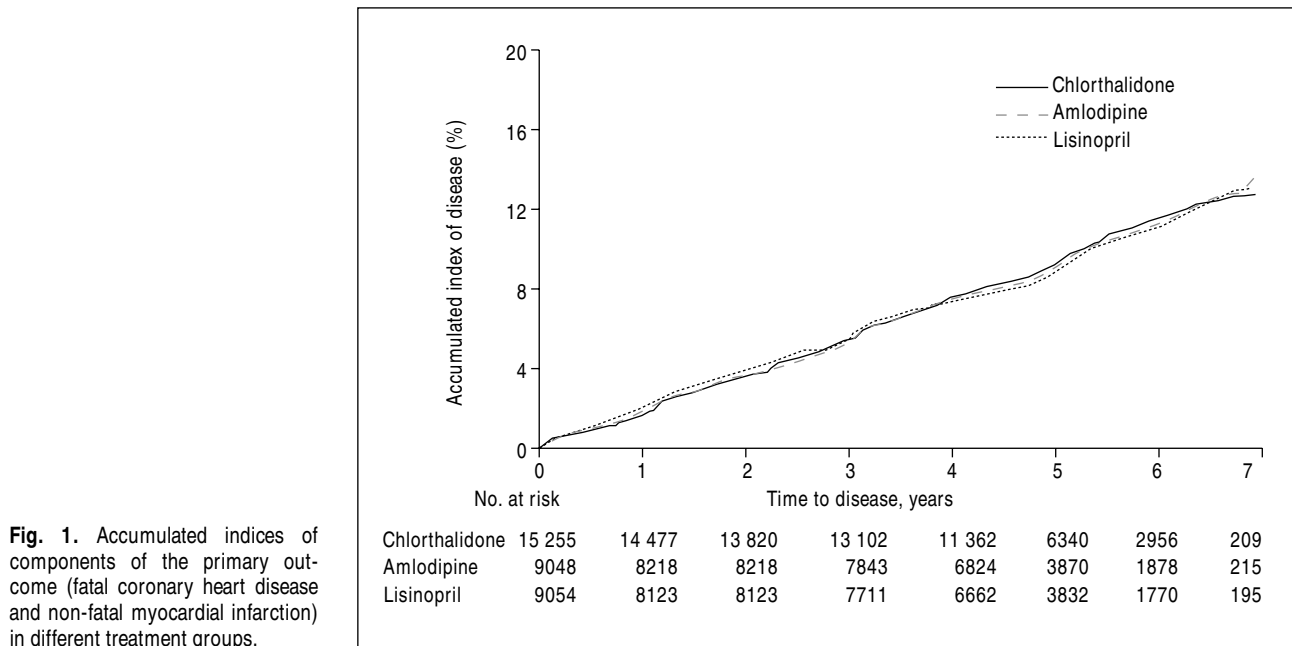


Fig. 1. Accumulated indices of components of the primary outcome (fatal coronary heart disease and non-fatal myocardial infarction) in different treatment groups.

along with the prior publication of the results from the doxazosin group, provide very relevant information on the choice of initial antihypertensive agent.^{16,17} This is the biggest study carried out with hypertensive patients. The study was a randomized, double-blind, multicenter trial sponsored by the National Heart, Lung, and Blood Institute in the United States. The design allowed to evaluate the incidence of fatal coronary heart disease or non-fatal myocardial infarction in high-risk hypertensive patients in the United States and Canada treated with a strategy based on a CA (amlodipine), an ACE inhibitor (lisinopril) or an alpha blocker (doxazosin), in comparison with a thiazide diuretic (chlorthalidone). A previous publication had shown that, compared to doxazosin, chlorthalidone provided better blood pressure control and protection against cardiovascular disease (based on a reduction in the risk of heart failure that could not be explained by differences in lowering of blood pressure), which led to the premature discontinuation of the doxazosin group.^{16,18} Secondary outcomes included all-cause mortality, fatal and non-fatal stroke, combined clinical presentations of coronary heart disease (components of the primary outcome, need for coronary revascularization or hospitalization for angina) and a combination of cardiovascular diseases (coronary heart disease, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease). The study design was highly powered to detect differences between antihypertensive agents: each treatment group included 9000 to 15 000 hypertensive patients and follow-up was prolonged (4.8 years). Most patients included had received antihypertensive treatment before

randomization and overall the mean basal blood pressure was 146/84 mm Hg. More than half the patients had a prior history of atherothrombotic cardiovascular disease, and 36% had type 2 diabetes mellitus. The mean age was 67 years, with similar numbers of men and women in the different groups. Slightly more than 35% of patients in each treatment group were Black (mostly Afro-Americans).

Patients randomized to receive a diuretic were given chlorthalidone at increasing doses of 12.5; 12.5 (repeated dose) and 25 mg/day. Those treated with an ACE inhibitor received 10, 20 and 40 mg/day of lisinopril, and those assigned to CA were treated with 2.5, 5 and 10 mg/day of amlodipine. Patients who did not manage to reach the blood pressure goal (<140/90 mm Hg) received 25-100 mg/day of atenolol, 0.05 to 0.2 mg/day of reserpine or 0.1-0.3 mg/twice a day of clonidine as an open label treatment in a second phase of the study. A third phase allowed the inclusion of 25-100 mg/twice a day of hydralazine.

At the end of follow-up, systolic blood pressure (SBP) was lower with diuretic treatment than with ACE inhibitor treatment (difference of 2 mm Hg after 5 years of follow-up, 4 mm Hg in the Black racial subgroup and 3 mm Hg in the subgroup aged over 65 years). The reduction of SBP was slightly greater with the diuretic, whereas amlodipine produced the largest reduction in diastolic blood pressure (DBP). In both cases, the reduction was the same (0.8 mm Hg). In the fifth year of follow-up, the blood pressure treatment goal (<140/90 mm Hg) was achieved in approximately two thirds of the patients in each group.

No significant differences were observed among

TABLE 1. Clinical complications in different treatment groups

	Chlorthalidone No. cases	Amlodipine No. cases	Lisinopril No. cases	Amlodipine versus chlorthalidone		Lisinopril versus chlorthalidone	
				RR (95% CI)	P	RR (95% CI)	P
Primary outcome CHD	1362	789	796	0.98 (0.90-1.07)	.65	0.99 (0.91-1.08)	.81
Secondary outcomes							
All-cause mortality	2203	1256	1314	0.96 (0.89-1.02)	.20	1.00 (0.94-1.08)	.90
Combined CHD	2451	1466	1505	1.00 (0.94-1.07)	.97	1.05 (0.98-1.11)	.18
Stroke	675	377	457	0.93 (0.82-1.06)	.28	1.15 (1.02-1.30)	.02
Combined CVD	3941	2432	2514	1.04 (0.99-1.09)	.12	1.10 (1.05-1.16)	<.001
TRD	193	129	126	1.12 (0.89-1.40)	.33	1.11 (0.88-1.38)	.38
Cancer	1170	707	703	1.01 (0.92-1.11)	.77	1.02 (0.93-1.12)	.67
Hospitalization for GI bleeding	817	449	526	0.92 (0.82-1.03)	.15	1.11 (0.99-1.24)	.07

CHD indicates coronary heart disease (fatal coronary heart disease, non-fatal myocardial infarction); combined CHD, fatal CHD, non-fatal infarction, coronary revascularization procedures and hospitalization due to angina; combined CVD (cardiovascular disease), fatal CHD, non-fatal infarction, stroke, fatal CHD and non-fatal myocardial infarction); combined CHD, fatal CHD, coronary revascularization procedures, hospitalization or treatment for angina, hospitalization or treatment for heart failure, peripheral vascular disease; TRD, terminal renal dysfunction; GI, gastrointestinal; RR, relative risk; CI, confidence interval.

TABLE 2. Clinical complications in different treatment groups

	Chlorthalidone No. cases	Amlodipine No. cases	Lisinopril No. cases	Amlodipine versus chlorthalidone		Lisinopril versus chlorthalidone	
				RR (95% CI)	P	RR (95% CI)	P
Components of CHF outcomes	870	706	612	1.38 (1.25-1.52)	<.001	1.19 (1.07-1.31)	<.001
Fatal/hospital CHF	724	578	471	1.35 (1.21-1.50)	<.001	1.10 (0.98-1.23)	.11
Angina, hospital/treated	1567	950	1019	1.02 (0.94-1.10)	.67	1.11 (1.03-1.20)	.01
Angina, hospital	1078	630	693	0.98 (0.89-1.08)	.68	1.09 (0.99-1.20)	.06
Coronary revascularization	1113	725	718	1.09 (1.00-1.20)	.06	1.10 (1.00-1.21)	.05
PVD, hospital/treated	510	265	311	0.87 (0.75-1.01)	.06	1.04 (0.90-1.19)	.63

CHF indicates congestive heart failure; hospital, hospitalized; PVD, peripheral vascular disease; RR, relative risk; CI, confidence interval.

groups for the primary outcome (Figure 1 and Table 1). Comparing the secondary outcome and the components of the secondary outcome for the amlodipine and chlorthalidone groups, the only significant difference was a greater incidence of heart failure in the group treated with amlodipine. This difference remained apparent for patients with fatal heart failure or heart failure that required hospitalization (Tables 1 and 2).

Similarly, treatment with an ACE inhibitor was associated with a greater risk of cardiovascular complications and a greater incidence of stroke and heart failure than the diuretic group (Tables 1 and 2). Analysis of the relative risks of stroke and heart failure adjusted for differences in blood pressure between patients receiving diuretics or an ACE inhibitor (2 mm Hg for SBP, 4 mm Hg for the Black racial subgroup) can only partially explain the differences observed.

The investigators of the ALLHAT study concluded that the thiazide diuretics (chlorthalidone) should be preferred as a first alternative in the treatment of hypertension because of their better cardiovascular protection and their excellent cost-benefit ratio.

AFTER THE ALLHAT TRIAL, WHAT DO WE KNOW ABOUT TREATMENT FOR HYPERTENSION THAT WE DID NOT KNOW BEFORE?

The results of the ALLHAT study are of particular clinical relevance because of certain characteristics of the study (for example the design, large sample size and lack of a commercial sponsor). The results provide strong support for the premise derived from previous studies that «lowering blood pressure to normal values is of utmost importance, without the particular drug used being of much consequence». The initial values for blood pressure are lower in this study than in the other numerous hypertension studies because most of the patients (90%) had been receiving prior treatment for hypertension. The population is nevertheless at a particularly high risk of cardiovascular disease because of the high proportion of patients with clinical atherothrombotic vascular disease and, above all, ischemic heart disease. We therefore see a high incidence of cardiovascular complications during follow-up, particularly those related with ischemic heart disease. In the latest hypertension studies, the incidence

of stroke exceeds that of acute coronary syndrome,^{3-6,12} whereas the incidence of episodes of ischemic heart disease was three times greater than that of stroke in the ALLHAT study. These differences might arise because of the lower age, the lower values of blood pressure and the greater prevalence of prior ischemic heart disease in the hypertensive patients participating in the study.

We are still awaiting publication of the results from the subgroup of hypertensive patients with ischemic heart disease, but the overall results from the ALLHAT study suggest that in this particular group, diuretic treatment, normally associated with BB, is accompanied by a prognostic benefit at least as great as that resulting from treatment with amlodipine or lisinopril, also associated with BB. The association of BB and an ACE inhibitor or a dihydropyridine CA is one of the most recommended strategies for treatment of hypertensive patients with ischemic heart disease. Recent guidelines published by the ACC/AHA for the management of patients with chronic stable angina recommend the combination of a BB with an ACE inhibitor based on the results of the HOPE study.¹⁹ Similar recommendations are made for secondary prevention in hypertensive patients with myocardial infarction. While the scientific evidence for this type of pharmacological association in hypertensive patients with ischemic heart disease is solid,²⁰⁻²² the results from the ALLHAT study hint that the combination of low doses of a thiazide diuretic (chlorthalidone) and a BB might be an acceptable alternative, at least in patients without ventricular dysfunction.

The results from the INSIGHT and NORDIL studies had shown that treatment of hypertension with CA was safe,⁴ questioning the conclusions of a meta-analysis indicating that these compounds (in particular dihydropyridines) could increase the risk of ischemic heart disease in hypertensive patients.^{23,24} The results from the ALLHAT study confirm that long-term treatment of high-risk hypertensive patients with a dihydropyridine CA (amlodipine) does not increase the risk of this type of complication, with no differences in the incidence of components of the primary outcome (fatal coronary heart disease or non-fatal myocardial infarction) among the different treatment groups. Up until present, large hypertension studies have not found significant differences in the primary outcome, but the results from the Second Australian Study of Hypertension in the Elderly published recently raise further questions.²⁵ For a given hypertensive efficacy, the results from this study indicated that a therapeutic strategy based on an ACE inhibitor (enalapril) was accompanied by greater protection against cardiovascular disease (particularly in men) than diuretic treatment (hydrochlorothiazide) and the difference in the incidence of myocardial infarction was particularly relevant. The higher initial and final values of blood pressure, the older patients (mean age: 72

years) and their lower risk profile compared to the hypertensive group included in the ALLHAT study could influence the results. Also, different diuretics (chlorthalidone and hydrochlorothiazide) and ACE inhibitors (lisinopril and enalapril) were used in the ALLHAT and Australian study, and such drugs might not necessarily provide «class effect» cardiovascular protection.

Different clinical trials and meta-analyses had suggested that treatment of hypertensive patients with CA was accompanied with a lower risk of stroke and lower protection against heart failure.^{4-6,14,15} In the ALLHAT study, no significant differences were observed in the incidence of stroke in groups of patients treated with amlodipine or chlorthalidone but the patients treated with lisinopril showed a significantly higher risk. Differences in control of SBP might justify this finding (difference in risk of 15%), although the differences in the subgroup of Afro-American hypertensive patients (40% greater risk) cannot be justified by different blood pressure control alone. Some investigators have suggested that ACE inhibitors have a smaller effect in Afro-American patients,²⁶⁻²⁸ and in particular provide a lower antihypertensive efficacy (in the ALLHAT study, the difference between the diuretic and the ACE inhibitor in the control of final SBP was 4 mm Hg), but recent results from the AASK study refute this. This study compared the efficacy of treatment based on amlodipine or ramipril in Afro-American hypertensive patients with kidney disease, showing the superiority of the ACE inhibitor.²⁹ But we emphasize here that, at the end of follow-up in the ALLHAT study, 71.2% of patients randomized to thiazide continued with treatment, compared to only 61.2% of those randomized to lisinopril. This lower persistence with lisinopril active treatment may have influenced the poorer results for this group. Apart from protection from heart failure, no significant differences were observed for different treatments in the diabetic subgroup. These data confirm the safety of dihydropyridine CA in diabetics.^{30,31} Furthermore, the data could challenge the superiority of blockage of the renin-angiotensin system suggested by the results of the MICRO-HOPE^{7,8} study, and more recently, the results with ARA II in diabetics with kidney disease,⁹⁻¹¹ though none of these were hypertension studies. The results from the diabetic group could be influenced by the worse control of SBP in the hypertensive group treated with lisinopril, suggesting that ACE inhibitors might be better when blood pressure control is similar.

We are witness to a continuous increase in the incidence and prevalence of heart failure associated with ageing of the population, the prevalence and poor control of hypertension and ischemic heart disease.^{32,33} The population of patients included in the ALLHAT study (high risk hypertensive patients with more than 50% prevalence of cardiovascular disease and 25%

TABLE 3. Index of episodes and relative risks (RR) of total heart failure and hospitalization or fatal heart failure

	Episodes per 100 patients after 4 years		Patients with episodes of heart failure		RR (95% CI)	P
	Chlorthalidone	Doxazosin	Chlorthalidone	Doxazosin		
Total CHF						
By randomization	4.46±0.26	8.14±0.43	420	491	2.04 (1.79-2.32)	<.001
Open label without treatment	2.64±0.31	6.63±0.79	144	227	3.10 (2.51-3.82)	<.001
Open label with treatment	6.93±0.59	8.75±0.72	276	264	1.42 (1.20-1.69)	<.001
With open label CHF treatment	6.91±0.69	9.81±0.95	207	214	1.45 (1.20-1.76)	<.001
Without open label CHF treatment	6.90±1.22	7.43±1.62	69	50	1.25 (0.87-1.80)	>0.2
Hospitalization or fatal CHF						
By randomization	3.53±0.23	5.77±0.37	327	346	1.83 (1.58-2.13)	<.001
Open label without treatment	2.03±0.28	3.69±0.57	109	139	2.52 (1.96-3.24)	<.001
Open label with treatment	5.64±0.54	6.77±0.62	218	207	1.39 (1.15-1.68)	<.001
With open label CHF treatment	5.86±0.64	7.83±0.87	172	172	1.38 (1.12-1.71)	<.001
Without open label CHF treatment	4.01±0.90	4.61±1.22	46	35	1.31 (0.85-2.04)	>.2

CHF indicates congestive heart failure; RR, relative risk; CI, confidence interval. Modified from Davis BR, et al.¹⁸

prevalence of ischemic heart disease) was at a high risk of developing heart failure and, indeed, the incidence of this complication was much greater in the ALLHAT study than in previous studies of hypertension. Erroneous diagnosis of heart failure could also contribute to this higher incidence. We have already mentioned that the doxazosin group was discontinued early because of an excess of cardiovascular complications, in particular heart failure. Patients treated with doxazosin had a relative risk twice that of patients treated with chlorthalidone, which could not be justified by the differences in blood pressure. The combination of another antihypertensive with doxazosin attenuated but did not eliminate this excess risk¹⁸ (Table 3).

The risk of heart failure was significantly greater in the group of patients treated with amlodipine and lisinopril than in the group that received a diuretic (Table 2). These differences persisted in the analysis of subgroups by age, sex, Afro-American or non Afro-American and diabetic patients or non-diabetic patients, and they were particularly relevant in the Black racial subgroup. The results of isolated systolic hypertension studies suggest that an increase of SBP by 3 mm Hg could correspond to a 10%-20% increase in the risk of heart failure.^{34,35} This might explain the differences observed in the lisinopril group, but not the greater risk in patients treated with amlodipine. Other explanations have been suggested apart from the possible protection afforded by CA against the risk of developing heart disease. Diuretics are a recognized treatment for edema, whereas this condition is a frequent adverse event after treatment with a dihydropyridine CA and could be erroneously interpreted as heart failure. Even so, the significant increase in risk of admission to hospital or fatal heart failure for the group of patients treated with amlodipine (Table 2) could not be justified using these

arguments. We do not know why hypertensive patients treated with amlodipine and doxazosin are less protected against heart failure. Our group has shown that doxazosin induces apoptosis in cultures of mouse and human cardiomyocytes, in agreement with work by other authors using prostate cells,³⁶ but clinical extrapolation of our experimental data, though plausible, should be treated with caution.

The design of the ALLHAT study has been questioned, particularly because the treatment combinations in the study are not normally used in clinical practice. There are physiopathological reasons to administer combinations of diuretics, CA and alpha-blockers with a BB, and the enhancement of the antihypertensive efficacy of such combinations has been demonstrated. Blood pressure control may have been worse than desired in some patients because a thiazide diuretic could not be combined with an ACE inhibitor, conditioning the cardiovascular prognosis of the patients.

Finally, we believe that the choice of antihypertensive treatment should be taken individually according to the characteristics of the patient, though the results of the ALLHAT study are good news for patients, institutions and countries that have to fight hypertension with cheap generic drugs such as diuretics and BB. The results also suggest that any strategy for patients who need more than one drug to achieve blood pressure control should include diuretics. Thus, given that many hypertensive patients benefit from treatment with ACE inhibitors or ARA II (diabetics, hypertensive patients with renal or heart dysfunction, heart failure, left ventricular hypertrophy with ischemic heart disease, stroke, etc.), combination of such agents with a low dose of thiazide seems an excellent therapeutic alternative. According to the results from the ALLHAT study, treatment with a

dihydropyridine CA is not associated with an increased risk of ischemic heart disease in hypertensive patients, in fact such agents seem a good alternative in patients not treated with diuretics. The results also suggest that doxazosin should not be considered as a treatment of choice, at least not in high risk hypertensive patients.

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