

Design and Conclusions of the ALLHAT Study

To the Editor:

An excellent editorial by González-Juanatey¹ on the ALLHAT study was published recently. Whereas we agree with his opinions, some of his conclusions on aspects of the design of the ALLHAT, particularly the claim that diuretics are the initial antihypertensive treatment of choice, require closer examination.

Bradford Hill laid the scientific foundations for clinical trials² and his definition of «a carefully and ethically designed experiment to answer a precise question» remains valid. Correct interpretation of a trial should be based on the question that it was designed to answer.

The hypothesis of the ALLHAT study³ is that the incidence of coronary heart disease would be lower in patients treated with drugs other than diuretics. After 4.9 years of follow-up, the incidence of coronary events was 11.5 per 100 patients for treatment during 6 years with chlorthalidone and 11.3 and 11.4 per 100 patients for treatment with amlodipine and lisinopril. No statistically significant differences were observed. A logical interpretation of this finding is to accept the null hypothesis and claim that the new drugs are not superior to diuretics, and indeed this is stated in the commentary section of the ALLHAT study. Surprisingly, the authors then conclude that thiazide diuretics should be the initial treatment in arterial hypertension and should be used, if possible, in association with antihypertensive agents.

If the aim is to test the superiority of one treatment over another, and the results show no difference, can the authors conclude that diuretics are preferable? The claim that diuretics are the initial treatment for hypertension is also incorrect because the number of patients receiving a diuretic as the initial treatment is unknown. Patients receiving antihypertensive treatment at the start of the study (enrolled with no washout from their normal treatment) comprised 90% of the study population, but we do not know what treatment they were receiving. Around 24% of the patients were changed to a different treatment group, and at the end of the trial almost 30% were not receiving the same drug they had been randomly assigned to at the start.

The defense of the preeminence of diuretics does not sufficiently emphasize that patients treated with chlorthalidone presented a significantly higher incidence of hypokalemia, hyperglycemia, hypercholesterolemia, increased creatinine or new diagnosis of diabetes. The authors' argument that this does not influence coronary events may be fallacious because the follow-up is too short for this influence to become apparent.

The results of the ALLHAT study suggest that lower blood pressure reduces the incidence of coronary events. But such a reduction is to be expected because we can assume that the incidence of such events would be greater in a group receiving no treatment than in one receiving treatment. We should point out that the incidence of coronary events in all groups is greater than expected.³

The ALLHAT study illustrates the need to combine drugs in order to control hypertension (40% of patients in the study received a combination of drugs). But the study does not demonstrate the advantages of some combinations over others because we do not know what combination the patients received and, moreover, the combined drugs were administered in an open-label manner. There are many possible combinations, and we cannot draw conclusions on the effects of one drug or another. The interpretation of the differences for the secondary objectives does not consider the complexity of treatment, and the comparison is based on the initial randomization group, which does not ensure that the patient received the corresponding drug.

The external validity of a trial depends on the similarity

between the study population and the target population in which the findings are to be applied. The study population is at high cardiovascular risk and aged over 55 years, so whether the same effects would arise in a lower risk population is mere conjecture.

The results of the ALLHAT study, as Meltzer⁴ noted, provide more support for the JNC IV report (1988) than for later updates, particularly, the JNC VII report, which uses the ALLHAT study to justify the choice of diuretics as the initial treatment. The lower cost of diuretics may justify - their use provided there are no contraindications or express indications for another drug, but the superiority of diuretics has not been proved by the ALLHAT study.

Recent guidelines have been issued jointly by the European societies of hypertension and cardiology.⁵ These documents criticize the interpretation of the ALLHAT study, are less restrictive regarding pharmacological treatment, and emphasize the importance of lowering blood pressure regardless of the drug used.

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Response

To the Editor:

I have read with interest the Letter to the Editor from Morales-Olivas and Estañ. First, I would like to thank him for his opinion on my recent editorial in the REVISTA ESPAÑOLA DE CARDIOLOGÍA. Some of his comments apply to one of the liveliest current scientific debates, namely, the choice of antihypertensive treatment in clinical practice. Researchers have been considering this issue for the last 25 years, although findings from recent studies on arterial hypertension (AHT) and new guidelines for clinical practice in this disorder have revived the debate. I would like to make the following observations on the topic.

Prevention of cardiovascular disease should be based on treatment that is adapted to the needs of the patient. Specifically,

treatment of AHT may involve thiazide diuretics as one of the possible first line therapies. Strong evidence on the effectiveness of these diuretics collected over the last 40 years supports the widespread presence of such drug in the therapeutic recommendations of recent American guidelines (JNC VII). Recent studies, in particular the ALLHAT study, have further confirmed this benefit. Some would wish that we had similar evidence in other areas of pharmacological prevention of cardiovascular disease that currently go unquestioned.

It is important to realize that most patients with hypertension need combinations of drugs to control blood pressure. All guidelines for the management of AHT in clinical practice agree that when a diuretic is not the initial antihypertensive agent, it should preferably form part of a combination of drugs. The combination of diuretics with drugs that block of the renin-angiotensin system are particularly favored. Thus the importance of the initial treatment is of only relative importance.

In addition to the goal of lowering blood pressure, the choice of class of antihypertensive drug will largely depend on adverse effects of the drug. Metabolic alterations associated with the chronic administration of thiazide diuretics, particularly at high doses, have been well known for some decades. However, the excellent results observed with these compounds in the ALLHAT study and the recommendations of the JNC VII seem to reject the possibility that we are suffering from an epidemic of diabetes associated with their use. Arguments along these lines are, at the very least, speculative. The real long-term clinical impact remains to be demonstrated.

The limitations in the design and follow-up of the ALLHAT study are well known. But to be fair, this is the most extensive study to date on the prevention of cardiovascular disease. Rates of drug discontinuation in this study are similar to those observed in other clinical trials on prevention whose conclusions have been used in guidelines for clinical practice. The characteristics of the patients included in this study, in particular their high risk, make the results particularly important. In patients treated with diuretics, many of whom also received beta blockers, the cardiovascular prognosis was at least as good as in those treated with amlodipine and lisinopril, which were also combined with beta blockers in a large number of patients. This finding is of particular clinical relevance. In cardiovascular medicine, differences between therapeutic regimens are easier to observe if the risk of the study population is higher, as seen in studies of heart failure and myocardial infarction.

Finally, I believe that diuretics should remain as first line treatment for AHT and that they deserve particular attention when other compounds are not specifically indicated e.g. blockers of the renin-angiotensin system (in patients with diabetes, kidney and heart failure, ischemic heart disease or stroke) and beta blockers (ischemic heart disease). Diuretics should also be considered in combination with other groups of antihypertensives.

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