Our Experience on Hypertension Clinical Trials in Elderly Patients

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Abstract
Hypertension causes 62% of strokes and 49% of coronary diseases in Western countries. These pathological findings are usually related to the late initiation of antihypertensive treatment, when organs such as brain, heart, or kidney are already damaged; hence, the importance of the early initiation of treatment making more effective hypertensive agents in order to avoid this circumstance. Clinical trials are also an important factor in this matter. The experience in our Hypertension and Lipid Unit is based on large clinical trials, such as SYST-EUR, HYVET, VALUE, CONVINCE, ONTARGET, TRANSCEND, and many others, as well as thousands of hypertensive patients treated to improve that clinical situation. We must remind that hypertension is usually asymptomatic and that these patients are not usually treated, leading to serious health complications. Nowadays, target blood pressure should be ≤ 130/80 mmHg to decrease or avoid cardiovascular events, to improve the quality of life, particularly in elderly patients, and to keep up the functional capacity of these patients.

ABBREVIATIONS
BP: Blood Pressure; CV: Cardiovascular; HYVET: The Hypertension in the Very Elderly Trial; CONVINCE: Controlled Onset Verapamil Investigation of Cardiovascular End Points; VALUE:Valsartan Antihypertensive Long term Use Evaluation; ACEI: Angiotensin-converting Enzyme Inhibitors; ARA II: Angiotensin II Receptor Antagonists,

INTRODUCTION
Elderly patients are being targeted in this paper. Hypertension causes 62% of strokes and 49% of coronary diseases [1]; even nowadays, many hypertensive patients start receiving pharmacological treatment when the symptoms are already developed, although physicians should intervene earlier before target organs such as kidneys, brain, heart, and peripheral vessels become damaged [2]. For that matter, there is a growing position for early and sustained blood pressure (BP) control to reduce cardiovascular (CV) events in patients with hypertension [3]. On top of that, imaging diagnostic systems are playing a crucial role in prompt recognition of events and patients prognosis. This context sets the framework in which clinical trials are developed.

For a long time, the deleterious effect of high BP is well known. This disease represents the first CV problem in western countries. Despite all this, the evidence of the benefits provided by therapy comes from epidemiologic and experimental research, large scale therapeutic trials and from the clinical experience, according to the subsequent guidelines for the management of hypertension [4].

HYPERTENSION AND LIPID UNIT
In the late 80's, I became interested in clinical hypertension when I found out that more than 80% of the stroke patients hospitalized at our Internal Medicine Service suffered from hypertension, and that most of them did not receive antihypertensive medication [5]. These findings have led us to decide, according to the hospital institution, to set up a Hypertensive and Lipid Unit aimed at improving that situation. Since March 1990, when this initiative started off, thousands of patients have been treated by our team; furthermore, some of them have taken part in different cardiovascular clinical trials.

So far we have conducted 168 clinical trials (including diabetes, cardiovascular events, and heart failure) from which 35.5% are about hypertension (Table 1). At this point, we proceed to mention the main findings on some clinical trials in which our team has collaborated.

DISCUSSION
The paper is targeting studies to prove that elderly patients need to be treated at BP 130/80 mmHg levels. Our experience...
accumulated for the last 24 years have allowed us to point out and establish some useful clinical aspects of the disease. SYST-EUR [6] was our first experience in this field. It was a multicenter, double-blind, international study in which 23 European countries were involved. A total of 4695 patients with isolated systolic hypertension (SBP > 160 mmHg, and DBP ≤ 90 mmHg) were randomized and followed up for a mean of ten years. The results pointed out that: a) There is a significant benefit for patients: a reduction of 13% in all causes of mortality, 30% in stroke and 23% in coronary diseases; b) active treatment (enalapril, nitrendipine, diuretic and all) is associated with less adverse effects on the quality of life of patients; c) hypertension is a prevalent condition associated with CV morbidity and mortality; d) the reduction in BP is related to the decreasing risk of CV events and the impairment in the elderly population; e) pharmacological therapy with a long-acting dihydropyridine protects against dementia in old patients [7,8]. Before publishing the Syst-Eur Trial data, most of physicians believed that reducing BP in old patients could be harmful, leading to ischemia and poor tissue oxygenation of target organs. However, this trial showed unequivocally the benefits of treatment versus placebo. In addition, the Hypertension in the Very Elderly Trial (HYVET) was designed to compare the benefits and risks of treating hypertensive patients aged 80 years or older. In the pilot trial, 1283 patients were included and after HYVET main study, 3845 patients were randomized. The results demonstrated the therapeutic benefits of indapamide treatment (sustained release) with or without perindopril in this population [9,10]. Since oral antihypertensive therapy has become available, target organs protection has also been reported [11].

The Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) was a double-blind, randomized, multicenter, international clinical trial that compares outcomes in hypertensive patients randomized to initial treatment with either controlled-onset extended-release verapamil or the investigator’s choice of atenolol or hydrochlorothiazide. The protocol for this study includes an increase of antihypertensive medication whenever the BP is not at goal (<140/90 mmHg) [12].

The valsartan Antihypertensive Long-term Use Evaluation (VALUE) [13] trial was designed to prove the hypothesis that for the same BP control, valsartan would reduce cardiac events more than amlodipine in hypertensive patients at high CV risk. A total of 15245 patients were included, 50 years of age or older with treated or untreated hypertension and high risk of cardiac events. The trial was a randomized, double-blind, parallel-group comparison of therapy based on valsartan or amlodipine. Patients from 31 countries including our center were followed up for a mean of 4.2 years. The primary endpoint of cardiac disease did not differ between both treatment groups. Also, the findings emphasize the relevance of prompt BP control of hypertension in patients with high risk of CV events.

The ONTARGET study was designed to compare the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients suffering from vascular disease or high-risk diabetes. Patients underwent double blind randomization: 8576 were assigned to receive 10 mg of ramipril per day; 8542 assigned to receive 80 mg telmisartan daily, and 8502 both drugs. The primary composite outcome was death from CV origin: stroke, ischemic heart disease, or hospitalization for heart failure. The results showed that ramipril and telmisartan were equivalent for vascular disease or high-risk diabetes. However, angioedema was less frequent in the telmisartan group. The combination of the two drugs showed more adverse events without an increase in benefit [14].

In spite of the amount of drugs available, it is still difficult to achieve right BP levels in these patients. Darusentan, a selective endothelin type 1 antagonist provides additional reduction in patients whose BP is not well controlled with three or more antihypertensive drugs. These are the results a study on 379 patients from 117 cities in North and South America, Europe, New Zealand and Australia, who underwent a randomized, double blind trial [15]. The data from 117 patients randomly assigned to receive spirolactone (n=59) or a placebo (n=58) as an add-on to their antihypertensive medication demonstrated that Darusentan is an effective drug for lowering systolic BP in patients with resistant arterial hypertension [16].

Significant progress has been made towards the knowledge of the complex nature of hypertension. Nevertheless, hypertension still remains the leading cause of cardiovascular fatal and non-fatal events, mostly of stroke and coronary disease over the past 30 years. Unfortunately, the number of patients in whom hypertension is well controlled (<130/80 mmHg) is less than 25 percent worldwide. There are plenty limitations that interfere with the control of hypertension, such as: difficulties in accessing health care, noncompliance treatment, absence of symptoms, side effects of antihypertensive drugs, risk factors (obesity, hypercholesterolemia, and smoking) or other diseases. Nowadays, this is the desirable target for BP levels ≤ 130/80 mmHg that should be kept and applied to clinical practice.

CONCLUSION

In conclusion, hypertension is a prevalent condition among the elderly and is associated with a risk of CV morbidity and mortality. The reduction of BP decreases the risk of CV events and improves the quality of life of elderly patients. As a result, the aim of therapy should be the reduction of CV risk while maintaining an acceptable quality of life and a high degree of functional capacity in these patients.

ACKNOWLEDGEMENTS

We thank Mrs. Esperanza Velasco Rodriguez for help for English translation.

Conflict of interest

The authors declare that any financial interest or any conflict of interest exist in this investigation.

Table 1: Summary of our Clinical Trials on Hypertension.

<table>
<thead>
<tr>
<th>Number of Clinical Trials</th>
<th>Phase</th>
<th>Pharmaceutical Companies</th>
<th>Drugs Used*</th>
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<tr>
<td>99</td>
<td>III IV</td>
<td>34 35</td>
<td>25 24</td>
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</tbody>
</table>

Abbreviations: *ACEi, diuretics, ARA II, anti-CA++*, β-blockers, α-blockers, renin inhibitor, endothelin inhibitor.
REFERENCES


