Editorial
Antihypertensive trials: all is not gold that glitters?

Cesare Dal Palù

Department of Clinical and Experimental Medicine, University of Padua Medical School, Padua, Italy

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Address:

Prof. Cesare Dal Palù

Via San Pietro, 29
35137 Padova
E-mail: dalpalu@tin.it

A huge number of articles about the pharmacologic therapy of hypertension have been published in the last decades and many studies have been conducted with the aim of evaluating whether some antihypertensive agents are better than others, if any is better as first-line therapy, or any association of antihypertensive agents is better than others. However almost all studies did not clearly define if they dealt with "antihypertensive therapy" or "therapy of hypertensive patients". These two views constitute, in my opinion, two different approaches to the therapy of hypertension.

"Antihypertensive therapy" means the use of all the therapeutic tools that are able to reduce blood pressure to normal or almost normal values. These include surgery (excision of aldosterone-producing adenomas and of pheochromocytoma, renal artery stenosis dilation) and pharmacologic agents (essential hypertension or secondary hypertension without surgical indication). The aim of therapy is to prevent those target organ damages that are "directly" provoked by high blood pressure: that is, those clinical complications that are considered as exclusively due to an increase in blood pressure and that usually occur in a short time in case of severe hypertension if the patient is not properly treated. In these cases the cardiovascular system is quickly remodeled to normalize wall stress: in the heart, the typical response is concentric left ventricular hypertrophy, while in the resistance arteries the wall thickness and the wall/lumen ratio are increased; hyalinosis can ensue. When high blood pressure values are not lowered with appropriate therapy, clinical complications may occur, including acute and chronic heart failure, artery aneurysms, aorta dissection, hemorrhagic stroke, and renal insufficiency. In case of malignant hypertension, immediate blood pressure reduction is mandatory, otherwise target organ damage such as hypertensive encephalopathy and renal insufficiency may lead to death. These complications were the rule until the half of the 20th century when no antihypertensive agents were available: at present time they may occur only if a patient is not treated properly and in time.

Since all antihypertensive agents actually available are effective in lowering blood pressure, the choice of an appropriate antihypertensive agent is relatively easy. The choice will be based on simple criteria: the preference of the doctor; some characteristics of the patient (race, sex; tachycardia or bradycardia; associate conditions such as the presence of asthma, diabetes and so on); the tolerability profile and the efficacy of that particular antihypertensive agent for that patient. In case of severe hypertension an association therapy is needed in almost 80% of cases to reduce blood pressure to normal values: all the combinations have been extensively described and reported and deserve no more comment.

The term *"therapy of hypertensive patients"* has a different meaning, because it refers to all those measures that significantly modify the "long-term" outcome of hypertensive patients, reducing their morbidity and mortality: in that case, the choice of an appropriate antihypertensive agent may be more complex, because the prevention of target organ damage due exclusively to high blood pressure is only one of the goals of therapy, most of the long-term complica-

tions being due to a different arterial pathology, more subtle and slowly evolving, namely atherosclerosis and to its main complication, thrombosis. In such cases hypertension is often only mild or moderate (from the beginning or made moderate by antihypertensive therapy) and the clinical events will not be heart failure, renal insufficiency or cerebral hemorrhage, but angina pectoris or myocardial infarction (eventually followed by postischemic heart failure), cerebral infarction due to thrombosis or to emboli, and chronic slowly evolving renal insufficiency. In these circumstances hypertension is only one of the so-called "risk factors" for atherosclerosis and its complications, the others being genetic, toxic, metabolic, inflammatory and possibly other that we do not yet know. Consequently, the goal of any antihypertensive treatment cannot be restricted only to the fall of blood pressure but has to take into account also the pathophysiology of arterial wall and possibly have a positive impact on the other risk factors.

These remarks may appear obvious, considering that the last European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines[1], unlike the Joint National Committee (JNC)-7[2], underline the importance of the "cumulative risk" of any hypertensive patient[3,4]. However, with regard to the pharmacologic treatment, even in the ESH-ESC guidelines no distinction is made between the prevention of target organ damage "directly" attributable to high blood pressure and that of "long-term" complications due to hypertension plus atherosclerosis. Moreover, referring to long-term complications, no distinction is made between "primary" prevention (i.e. the prevention of atherosclerosis) and "secondary" prevention (i.e. the prevention of complications of atherosclerosis). Since the many drug classes reduce blood pressure trough various mechanisms, different effects on the arterial wall and on the progression of atherosclerosis may be postulated and the choice among the various antihypertensive agents may become more difficult, depending on properties of the various drugs that can be different from those that induce the fall of blood pressure.

Let us see how the problem of long-term antihypertensive treatment has been faced up in the more recent literature.

Primary prevention of atherosclerosis in hypertensive patients

Very few studies have been performed in humans concerning antihypertensive therapy and progression/regression of atherosclerosis.

In animal models of atherosclerosis it has been clearly established that hypertension contributes to the progression of the disease[5-7]. Moreover, some antihypertensive agents, such as calcium antagonists, beta-blockers, angiotensin-converting enzyme inhibitors, have been considered to be able to reduce the extension and progression of experimentally induced atherosclerotic lesions: in some studies these effects were independent of blood pressure reduction[5-8].

In man, the progression of atherosclerotic plaques was studied mainly in the carotid arteries by means of ultrasound examination. Several studies demonstrated a continuous relationship between carotid artery intima-media thickness and cardiovascular events[9,10]. Only a few studies have addressed the effects of antihypertensive agents on the progression and/or regression of atherosclerosis on the arterial wall (VHAS, MIDAS, INSIGHT-IMT, ELSA)[11-15]. Their results were not conclusive because of reading drift (MIDAS) or too small studies (VHAS, INSIGHT); the ELSA study was more conclusive but the follow-up was not long enough to demonstrate a clinically relevant progression or regression of atherosclerotic plaques, even if the differences of carotid lesions between the two treatments reached the statistical significance.

Indeed, in order to clarify the impact of any antihypertensive treatment on atherosclerosis, we need studies beginning in young or middle-aged hypertensives with a long follow-up, because atherosclerotic plaques start early and their progression is usually slow. Moreover, since not all hypertensives are liable to atherosclerosis, any effect of therapy in preventing the disease will be much diluted and a huge number of patients should be enrolled and followed for too many years. Such type of studies are at present quite impossible, because too much time and money would be needed: they will be become feasible only when we will know more about the genetic factors predisposing to atherosclerosis, so that the selection of young patients at high risk for the disease can overwhelm the length of follow-up.

At the present time we only know that different antihypertensive drugs have different effects on physiology and biology of the arterial wall, and that these effects can interfere with the development of atherosclerosis.

Anyhow, even if the fundamental problem of the choice of the best antihypertensive drug for the primary prevention of atherosclerosis in hypertensives is still unsolved, we do not find in the more recent medical literature much attention to it.

Prevention of events in hypertensive subjects

Secondary prevention, that is the prevention of long-term clinical events in hypertensives, has attracted much more attention than the development of atherosclerosis: the results of a large number of randomized trials concerning this topic have been published since the last decades of the 20th century and constitute the ground for the so-called "evidence-based medicine" in hypertension[16-25]. The recommendations of the experts for the management of arterial hypertension are founded on such trials. However, all is not gold that glitters.

Let's summarize the main features of these clinical trials and their drawbacks:
a) the follow-up was generally quite short, their mean duration being 3-5 years. We do not know what will happen after this short lapse of time;
b) the endpoints were cumulative cardiovascular events (myocardial infarction and stroke) and mortality; in many trials, any single event and/or mortality were considered separately;
c) patient entry criteria were not uniform. Study populations were often heterogeneous, even in a single trial, with regard to race, type and seriousness of hypertension, cumulative cardiovascular risk, presence or absence of dysmetabolism. Due to this heterogeneity, interpreting the results of a trial and comparing trials each other may be extremely difficult;
d) the mean age of the patients enrolled was rather high, usually starting from 50-55 years, but in many studies they were more than 65-70 years old. We do not know what would happen starting the same treatments 10 or 15 years before;
e) we ignore how many of the enrolled patients had atherosclerotic plaques before treatment: therefore we do not know if the benefits of treatment relate to patients with or without plaques;
f) different antihypertensive agents have been employed and compared with placebo or with other antihypertensive drugs. Additional antihypertensive therapies were permitted, but they were not uniform.

The features of the trials enlisted above do not need further comment, being easily verifiable in all the papers published on this subject. They underline the difficulties and the limits of the matter. Often these difficulties have been ignored in the comments of the experts, unless undesired results came out from some trials (for example the ALLHAT trial)[22].

Let's now consider the main results of the clinical trials:
a) antihypertensive therapy reduces the number of cardiovascular events in hypertensives. The reduction is for the most part statistically significant but the clinical impact is not as remarkable as one would expect: benefits are quite little for myocardial infarction (14-20%) more evident but not exciting for stroke (40-45% in some trials). The results of some trials may differ from others sensationally (see the SHEP study[16] compared to the Syst-Eur study[18]);
b) all the antihypertensive drugs did reduce the incidence of cardiovascular events, the differences among the various agents being small or null. Some authors[26] suggest that diuretics (and perhaps AT_1-receptor blockers) should be preferred because they induce a more marked fall of blood pressure: in their opinion the different mechanism of the various drugs are negligible compared to their blood pressure lowering effects;
c) in a few clinical trials benefits were observed with some antihypertensive drugs also in patients with high cardiovascular cumulative risk but who were not hypertensives (HOPE study)[25]. Some authors suggest that in these cases the benefits can be fully explained by the small decrease in blood pressure induced even in these subjects by antihypertensive therapy[27];
d) most of these trials have been subjected to meta-analyses, either to arrive at more precise and generalizable conclusions, or to answer questions on subgroups, which could not be addressed in individual studies. These meta-analyses appear questionable because they put together quite different trials. Anyway the results of meta-analyses confirm those of the main trials: antihypertensive drugs reduce more than placebo the incidence of all endpoints; no clear difference can be seen using various antihypertensive drugs[28,29];
e) a few clinical trials have shown that some antihypertensive drugs are better than others in reducing clinical events, such as stroke and renal insufficiency, even in the absence of any blood pressure difference between the treatment groups (LIFE[29,30], RACE[31], ANBP2[32], IRMA2[33]). These latter observations are in contrast with the previous ones, stressing the importance of the different mechanism of the various antihypertensive agents and the opportunity of a well pondered choice before starting any therapy.

Do we need more antihypertensive trials?

A very interesting summary of the state of the art of hypertension treatment, after so many clinical trials, has been illustrated by Volpe[34] in four summarizing tables, three of which reproduce the indications for treatment of the three sections of the ESC-ESH and JNC guidelines. They are so complicated and complex that no general practitioner, nor a specialist, could take unequivocal commitment in order to the best treatment for his hypertensive patients.

Actually, the only clear indication coming out from the trials is that treatment is better than placebo in preventing cardiovascular events and that the best way for reducing the number of events is to lower drastically blood pressure no matter how[26]. Many authors maintain the same opinion[27,29]. Obviously, if the benefits of antihypertensive therapy are exclusively due to the blood pressure lowering effect, our conclusion should be, after so many trials and thousands of patients treated, that having a normal blood pressure is better than being hypertensive: a conclusion that can be attributed to the author of the song about Monsieur de La Palisse. But, as we have seen, not all agree with this oversimplified conclusion.

Many questions remain unanswered after so many clinical trials.

First of all, as we have said above, the problem if any of the antihypertensive drugs can reduce the extension and progression of atherosclerotic plaques: such a question, that is crucial, needs a different and more sophisticated approach.

Second, it is not clear how and why antihypertensive drugs block that process for which an atherosclerotic plaque undergoes complications. Since any complications of the atherosclerotic plaque is due to inflammation, rupture and thrombosis we should assume that plaque instability is mainly due to an increased blood pressure: an hypothesis that deserves more demonstration.

We do not know why antihypertensive agents reduce to a larger extent stroke than myocardial infarction[35-37]: are cerebral complications more strictly related to high blood pressure than coronary ones? Is it because the coronary flow occurs mainly during the diastolic phase of the heart cycle and diastolic pressure is lower in elderly hypertensives who usually have systolic hypertension?

Moreover, if blood pressure reduction is efficacious in stroke prevention, which type of stroke will mainly benefit from blood pressure reduction: the atherothrombotic? small vessel or lacunar? embolic from large cerebral arteries and aorta plaques? cardioembolic?

At last, it is not yet clear if we have to reduce more the diastolic blood pressure (HOT study)[38] or the systolic one (STOP Hypertension, SHEP, etc.).

In conclusion, after so many clinical trials, too many problems remain open: because this type of approach will never give those answers that we are expecting. For this reason, it seems to me superfluous planning further mega-trials that are expensive and devoid at this point of any real interest. Eliminating the trials, we will be deprived of some appealing acronyms: but new approaches will give us more gratifying and scientific results.

Which therapy for our hypertensive patients?

Being so much what we still ignore, I wonder if we have the authority of advising practitioners about the choice of antihypertensive treatments according to the results of the clinical trials: the "evidence-based medicine" in hypertension is still an utopia, at least on the basis of the studies done till now in hypertensive patients. I suspect that this is the very reason why doctors, in their everyday practice, continue following those simple principles of choice that have been illustrated in the first part of this article, not taking much notice of the recommendations that different published papers have turned out in these last years.

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