Systemic arterial hypertension (SAH) is the main risk factor for premature death in the world and in Mexico. Around 15.2 million Mexicans have been estimated to be diagnosed with SAH, out of which 7.48 million are affiliated to IMSS (evaluation of the financial risks considered in the Institutional Risk Management Program, ENSANUT, 2018). SAH is a complex, chronic disease that requires continuous medical attention with multifactorial risk reduction strategies, which go beyond numerical control in mm Hg of blood pressure and have been shown to be effective in reducing the vascular, cardiac and renal complications of the disease, as well as its impact on premature death. Continuous education and support in SAH self-management are essential to overcome the main challenges: treatment adherence and self-monitoring by the patient for the rest of his/her life.

In the American Heart Association and American College of Cardiology (AHA/ACC) 2017 guidelines, which update the Joint National Committee seventh report, reducing the cutoff point for the diagnosis of SAH to ≥ 130/80 mm Hg was proposed, as well as starting pharmacological treatment in patients at stage 1 (130-140/80-90 mm Hg) and with high risk. On the other hand, the new recommendations of the European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guidelines indicate that, in patients with borderline or elevated blood pressure (130-139/80-89 mm Hg), only lifestyle changes, diet and exercise should be indicated. These apparent divergences have generated uncertainty, especially among experts. Another innovative aspect is the recommendation to use double or triple combination therapy, either separately or in a single pill, as first-line treatment in patients with SAH, especially with blood pressure levels ≥ 160/100 mm Hg or ≥ 140/90 mm Hg if the subject has high-risk factors.

In Mexico, as in most Latin American countries, there are serious lags in SAH timely detection, as well as in risk stratification, timely treatment initiation, optimal control, control follow-up and treatment adherence.

**Whom to give double or triple combination therapy?**

The most recent guidelines (AHA/ACC and ESC/ESH) recommend starting treatment with two drugs, preferably in a single pill, in patients with blood pressure ≥ 160/100 mm Hg or ≥ 140/90 mm Hg when they are classified as being at high risk or have target organ damage (retinopathy, left ventricular hypertrophy, kidney disease, diabetes). Furthermore, approximately 25 % of patients will require three antihypertensive agents to achieve treatment goals, which have become stricter (<130/80 mm Hg but not <120/70 mm Hg).

We do not fully agree with some ACC/AHA criteria established in the 2017 guidelines.
The 130/80 mm Hg threshold to determine the presence of hypertension, under the premise that most patients at stage 1 (130-139/80-89 mm Hg) can be controlled with non-pharmacological strategies and that only patients with high cardiovascular risk require pharmacological treatment and only with one drug.

A blood pressure goal < 130/80 mm Hg, given that the context in Mexico is very different and that the goal with the highest net clinical benefit (effectiveness/side effects) is the level accepted by the 2018 European guidelines, i.e., < 140/90 mm Hg and only if the patient tolerates it, < 130/80 mm Hg but not less than 120/70 mm Hg.

We agree with the tendency in both guidelines to start with a double pharmacological combination, preferably in a single pill, given that most patients are of medium-high risk, except for older, frail and high-risk younger patients with blood pressure > 130/80 mm Hg, in whom monotherapy would be indicated.

**With what? Double and triple combination therapy**

The simultaneous effect of the renin-angiotensin-aldosterone system, autonomic nervous system, vascular reactivity and endothelial function, among others, shows that the blockade of a single mechanism may not be sufficient and monotherapy is therefore insufficient, whereas the combination of two antihypertensive agents with a different mechanism of action can reduce coronary events by up to approximately 35 % and cerebrovascular events by 54 %.7

If there is sufficient evidence of multiple pathophysiological aspects, why does the prescription of monotherapy predominate? The reason most commonly expressed by the general practitioner is related to the fear of suddenly and extremely lowering blood pressure. However, there is increasing evidence that with the combination of drugs, control figures with higher consistency and without side effects are achieved. A calcium channel blocker (CCB) with a diuretic or an angiotensin II receptor blocker (ARB) or an angiotensin converting enzyme inhibitor (ACEI) with a diuretic, or an ACEI or ARB with CCB are the combinations popularized as “double combination antihypertensive therapies”, which already even exist in a single pill, which in turn facilitates their prescription and treatment adherence by the patient.8

The use of a beta-blocker with a diuretic is also a double combination therapy; however, it is only recommended in certain patients (with ischemia, tachyarrhythmia, or heart failure). There are combinations that should not be used, such as two agents that inhibit the renin-angiotensin axis (on April 20, 2012, the Food and Drug Administration issued a warning on the subject), specifically an ACEI with an ARB.9 Combinations of diuretics with beta-blockers have been observed to have the tendency to increase the risk for developing type 2 diabetes, as recorded in the ASCOT trial,10 and thus they should be used with caution, especially in

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**Figure 1. Stepwise approach to the treatment of high-risk patients with stage 1, 2 and 3 systemic arterial hypertension.** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; CCB, dihydropirine calcium channel blocker. Adapted from the European guidelines (ESC/ESH).
When to prefer double combination therapy with a diuretic and when with a calcium channel blocker?

In patients with obesity or predisposition to metabolic problems, the combination of ACEI or ARB with dihydropyridine CCB (amlodipine, nicardipine, felodipine) is preferable, if there is no obesity or metabolic problems but there is evidence of fluid retention, the combination of an ACEI or ARB with a thiazide diuretic is preferable if the renal function is preserved (glomerular filtration rate > 40 mL/minute) or a loop diuretic if renal function is impaired (< 30 mL/minute).11-16

The ACCOMPLISH trial included 11,462 patients older than 50 years with high cardiovascular risk (60.4% with diabetes mellitus). They were divided into two groups: one group received the benazepril plus amlo-dipine combination, and the other group received benazepril plus hydrochlorothiazide. Trial duration was designed for five years; however, the study was suspended at month 39 because the calcium channel blocker plus ACEI combination was found to be superior to the ACEI plus hydrochlorothiazide combination in the reduction of cardiovascular, cerebrovascular and renal events.16

Conclusion

By blocking several pathways of blood pressure increase, combination therapy has higher antihypertensive power than high-dose monotherapy, in addition to providing greater protection to target organs and having less potential for side effects.

The most commonly used combinations include an ACEI or ARB associated with a calcium channel blocker or a natriuretic agent. Combinations that include a diuretic have yielded better results in patients with heart failure or impaired kidney function.

A significant percentage of patients will require triple therapy: an ACEI or ARB, a CCB and a natriuretic agent, which should be administered to patients who fail to respond to double combination treatment at six to eight weeks, since the benefit is beyond the shadow of a doubt. The use of these combinations in the form of a single tablet has a highly favorable impact on treatment adherence by the patient.

Conflict of interests

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Ethical disclosures

The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data

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Right to privacy and informed consent

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