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A review of non-pharmacological and pharmacological therapies to treat high blood pressure

Una revisión de las terapias no farmacológicas y farmacológicas para tratar la hipertensión arterial

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Palabras clave:
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ABSTRACT

Despite the wide availability of therapeutic options to treat high blood pressure (HBP) in market and healthcare systems, there is a low proportion of patients who achieve blood pressure goals. In this work, we review essential non-pharmaceutical measures, along with current and novel pharmacological approaches which have been recommended in the management of HBP. In summary, weight loss, increased physical activity, diminishing sodium and potassium using DASH and Mediterranean regimes, along with cessation of tobacco consumption, are widely proven non-pharmacological interventions that have demonstrated an impact in decreasing arterial blood pressure. Regarding pharmacological approaches, most of them have been focused on the renin-angiotensin-aldosterone system (RAAS), for which angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) stand for the most widely used antihypertensives, as well as being cost-effective strategies to decrease arterial blood pressure. Combining diverse antihypertensive medications has also demonstrated a good approach when the formulations are implemented within one-pill administration. Nevertheless, the diverse combination with other antihypertensive regimes needs to be individualized for the clinical characteristics of each patient. Finally, novel strategies are currently being studied to handle HBP in the future.

RESUMEN

A pesar de la amplia disponibilidad de opciones terapéuticas para tratar la hipertensión arterial (HTA) en el mercado y en los sistemas sanitarios, hay una baja proporción de pacientes que alcanzan los objetivos de presión arterial. En este trabajo se revisan las medidas no farmacéuticas esenciales, junto con los enfoques farmacológicos actuales y novedosos que se han recomendado en el tratamiento de la HTA. En resumen, la pérdida de peso, aumento de la actividad física, disminución del sodio y el potasio mediante los regímenes DASH y mediterráneo, junto con el cese del consumo de tabaco, son intervenciones no farmacológicas ampliamente probadas que han demostrado un impacto en la disminución de la presión arterial. En cuanto a los enfoques farmacológicos, la mayoría de ellos se han centrado en el sistema renina-angiotensina-aldosterona (SRAA), por lo que los inhibidores de la enzima convertidora de angiotensina (IECA) y los bloqueadores de los receptores de angiotensina (BRA) son los antihipertensivos más utilizados, además de ser estrategias rentables para disminuir la presión arterial. La combinación de diversos medicamentos antihipertensivos también ha demostrado ser un buen enfoque cuando las formulaciones se implementan dentro de la administración de una sola píldora. No obstante, la combinación diversa con otros regímenes antihipertensivos debe individualizarse en función de las características clínicas de cada paciente. Por último, se están estudiando nuevas estrategias para el manejo de la HTA en el futuro.

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INTRODUCTION

During the last decades, healthcare systems worldwide have experienced a transition towards late medical care, which prioritize secondary or tertiary medical attention instead of primary care. Despite the wide availability of therapeutic options to treat high blood pressure (HBP) in the market and in healthcare systems, there is a low proportion of patients who

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achieve therapeutic goals. Furthermore, HBP is further combined with cardiometabolic health diseases like diabetes and overweight, which further increase the risk for the onset of CVD. The Global Status Report 2014 (GSR-2014) has proposed an initiative to reduce the burden of cardiovascular disease (CVD) through the implementation of public health policies that sought to target four main objectives of manage HBP: 1) reduce the burden of alcohol and tobacco intake, 2) improve actions to promote physical activity, 3) reduce the food intake of sodium and 4) promote the early diagnosis of high-blood pressure in all healthcare settings.[1] Nevertheless, there is still a debate regarding what could be the long-term effects of these public health policies that prioritize non-pharmaceutical interventions. In this work, we review essential non-pharmaceutical measurements, along with pharmacological approaches that have been recommends in the management HBP in a primary care approach.

Non–pharmaceutical measures for high blood pressure

It has been widely proven that increased fat accumulation, a high intake of sodium (> 3 grams per day), potassium, fatty foods (more than 7% of total fat), use of tobacco, along with low physical activity are well-documented risk factors that end-up promoting a high-risk atherosclerotic profile (high level of LDL-C and low HDL-C). Therefore, most of the non-pharmaceutic therapeutic actions have been aimed towards reducing the previously mentioned risk factors. In *Table 1*, we present a summary of targeted interventions that have demonstrated a beneficial effect in decreasing blood pressure in adults, along with the literature that have supported these statements.

A well-documented intervention is the DASH (Dietary Approach to Stop Hypertension) diet, as it has been demonstrated that it could reduce 8 to 14 mmHg of SBP. The DASH

Table 1: Non-pharmaceutical measures for high blood pressure.

Interventions	Targeted goals	Estimated effect	Reference
Weight loss	Ideal body mass index between 18.5 and 25 kg/m^2 Net weight reduction of -5.1 kg (95% confidence interval [CI], -6.03 to -4.25) Individualize the use of medication and bariatric surgery	4.4 mmHg in SBP 3.6 mmHg in DPB	(32,33)
Abdominal circumference	< 94 cm on men < 88 cm on women		(7,34)
Physical activity	At least 30 minutes per day for 5 days in a week including isometric exercise	8.3 to 5.2 mmHg in SBP	(35)
Low sodium intake	< 5 g of salt per day Reduction of intake of the size of a table teaspoon (~3 g of salt)	2.0 to 4.0 mmHg in SBP	(36)
Consumption of food with potassium	A maximum intake of 90 mmol or 3,510 mg per day	Up to 11 mmHg in SPB	(37–39)
Mediterranean diet or DASH	High intake of fruits and vegetables, along with a low consumption of high calorie foods and low fat	Up to 11 mmHg in SPB	(2–4)
Coffee consumption	Protective effect with < 5 cups per day	5 to 15% reduction on CVD risk	(40)
Low tobacco consumption	Full suspension		
Low alcohol consumption	14 units per week in men 8 units per week in women 1 unite = 125 mL of wine and 250 mL of beer	~5.50 mmHg in SBP ~3.97 mmHg in SBP	(7,41–43)

regime implies in a reduction in carbohydrate consumption, and promoting an intake in whole grains, bird meat, fish, a low in fat intake and a consumption of nine to eleven fruit and vegetable per day. Furthermore, the DASH regime has shown an increased benefit within older adults. Another accepted and well-studied dietary regime is the Mediterranean diet, which is comprised of a high consumption of vegetables, fruits, olive oil, low-fat cheeses, sugar-free yoghurt, whole-bean cereals, a small portion of wine and a substitution of red meat ingestion with white-fish and chicken.[2-5]

All these recommendations have been posed as effective strategies to manage blood pressure in primary care settings. However, it is crucial to promote empowerment in each patient as an essential component in the application of these approaches. Edward Wagner and et al developed a model that sought to promote empowerment using a dual combination of self-monitoring and care alongside with a closer interaction with its healthcare provider.[6] The main purpose of the empowerment model is to implement efficient lifestyle changes that end-up reducing the impact of prevalent CVD risk factors. This perspective could be applicable to patients living with HBP, along in subjects that sought to prevent or delay the disease. Finally, according to the European Society of Hypertension, it is recommended that a follow-up assessment should be made every three months since the start of the initiation of lifestyle changes to reevaluate and perform modifications.[7]

Although these actions seek to promote simple strategies, it has been documented that the efficacy of non-pharmacological interventions may be restricted in vulnerable socioeconomic groups given to a low income and lower educational attainment.[8,9] Therefore, there is a need of research for simple and low-cost strategies that could benefit vulnerable communities, and in consequence, diminish the burden of high-blood pressure.

Overview of the pharmacological therapies to reduce high-blood pressure

Pathophysiological implications. Patients living with primary HBP are usually treated with a wide variety of pharmacological interventions that have their main therapeutic action via different pathophysiological mechanisms *(Figure 1)*. In *Table 2*, we summarize the mechanism of the most efficient commercially available antihypertensive drugs that decrease central venous pressure, systemic vascular resistance and improve cardiac output by diverse associated mechanism.

Renin-angiotensin-aldosterone system. The renin-angiotensin-aldosterone system has (RAAS) has a fundamental role in balancing blood pressure. The RAAS has been described as a sequence of organized biochemical reactions that helps maintain blood pressure homeostasis. After discovering its essential components, a century ago, the RAAS marked a whole chapter within the pathogenesis of HBP and led to an entire pharmacological research area for managing cardiometabolic diseases.

The kidneys are the only site where prorenin is metabolized into renin and then transported into the plasmatic circulation. Afterward, in the liver, renin metabolizes angiotensinogen to create angiotensin. Nevertheless, other sites where it has been described as capable of producing angiotensinogen are brain, kidney, heart, large arteries, and adipose tissue. Angiotensinogen is then proteolytically converted into angiotensin-II by a crucial enzyme named angiotensin-converting enzyme (ACE) in the lungs. Other sites where this step could be performed are blood vessels, kidneys, heart, and brain, which could metabolize angiotensin II independently of ACE (via chymase, carboxypeptidase cathepsin G, and plasminogen activator pathways). Angiotensin II then produces diverse physiological reactions driven by the widely spread type 1 (AT1) receptors rather than type 2 (AT2) within the body. The effects produced by the stimulation of AT1 and AT2 are shown in *Table 1*. Finally, angiotensin II triggers the release of aldosterone and vasopressin (antidiuretic hormone), which are produced by the adrenal and pituitary glands, respectively. Both aldosterone and vasopressin acts as sodium and water restrictors, leading to an increasing blood volume and blood pressure.[10]

Another critical system involved in the counterregulation of blood pressure is the renal

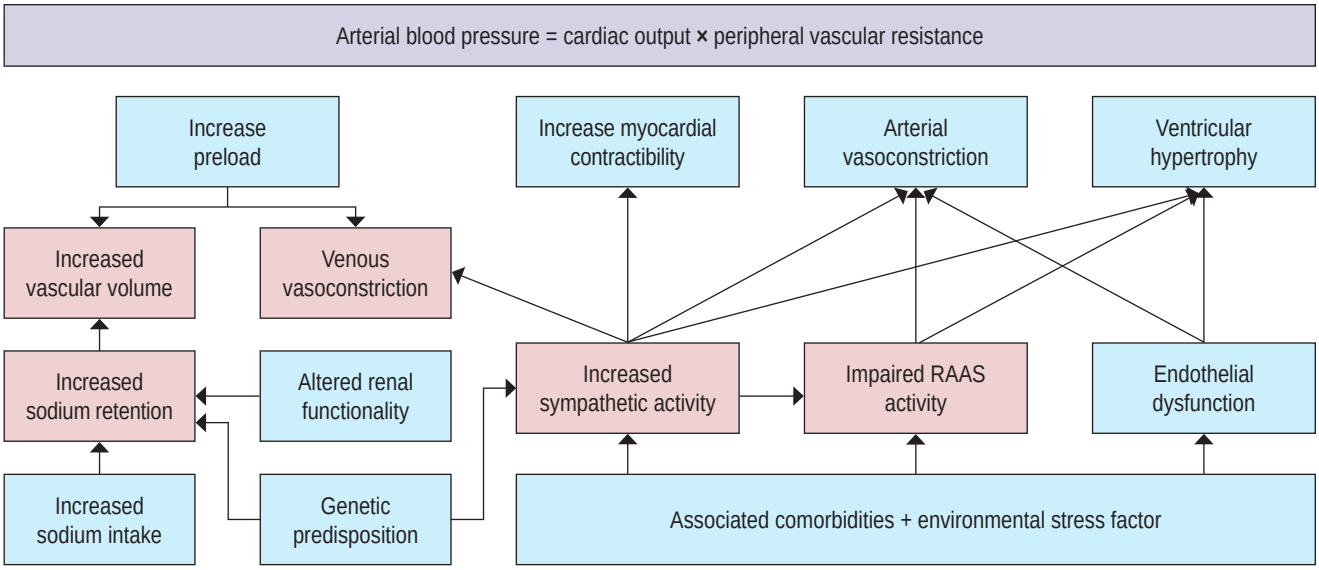

Figure 1: Brief pathophysiology of high blood pressure.

Table 2: Summary of the mechanism of action for the most efficient commercially available antihypertensive drugs.

Type	Mechanism of action	Final effects
Diuretics	Decrease blood volume through sodium and water excretion.	— Decrease in cardiac output and diminishing ventricular preload via Frank–Starling's mechanism. — Improvement on systemic vascular resistance.
Beta-blockers	Blocking the sympathetic system from the cardiovascular system.	— Decreasing heart rate, cardiac contractility, and stroke volume. — Useful in managing "hyperdynamic syndromes", characterized by an increase in the cerebral RAAS. — Decrease sympathetic stimulation that promote catecholamines cascade.
Non - dihydropyridine calcium channel blockers	Decreasing cardiac output through dropping heart rate and myocardial contractility	— Highly cardio selective pharmacotherapeutic action.
Dihydropyridine calcium channel blockers		— More selective for the systemic vasculature — Promotes a reduction in systemic vascular resistance.

kinin –kallikrein– prostaglandin system. The first steps are promoted by kinin and kallikrein secretion induced by mineralocorticoids receptors. The system promotes a reduction in the reabsorption of sodium in the ascending part of Henle's loop and promote the release of renal prostaglandins, hence, restricting vasodilatation of renal efferent arterioles and promoting sodium excretion. In people living with HBP, it has been described a decrease in the activity on the kinin –kallikrein– prostaglandin system. Nevertheless, this system continues to be an area of further research.[11]

Considerations in using angiotensin converting enzyme inhibitors. In 1970, the Brazilian pharmacologist Sergio H. Ferreira, discovered that the *Bothrops Jaraca*'s venom contained a peptide capable of inhibiting the action of Kinase II, an enzyme involved in the degradation of bradykine. He identified that

this peptide could be used for therapeutic use, thus, motivate him into synthetize captopril as the first ACEIs of its kind.[12] Nowadays, several ACEIs have been synthetized and have been positioned as the first line of action in diverse hypertensive related disorders, including heart failure with history of heart attack, diabetes, diastolic dysfunction, and within patients living with chronic kidney disease.[13]

Regarding combined therapies, it has been described that ACEIs are usually mixed with thiazides or loop diuretics as their joint effects prevent the synthesis of angiotensin II secondary to the secretion of renin associated to diuretic intake. Furthermore, the combination of ACEIs with calcium antagonists is also an effective approach, since both families block the stimulation of RAAS activity, especially from the dihydropyridine family. Other mechanisms that have been described as complementary mechanism of action for ACEIs are related to a decrease in the metabolism of angiotensin II from angiotensin I, a decrease in aldosterone secretion stimulated by angiotensin I, and a decrease in degradation of bradykinin. Likewise, ACEIs have been studied as cardioprotective agents in patients classified with high risk of a cardiovascular event.

A group of interest where ACEIs have been posed as essential pharmacological tools are in patients living with diabetes and HBP as it has proven that they could reduce renal albumin excretion. Furthermore, ACEIs have shown a consistent decrease in the progression on chronic kidney disease, along with a decrease in the risk of incident cerebrovascular and peripheral artery diseases, without necessarily impairing cerebral or peripheral blood flow.[13,14]

Regarding the limitations of using ACEIs, it has been described that hypotension is the main adverse effect reported during the first weeks of usage. However, its risk could decrease after using prolonged ACEIs (E.g., ramipril, perindopril and trandolapril) and reduce the dosage of any other simultaneously combined antihypertensive. Other commonly associated adverse effects related to the use of ACEIs include non-productive dry cough, isolated cases of angioedema and hypersensitivity to its components. A serious adverse effect is hyperkalemia, therefore, it is highly recommended that plasmatic potassium levels should be assessed before starting any ACEIs and should be periodically monitored in follow-up visits.[15,16] Finally, it is highly recommended that serum creatinine and glomerular filtration rate (GFR) should be measured before starting this therapy. Any impairment higher than 30% from baseline in either creatinine or GFR during the first weeks after starting whichever ACEIs or when making a dosage increase should be warranted as an immediate suspension of the medication.[13,15,16] Circumstances where the use of ACEIs is contraindicated are during pregnancy and lactation. Nevertheless, when the situation could limit its suspension or changing by any other approved antihypertensive, it should be closely monitored, and extreme precaution is warranted. Other situations that could limit its use are in HBP with vascular-renal origins. The situations where we conseil to use ACEIs with caution are listed in *Table 3*.

Considerations in using angiotensin receptor blockers. Since 1970, it has been an increasing trend in the development of angiotensin receptor blockers (ARBs) being the first compounds synthetized only for intravenous use. Nevertheless, in 1990 the first oral presentation of ARBs appeared for commercial use, in which Losartan was the first ARBs used to treat HBP. Afterwards, other ARSs were synthetized, such as valsartan, ibersartan, candersartan, telmirsartan, olmersartan, and others.

Similarly, with ACEI inhibitors, the ARBs act of the blockade of RAAS through specific antagonism in angiotensin II AT1 receptor. Diverse observational studies within patients living with diabetes have shown that ARBs may change or slow down the progression of renal disease along with an overall reduction in cardiovascular risk. Furthermore, it has been proposed that the dual combination of ACEI with ARBs could improve clinical results hypothesized by a greater RAAS blockade. Nevertheless, there is still debate whether this should be a systematic strategy for threatening HBP. Evidence from the COOPERATE (combination treatment of angiotensin-II preceptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease)

Table 3: Considerations for the individualization of high blood pressure treatment

Situations	Recommendations for antihypertensive treatment
Heart failure with reduced LVEF	ACEIs, ARBs, beta-blockers, thiazides, mineralocorticoid receptor inhibitor
Ischemic heart disease	ACEIs, ARBs, beta-blockers, mineralocorticoid receptor antagonist
Chronic kidney disease	ACEIs, ARBs
Atrial fibrillation	ACEIs, ARBs, and/or beta-blocker, non – dihydropyridine calcium antagonist
Contraindications	**Antihypertensive drug**
Angioedema	Avoid ACEIs
Heart failure	Avoid non – dihydropyridine calcium antagonists (E.g., verapamil, diltiazem)
Pregnancy	Avoid ACEIs, ARBs, or direct renin inhibitors
AV conduction block or extreme bradycardia	Do not use beta-blockers

and ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) studies have found contradictory results. Both studies demonstrated thar the combination of ACEI and ARBs failed to slow down the evolution of kidney failure. Even more, the same studies have reported some cases where there were significant impairments within renal function and increased risk of hyperkalemia.[17,18] These studies along with several experts' opinions have recommended their combined use only on those patients with proteinuria nephropathies or in those patients who could well-tolerate low-grade doses of both ACEIs and ARSs with strict supervision of proteinuria and renal functionality.

The main indications to implement ARBs are similar for ACEIs, although the beneficial effect is observe gradually compared to what it is expected from ACEIs, mainly due to an absence of action in bradykinins. Conversely for what happens in ACEIs, the decrease in blood pressure with the use of ARBs are usually not accompanied by a reflex tachycardia, dry cough, or angioedema. This makes ARBs are particularly good prescription option on patients that have presented a favorable response to ACEIs but were suspended due to their associated adverse effects. Finally, there has been described some sceneries where the ARBs have a higher benefit compared with ACEIs, which are cases of severe HBP with electrocardiographic evidence of left ventricular hypertrophy (E.g., LIFE trial).

Combination of antihypertensive therapies

It has been described that the use of monotherapy, even at optimal doses, could not be enough to achieve arterial pressure goals. The increasing disability of controlling arterial blood pressure using single antihypertensive regimes indicates a need to have novel therapeutic strategies. The European Society of Cardiology Working Group (ESCWG) emphasize the urgent necessity to change the current approaches since ESC guidelines have recommended more conservative blood pressure targets (≤ 130/80 mmHg in the general population and ≤ 140/90 for older adults), which makes a whole challenge to control blood pressure.[7,19,20]

Diverse clinical studies have suggested a need to combine antihypertensive regimes due to diverse clinical and non-clinical factors associated with the management of each patient. Nevertheless, the use of two pills could restrict or even limit the adherence and tolerance to the medication. Consequently, a novel approach to combine antihypertensive was found within combined pills that had a combination of two types of antihypertensive.

These novel approaches are then translated into a way to use fixed combination of single pills to improve efficacy and adherence in treatment. Most of the clinical trials that have been performed an evaluation to evaluate the effect of two antihypertensives have found improvements in blood pressure goals. In the ACCOMPLISH study, the dual combination

with an ACEIs and a calcium channel blocker proved superior to an ACEIs combination plus a thiazide diuretic to prevent primary CV complications. Nevertheless, the ASCOT study demonstrated that the combination of an ACEIs, BCC, and a beta-blocker or thiazide diuretic on the ASCOT study did not prove any superior efficacy. Exceptions to these findings were studied that sought a combination of diuretics, ARBs, or ACEIs plus a beta-blocker channel (BBC). Furthermore, a combination of a diuretic plus a BBC has proven to reduce cardiovascular complications. Nevertheless, the combinations of a diuretic with a BBC were associated with a higher incidence of diabetes than other combinations.[17,21,22]

Since 1999, the WHO proposed that the expected mean decrease in blood pressure levels using monotherapy ranges from 8 to 12 mmHg for systolic and 4 to 8 mmHg for diastolic pressure. Conversely, there is an expected average reduction of 12 to 22 mmHg for systolic and 7 to 12 mmHg for diastolic pressure for dual combination therapy. Finally, results from the PIANIST study showed that a triple combination therapy led to a maximum decrease in systolic and diastolic blood pressure of 45 mmHg and 21 mmHg, respectively.[23]

Overall an approach based on combined therapy could be an appropriate option to begin, whether systolic blood pressure levels is ≥ 150 mmHg or when there is a high cardiovascular risk level estimation. Calcium channel blockers or diuretics could complement the selection of RAAS inhibitors whether blood pressure goals are not achieved. A visual summary based on 2018 ESC recommendations is presented in *Figure 2*. This algorithm sought to make easier clinical decisions in all care settings.

New pharmacological strategies

In recent years, it has been demonstrated within animal models that prolonged activation of RAAS has diverse effects on the central nervous system, increasing peripheral vascular resistances and stimulating the secretion of arginine and vasopressin, which ultimately lead to impairments in blood pressure management. Aminopeptidase A (APA) is an enzyme responsible for the conversion of angiotensin II to angiotensin III, leading to a tonic stimulatory in blood pressure within mice models. Therefore, APA has been tagged as a candidate for HBP treatment. A recent compound in phase II studies named «RB150» has been proposed as a prodrug capable of inhibiting APA with encouraging results.

Another pharmacological target relies on endothelin-1 (ET-1), an endothelium-derived contractile factor released by vascular endothelial cells. It has been described that ET-1 is a potent vasoconstrictor and an essential regulator of vascular tension. ET-1 can bind

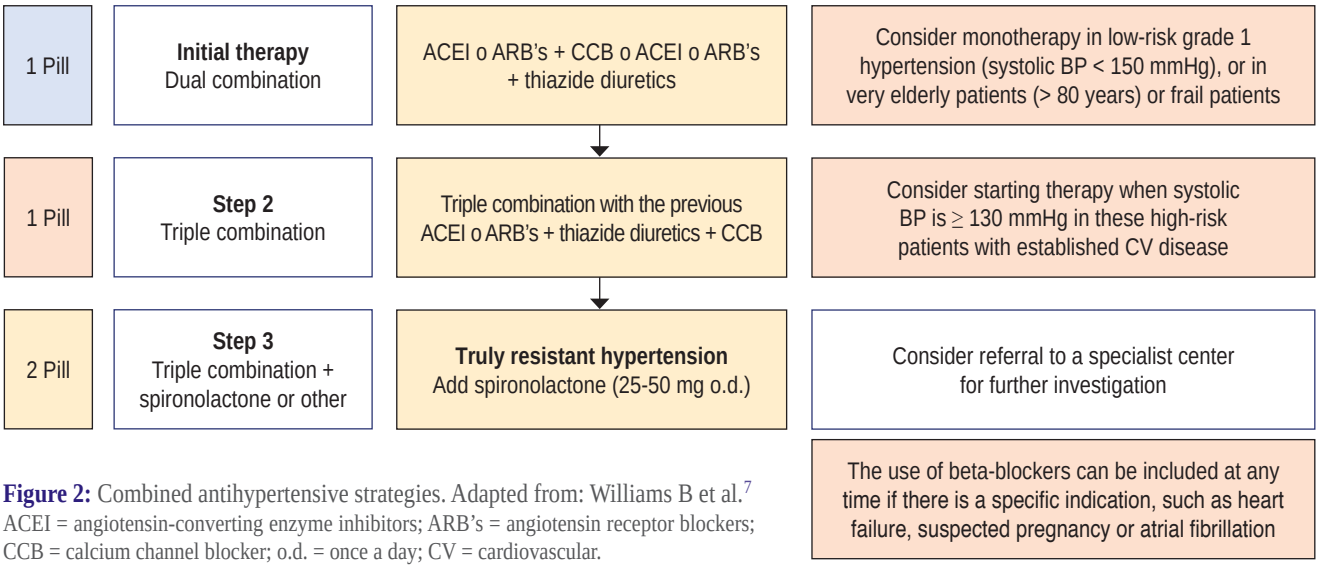

Figure 2: Combined antihypertensive strategies. Adapted from: Williams B et al.[7]
ACEI = angiotensin-converting enzyme inhibitors; ARB's = angiotensin receptor blockers; CCB = calcium channel blocker; o.d. = once a day; CV = cardiovascular.

with specific ET receptors, including ETAR and ETBR, promoting vascular vasoconstriction, cell proliferation, tissue fibrosis, and vascular endothelial injury, which are involved in the pathogenesis of HBP. ET-1 binding to ETBR can also activate endothelial cells by producing nitric oxide, therefore relaxing the vascular smooth muscle, and inhibiting vasoconstriction and cell proliferation. Hence, ETAR inhibition might be a novel pharmacological target for the treatment of HBP. In recent years, it has been developed diverse antagonists of ETR divided by their selective actions (E.g., darusentan and ambrisentan), non-selective (E.g., bosentan, and macitentan), a selective antagonist of ETBR, and dual antagonist of ETAR/EYBR (E.g., macitentan, and aprocintentan).

Is there any news on high blood pressure treatment? Nowadays, there has been better consistent evidence concerning cardiovascular risk decrease through reasonable blood pressure control and early initiation of dual therapy. This has shed light on novel pharmacological approaches, such as neuromodulations therapies. The objective of neuromodulations therapies is to improve downregulation on sympathetic outflow and improve blood pressure management. This approach is currently being studied in diverse ways of administration, such as oral pharmacological treatments (E.g., LCZ696, ARNI's) and direct interventionalists (E.g., catheter-mediated renal denervation). Other drugs, such as sodium-glucose cotransporter-2 (SGLT2) Inhibitors, have shown excellent benefits in other pathologies such as diabetes and heart failure. Therefore, current studies have been performed to explore their potential contribution to blood pressure management.

A particular physiopathological mechanism identified within HBP is related to the blood-brain barrier impairments. It has been described those disruptions within this system promote an autonomic dysfunction that causes an increase in blood pressure. Moreover, there is a phenomenon of secondary neuroinflammation and astroglia dysfunction hyperactivation of the RAAS, oxidative stress, and the release of inflammatory cytokines. The description of this pathway has led to the development of novel therapies targeting central nervous systems that can cross the blood-brain barrier.[24,25] For example, firibastat is a drug that lowers blood pressure by reducing vasopressin and cerebral Angiotensin III (NEW HOPE study).[26] Another drug capable of crossing the blood-brain barrier is Minocycline, which is currently being studied as an inhibitor of Microglia activation. Finally, aprocitentan is an antagonist of endothelin type A and type B receptor, which have shown to be a promising alternative given their results in phase II of the study against lisinopril (PRECISION Study).[27]

Finally, some promising therapies include vaccines that target alpha 1D adrenergic (ADRQβ-004) and angiotensin II (AngQb and AGMG0201) receptors.[28,29] Another currently being studied therapy is allopregnanolone, which selectively modulates the receptor for gamma-aminobutyric acid.[30] Other promising approaches are related to natriuretic peptide receptor agonists, vasopressin antagonists, vasoactive intestinal peptide analogs, dopamine beta-hydroxylase inhibitors, and others.[31-43]

CONCLUSION

The comprehensive understanding of the RAAS has led to the manufacture of diverse antihypertensive strategies focused on developing pharmacological agents capable of inhibiting the production or blocking the action of RAAS components. The creation of renin inhibitors, ACE inhibitors (ACEIs), selective and non-selective angiotensin II receptor blockers, β-adrenergic receptor blockers, and inhibitors of the activity and synthesis of aldosterone, among others have revolutionized the way we manage cardiovascular and renal diseases. Further investigations will continue to identify new elements of the RAAS that will help clinicians to improve our understanding of its functioning and the possibility of developing new therapies that will be more selective and efficient. In the meantime, the RAAS will continue to be the center of our attention for many years to come.

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