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Review Article

What are the Best Drugs and Combinations in Afro-Descendant Hypertensive Patients?

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Abstract

Hypertension in African descendants occurs early, with high rates of cardiovascular events compared to Caucasians. In addition, genetic influence, low levels of plasma renin activity, greater sensitivity to salt, low sodium secretion, and other mechanisms are involved and discussed in this article. For pharmacological treatment, several studies were evaluated, such as CREOLE, ALLHAT, CARDIA, JHS, REGARDS, AASK, ACCOMPLISH, review articles and meta-analyzes and some guidelines, such as European, American, Brazilian to compare treatment indication. Several pharmacological classes, such as calcium channel blockers, ß-blockers, renin angiotensin system inhibitors, aldosterone and diuretics were included in present review in order to compare utilization and indication for Afro-descendant hypertensive patients. We concluded that several relevant points should be considered in the pharmacological treatment of African descendants that include pathophysiological characteristics, early development of lesions in target organs, in addition to higher rates of cardiovascular and renal events. In addition to lifestyle changes, improved nutrition, combined treatment, probably as a first-line treatment, should be considered as an approach, and the drugs used should aim at blood pressure control and inhibition of the inflammatory process, which results in worse outcomes. It is important to highlight that the representativeness of the Afro-descendant population was unsatisfactory for a robust conclusion. in this population, we can infer from the initial pharmacological treatment the use of thiazide-like diuretics, or dihydropyridine calcium channel blocker should be considered, although the institution of fixed combinations with angiotensin enzyme conversion inhibitors or angiotensin receptor blockers are important in the protection of target organs that occurs earlier and more seriously.

Keywords: Hypertension; Hypertension in people of african descendants; Pharmacological treatment

Introduction

Data from the literature indicate that arterial hypertension in African descendants occurs earlier, from younger age groups compared to white individuals, with mean blood pressure, prevalence of stage 3 arterial hypertension and higher rates of cardiovascular events, such as 1.3 and 1.8 times greater for non-fatal and fatal stroke, respectively, 1.5 times for coronary events [1-3] and 50% higher mortality from heart failure [4] and 3 to 5 times greater risk of renal complications and progression to kidney disease terminal when compared to Caucasian individuals [5]. In this hypertensive population, greater variability in Blood Pressure (BP) is described from visit to visit, and a higher percentage of "non-dipping" pattern than in population of other ethnic groups [6,7].

The earlier involvement of the target organs of hypertensive disease in this population was demonstrated in the CARDIA [8] study and in a cohort of the ARIC [9] study, where the Afro-descendant population had a larger left ventricular mass that independently correlated with Systolic Blood Pressure (SBP) levels and carotid arteries more rigid than Caucasians, respectively, suggesting that this alteration occurs earlier or has faster progression.

More recently, the Jackson Heart Study [10] (JHS) and REGARDS [11] studies estimated that 32.5% of cardiovascular risk was attributed to high blood pressure.

Thus, the choice of pharmacological treatment for arterial

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hypertension in patients of African descent is related to the pathophysiological mechanisms that result in persistent elevation of blood pressure levels.

Known Mechanisms in the Genesis of Arterial Hypertension in Afrodescents

Despite being widely studied, the mechanisms involved in the genesis of arterial hypertension in people of African descent are still not fully understood. Several studies point to an extremely important genetic influence, with the detection of multiple variants and variable expressions depending on the subgroup of the Afro-descendant population evaluated [12,13] in addition to lower levels of plasma renin activity, greater sensitivity to salt, and lower capacity to excrete sodium when compared to white individuals [14], increased vascular resistance [15], lower endothelium-dependent vasodilatation due to lower availability of Nitric Oxide (NO) [16,17], greater vasoconstriction in response to beta-adrenergic stimulation [18], among other proposed mechanisms.

The greater sensitivity to salt, in turn, seems to be related to the expression of genetic variants, the most frequent being the replacement of threonine by methionine, T594M, which would affect renal tubular absorption of sodium and water, with this mechanism mediated by epithelial channels of sodium in the renal tubule [19]. Another potential mechanism linked to salt sensitivity would be the elevation of the inflammatory cytokine GFR (transforming growth factor), which would lead to an increase in the intracellular matrix and fibrosis with possible progression of the lesion in the target organ [20].

More recent studies suggest that the greater activity of creatine kinase would result in vasoconstriction by the consumption of APT and this demand associated with the elevation of creatine kinase could lead to a relative lack of L-arginine and nitric oxide [21].

The rationale for this interaction is that the NO and creatine kinase systems share a common precursor, L-arginine, exhibiting antagonistic effects. NO inhibits creatine kinase, reducing blood pressure and promoting cardiovascular health, since the greater activity of creatine kinase would result in sodium retention and greater vascular contractility, with the detection of low renin as a potential epiphenomenon [21,22].

Other investigations have demonstrated a central role of the greater activity of sodium/potassium ATPase (determinant of sodium retention by the kidney) and of calcium-ATPase and myosin ATPase (involved in vascular contractility), which would lead to increased blood pressure levels, with the detection of low - x renin levels resulting from volume expansion [23,24].

We also cannot fail to mention external factors, resulting from changes in eating habits and factors such as obesity and sedentary lifestyle, in addition to more restricted access to health, which are also extremely relevant in the choice of treatment, whether in monotherapy or in combinations free or fixed-dose combinations.

Classes of Anti-Hypertensive Agents and their Indication in Afrodescents: What do Available Data Show?

In a recent systematic review and meta-analysis, Seeley et al [25] evaluated pharmacotherapy for hypertension in the sub-Saharan population, considering 32 studies with 2860 patients. The results of that study showed that most studies compared monotherapy against placebo, with only three studies evaluating combination therapy. When compared to placebo, general pharmacotherapy provided a reduction of 8.5 mmHg and 8.0 mmHg in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), respectively, with the class of calcium channel blockers was the only one to show evidence of reduction in SBP and DBP, reaching reductions of 18.5 mmHg in SBP and 11.6 mmHg in DBP with a control rate of 64% with monotherapy alone. In this study, diuretics were also effective in reducing blood pressure, but to a lesser extent.

The use of Angiotensin Enzyme Conversion (ACE) inhibitors was not better than placebo when used in monotherapy, and beta-blockers were equally effective in reducing DBP when compared to placebo, but they were not more effective than placebo in reducing SBP.

Thus, the authors concluded that in the Afro-descendant population, calcium channel blockers seem to be the most effective agent in reducing blood pressure, due to the dual action of these agents in reducing the concentration of creatine kinase and increasing levels of nitric oxide, which result in less contractility of the smooth muscle of the vessel [23].

Another study that evaluated the combination therapy was the CREOLE [26] study. The primary objective was to evaluate which Amlodipine/Hydrochlorothiazide (A+HCTZ), Amlodipine/Perindopril (A+P) and Perindopril/Hydrochlorothiazide (P+HCTZ) combination therapy would be most effective in controlling systolic blood pressure using the Ambulatory Blood Pressure Monitoring (ABPM) after six months of treatment. The results of this study showed that the A+P and A+HCTZ combinations were more effective in reducing SBP on ABPM than the P+HCTZ combination, 18.1 mmHg, 17.1 mmHg and 14.2 mmHg, respectively.

In this study, the combination of a Calcium Channel Blocker (CCB) with ACEI or Thiazide Diuretic (DTZ) proved to be more effective than the combination of an ACEI with DTZ, reinforcing the indication of a CCB as the first agent in treatment of African-American hypertensive patients.

In a study carried out at the University of Mississippi [27], the authors retrospectively analyzed data from the Medical Center of the University of Mississippi, composed of 5,973 white and 10,731 black individuals. The results showed that RAS inhibitors did not significantly improve the control rate among black patients when compared to untreated patients. However, the data suggested that ACEIs or ARBs are beneficial when combined with DTZ compared to untreated patients and when compared with DTZ alone. The study further concluded that the observed data support the use of a fixed formulation of ACE inhibitors or ARBs with a DTZ for the first-line treatment of high blood pressure in blacks.

Classes of Anti-Hypertensive Agents and their Indication in Afrodescentes: Considering The Mechanism of Action

Diuretics

The main mode of action of DTZ is the inhibition of the Na+Cl- cotransporter activity in the distal convoluted tubule, blocking sodium reabsorption in the luminal membrane. This sodium absorption is driven by the NA+K+ATPase pump [28].

Although the use of diuretics in people of African descent seems to be a logical treatment option due to the pathophysiological mechanism, the International Society of Hypertension in Blacks recommends that most patients will need combination

therapy, many as a first-line choice, to reach the recommended goal [29].

Calcium Channel Blockers

The proposed mechanism of action for the vasodilatation promoted by Dihydropyridine (DHP) Calcium Channel Blocker (CCB) involves the reduction in the intracellular calcium concentration in the smooth muscles of the vessels. This occurs by blocking slow calcium channels, subtype L, sensitive to voltage in cell membranes and calcium output from the sarcoendoplasmic reticulum [30,31] but it is also known that this class provides greater bioavailability of NO in cells. endothelium, and decreased NO degradation by free radical scavengers and reduces oxidative stress products [32-34].

Although most studies have used amlodipine for evaluation, this seems to be a class effect, and thus, the DHP CCB would be similarly effective in controlling blood pressure in African-American patients.

Inhibitors of the Renin-Angiotensin-Aldosterone System

The main mode of action of ACE inhibitors is the reduction of ACE activity and possibly angiotensin, aldosterone and sodium retention. Furthermore, ACE inhibitors promote NO endothelial synthesis [35]. Thus, the lower availability of NO in African-American patients could, in part, explain the lower response to these agents.

The molecular mechanisms involved in the action of ACEIs included upregulation of NOS activity in endothelial cells and increased NO bioavailability [36]. From the above, it can be inferred that despite the low renin profile, classically pointed out in studies with African descendants , currently other molecular alterations seem to contribute to the lower effect of circulating or tissue ACE inhibition [12,31,37].

The use of renin-angiotensin aldosterone system inhibitors: ACE inhibitors and Angiotensin Receptor Blockers (ARB) is also indicated in this population due to the reduction in TGB-β1 stimulation mediated by angiotensin II, and although the reduction in blood pressure levels is less expressive in this population of patients, the blockade exerted by these agents has an impact on the progression of lesions in target organs.

Although not recommended for initial monotherapy, ACE inhibitors and ARBs play a role in target organ protection, therefore their use in combination with CCB or thiazide diuretics appears to offer additional protection in this population.

Beta Blockers

Clinical evidence indicates that monotherapy with ß-blockers (ß-block) and other agents are equally less effective in reducing blood pressure in this population compared to the Caucasian population [38-41]. The reduction in blood pressure with ß- bloq is primarily due to reduced Cardiac Output (CO) rather than reduced Peripheral Vascular Resistance (PVR).

Although ß-blocks are not superior in African-American patients [42,43], the heterogeneity in terms of their pharmacological properties should be highlighted [44,45]. It can be mentioned, for example, that some drugs are more selective for B1 adrenergic receptors (found mainly in the heart), when compared to S2 (bronchial) [46]. Other drugs block alpha receptors, found in vascular smooth muscle, as well as ß-receptors. Nebivolol, ß1-block, cardioselective [46] stands out, which produces endothelium-dependent vasodilation [47-51], which demonstrated 320 times greater affinity for ß1 receptor than for ß2, in addition to greater ß1 selectivity of these subtypes, including bisoprolol and metoprolol [52]. It also reduces the heart rate other mechanisms of action, in addition to maintaining CO, systolic volume and reducing PVR [53]. These characteristics of nebivolol seem to reflect a combination of ß1 blockade associated with arterial vasodilation [53] and may have more favorable characteristics than other b-blockers non-vasodilators for the treatment of hypertension.

Data from Outcome Prospective Clinical Studies

Although outcome studies carried out in the last two to three decades have provided valuable information on the best therapeutic regimens for reducing cardiovascular mortality, only a few have included a higher percentage of African-descendant participants.

AASK (The African American Study of Kidney Disease and Hypertension)

The AASK [54] compared the effectiveness of three antihypertensive drugs (ramipril, amlodipine, metoprolol) on the progression of kidney disease. The results showed that in African descendants, those treated with ramipril had a significantly lower incidence of the primary outcome (reduction in glomerular filtration rate, end-stage renal disease or death), especially in the presence of proteinuria, when compared to patients who received the BCC or ß-block. These data suggest that in addition to BP reduction, recognition of the pleomorphic effects of ACEI should be considered.

Allhat (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)

This study, ALLHAT [55], included more than 15,000 participants of African descent, about 35% of the total sample.

In terms of blood pressure control, after five years of follow-up, systolic blood pressure was significantly higher in the amlodipine and lisinopril groups compared to the chlorthalidone group, and diastolic blood pressure after five years was significantly lower with amlodipine.

In this group of patients, the use of amlodipine or chlorthalidone did not confer different results in terms of pressure reduction or events, but in patients treated with lisinopril and compared with those who received chlorthalidone, the results showed higher systolic blood pressure (on average 4 mmHg) and higher risk of cardiovascular events (~19%), being higher for the risk of stroke (~40%) and heart failure (~32%) [56].

Accomplish Study

ACCOMPLISH [57] was the only multicenter, double-blind study designed to compare initial combination therapy on cardiovascular outcomes that compared morbidity and mortality rates from cardiovascular causes of two different combinations: benazepril + amlodipine (B+A) compared to benazepril + hydrochlorothiazide (B+HCTZ). In the B+A group and in the B+HCTZ group, there were 12.1% and 12.5% of African descendants, respectively.

Results in this population showed that the outcomes observed for groups B+A and B+HCTZ were not statistically different, CV disease and CV mortality: 6.6 vs. 8.9% (p=0.10); stroke 2.2 vs. 2.1% (p=0.97), CI 1.7 vs. 2.2% (p=0.50) and kidney dis-

ease 3.9 vs. 4.2% (p=0.75). Furthermore, B+A was not different from B+HCTZ in delaying the progression of kidney disease in African Americans.

Brewster et al. [58] evaluated the results of studies with a subgroup of African descendants and the recommendations of the 2017 American guideline. These evaluations allowed inferring that most patients will need multiple medications to achieve adequate control, the results obtained were better with the use of therapy based on BCC or DTZ than on Renin Angiotensin Antagonist System (RAAS) inhibitors, even when combined with other classes of anti-hypertensive drugs. Furthermore, the authors indicate that at present, there is no evidence of the best second option for reducing cardiovascular morbidity and mortality, as there is no data on the initial use of the combination of DTZ and BCC.

The authors point out that early control of blood pressure levels reduces cardiovascular morbidity and mortality.

Recommendations from Recent Guidelines for the Treatment of Hypertension in Afrodescents

The International Society of Black Hypertension (ISHIB) guideline published in 2010 discusses that most patients will need to start treatment with two classes of antihypertensive drugs to reach the desired goal, and recommends that if blood pressure is ≤10 mmHg above target, use of a diuretic or CCB as initial therapy is preferred, but if blood pressure is ≥15/10 mmHg above target, then combination therapy is recommended, options being a combination of a CCB + inhibitor RAAS, or in edematous states or volume overload the combination of a thiazide diuretic with a RAAS inhibitor [59].

The 2017 American guideline recommends the use of DTZ or similar thiazide or BCC in monotherapy or as the initial agent in a multiple treatment regimen in hypertensive afro-descendants, but makes the caveat that these options refer to patients with heart failure or kidney disease chronic, where the association with ACEI or ARB would be justified [60].

The 2018 European hypertension guideline [61] recommends the use of a two-class, fixed-dose combination as initial therapy to be used in most African-American patients, and should include a diuretic or CCB in combination with the RAAS inhibitor. The 2020 guideline of the International Society of Hypertension [62] recommends, similarly to the European guideline, the use of a fixed-dose combination of a similar diuretic with CCB or CCB combined with ARBs, and emphasizes that ARBs may be more indicated, a since the risk of angioedema with ACE inhibitors is three times higher in this population [62].

Finally, the 2021 Brazilian guideline does not make any specific recommendation for this patient population, indicating only that treatment should be individualized according to the patient's characteristics [63].

Final Considerations

Relevant points that should be considered in the treatment of arterial hypertension in African descendants include the pathophysiological characteristics, the earlier development of lesions in target organs and higher rates of cardiovascular and renal events. In addition to changing lifestyle and improving diet, combined treatment, probably as a first-line treatment, should be considered, and the drugs used should aim at controlling blood pressure and inhibiting the inflammatory process that results in worst outcomes.

It is important to highlight that in the prospective studies carried out, the representativeness of the Afro-descendant population was often unsatisfactory to reach a more robust conclusion, and the lack of pressure reduction in the first weeks or months of follow-up was probably the determining factor for the higher risk of stroke shown in some studies, but the other cardiovascular outcomes showed similarities with the treatment schemes used.

Thus, so far we are able to conclude, by listed studies and based on international hypertension guidelines: The initial treatment of hypertensive patients of African descendant using of thiazide-like diuretics, or BCC DHP should be considered, although the prescription of fixed combinations involving the use of ACE inhibitors or ARBs plays an important role in protecting target organs from hypertensive disease, which is known to occur earlier and more severely.

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