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REVIEW ARTICLE

The Rationale for Using Fixed-Dose Combination Therapy in the Management of Hypertension in Colombia: A Narrative Review

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Abstract

Hypertension is a major risk factor for cardiovascular disease and the leading cause of death in Colombia. While the rate of hypertension awareness in Colombia is generally high, rates of treatment initiation, adherence, and blood pressure (BP) control are suboptimal. Major international hypertension guidelines recommend starting treatment with a combination of antihypertensive agents, and the use of a single-pill combination (SPC) to maximize adherence. In contrast, Colombian hypertension guidelines recommend starting treatment with diuretic monotherapy in most patients, and only initiating combination therapy in those with BP > 160/100 mmHg. Therefore, the aim of the current narrative review is to examine the rationale for using SPCs to treat hypertension in Colombia, in the context of the major issues for BP control there. There is evidence of widespread therapeutic inertia in hypertension management, particularly in primary care, in Colombia. Moreover, combination therapy, angiotensin-converting enzyme inhibitors, and long-acting calcium channel blockers, which are internationally recommended as first-line drug therapies, are underutilized there. Adherence to antihypertensive therapy is low in Colombia and may be enhanced by use of SPCs as well as better patient education and follow-up. While there are promising national initiatives to improve BP management, more needs to be done by individual physicians. Antihypertensive SPCs are available on the national essential medicines list and may help to overcome some of the problems with suboptimal adherence, therapeutic inertia, and low rates of BP control that contribute to the high cardiovascular death rate in Colombia.

1 Introduction

Hypertension is a major risk factor for the development of cardiovascular disease (CVD) and stroke and is one of the most important modifiable contributors to the global burden of these conditions and mortality [1]. During the 78th Session of the United Nations General Assembly, the World Health Organization (WHO) declared that "The number of people living with hypertension (blood pressure [BP] of 140/90 mmHg or higher or taking medication for hypertension) doubled between 1990 and 2019, from 650 million to 1.3 billion" [2]. The WHO reported that at least three-quarters of adults with hypertension live in low or middle-income countries (LMICs), at present almost half of people with hypertension worldwide are unaware of their condition, and four out of five people with hypertension are not adequately treated [2]. It was concluded that, if the number of patients effectively treated for hypertension in LMICs can be upscaled to the levels observed in high-income countries, 76 million deaths, 120 million strokes, and 79 million heart attacks could be avoided between now and 2050 [2].

Effective management of hypertension requires four elements: (1) detection/awareness, (2) initiation of treatment, (3) adherence to treatment, and (4) treatment sufficient to achieve and maintain BP control [3]. In Latin America and the Caribbean, rates of hypertension awareness are higher than the global average (72% in women compared with 59% in women globally, and 57% in men compared with 49% globally), but rates of BP control remain low (35%

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Key Points

Colombia is an upper-middle income country in South America.

Despite affordable healthcare, high rates of hypertension awareness, and promising regional initiatives, blood pressure control in Colombia is suboptimal, resulting in a high cardiovascular death rate.

More widespread use of antihypertensive single-pill combinations may assist in improving adherence, therapeutic inertia, and blood pressure control in Colombia.

in women and 23% in men) [4]. In this region, suboptimal hypertension management is mainly related to suboptimal treatment strategies (rather than low rates of detection) as well as low adherence and persistence with lifestyle modifications and pharmacological treatment [4, 5].

Colombia is an upper-middle-income country located in northern South America. Ischemic heart disease (IHD) is the leading cause of death in men and women in Colombia [6], and hypertension is a leading risk for IHD, as well as being a risk factor for heart failure, atrial fibrillation, chronic kidney disease, and dementia [7]. Among the modifiable risk factors, hypertension is responsible for the highest fraction of the population attributable risk (18.7%) for CVD in South America, ahead of obesity (15.4%), smoking (13.5%), and diabetes (5.3%) [8], and is a significant contributor to the risk of dementia in Latin America and the Caribbean (18.0% of the population attributable risk) [9]. Yet, rates of BP control in Colombia are low [10, 11], possibly because of underutilization of combination therapy and poor patient adherence.

The current narrative review aims to examine issues in the management of hypertension in Colombia to summarize the evidence that may be useful to improve control of hypertension and favorably impact the public health of the country. The review places special emphasis on modifying the generalized recommendation of the use of monotherapy in the first step of antihypertensive treatment and highlights the more frequent use of single-pill combinations (SPCs).

2 Literature Search

We conducted a search of the PubMed database in July 2023 and again in September 2023 using the MeSH term "hypertension" and a free text search for "Colombia" in the title, abstract, or author affiliations. No date limits were set. Results were searched for relevant articles on arterial hypertension, excluding pulmonary, intracranial, or ocular hypertension and hypertension in pregnancy. Articles were selected if they provided relevant information on the epidemiology or treatment of hypertension in Colombia and were written in either English or Spanish.

3 Epidemiology of Hypertension in Colombia

Colombia has five key geographic regions: the Atlantic lowlands, the Pacific coast, the Andean region (where most of the large cities are), and the poorly populated Llanos (grasslands) and Amazonian rainforest. The population of ~50 million people is mostly of mixed race, with small populations of European, Indigenous, and other races/ethnicities. Colombia experienced a 52-year period of armed conflict between 1964 and 2016, which had profound effects of the lives and health of many individuals and communities and affected healthcare delivery [12, 13].

Today, Colombia is classified by the World Bank as an upper-middle-income country (i.e., the gross national income per capita is between $4046 and $12,535). It has a universal healthcare system that has compulsory primary health insurance collected from ~ 98% of the population, and that provides healthcare at a fixed cost related to income sector or at no or very low cost to the poorest sector [14]. Private health insurance is also available for those who choose to purchase it. Therefore, primary care for hypertension is available and affordable for most of the Colombian population.

The reported prevalence of hypertension in Colombia depends on the sampled population (Table 1), but hypertension affects between 28 and 44% of the adult population [10, 11, 15–18]. The prevalence increases with age [17, 19], body mass index (BMI) [16, 17, 20], comorbidities [21], and correlates of low socioeconomic status, such as low education level and Afro-descendent ethnicity [15, 17, 18]. In Colombia and other middle-income countries, there is a clear relationship between wealth index and undetected hypertension, with poorer populations having lower rates of detection [14]. Part of the burden of hypertension and CVD in Colombia can be attributed to the effects of the armed conflict [22], with early-life displacement due to armed conflict being an additional significant risk factor for hypertension [20].

Table 1 Rates of awareness, treatment, and control of hypertension in Colombia

Study	Population	*N*	Prevalence (%)	Awareness (%)	Treatment, % of aware patients	Control, % of treated patients
Camacho (2016) [17]	Urban and rural residents aged 35–70 years	7444	37.5	51.9	77.5	37.1
Barrera (2019) [19]	Community-dwelling adults aged ≥ 60 years (SABE population)	23,694	57.7	93.9	88.8	50.1
Barrera (2020) [44]	Primary care patients with hypertension aged > 18 years	1358	–	–	–	38.4
Hessel (2020) [18]	Community-dwelling adults aged ≥ 60 years (SABE population)	3984	32.4	–	–	–
Londoño Agudelo (2021) [10]	Low-income urban residents of Medellin aged ≥ 35 years	1873	43.5	64.9	93.4	66.4
Lopez-Jaramillo (2021) [11]	Individuals assessed during May Measurement Month 2019	48,324	27.9	63.7	60.0	64.0
García (2022) [14]	Individuals aged ≥ 60 years participating in the SABE project	5228	–	82	–	35[a]
Lopez-Lopez (2022) [15]	Urban and rural residents aged 35–70 years participating in the PURE study	3745	39.1	–	–	–
Smith (2022) [16]	Insured individuals aged 18–74 years living in Northern Colombia	2613	30.2	–	–	–
Mendivil (2023) [21]	Individuals with diabetes on the NRCKD	1,352,846	66.6	–	–	57.3[b]

NRCKD National Registry of Chronic Kidney Disease (contains patients with diagnosed diabetes, hypertension of chronic kidney disease), *PURE* prospective urban rural epidemiology, *SABE* Healthcare, Welfare and Ageing Survey (acronym based on name in Spanish)

[a]The denominator is the group of individuals aware of their hypertension (not necessarily treated)

[b]Defined as systolic blood pressure < 130 mmHg

4 Issues in Hypertension Management

In the continuum of care for hypertension, there are distinct points at which healthcare physicians can influence the rate of diagnosis, treatment, and control (Fig. 1). Research shows that, in upper-middle-income countries such as Colombia, patients show a low rate of movement from one stage of the treatment continuum to the next in hypertension (e.g., from diagnosis to treatment, or from treatment to control) [23]. However, rates of retrograde movement along the continuum (e.g., treatment discontinuation or loss of BP control) are high [23]. Therefore, strategies to improve hypertension management that focus on improving diagnosis and starting treatment may be insufficient to improve BP control without more attention on reaching target BP and maintaining adherence.

Among Colombian patients treated for hypertension, ~ 65% achieve BP control, but because many patients do not receive treatment, this equates to BP control in only ~ 39% of patients with hypertension [10, 11]. In the 2016 Colombian National Survey of Health, Welfare and Aging, factors associated with poor BP control were age > 74 years and living in a rural area [24]. In low-income urban settings, poor BP control is associated with older age, concomitant diabetes, poor adherence to treatment, and poor advice about nonpharmacological therapies [10]. The data therefore suggest that, while hypertension detection can still be improved, physicians in Colombia are performing particularly poorly in the following steps in the hypertension management continuum: (a) initiation of treatment, (b) adherence to treatment strategy, and (c) treatment escalation to achieve BP targets.

4.1 Treatment Initiation

The impact of antihypertensive medication on cardiovascular outcomes is directly proportional to the reduction in systolic BP (SBP) [25]. A reduction in SBP of 5 mmHg reduces the relative risk of a major cardiovascular event (MACE) by about 10% in both the primary and secondary prevention settings. However, while these relative reductions are the same, and independent from baseline BP or risk, the absolute risk is greater in patients with higher baseline BP and risk [25]. Therefore, it is important for physicians to initiate treatment as soon as hypertension is diagnosed. A Monte Carlo model showed that failing to promptly initiate

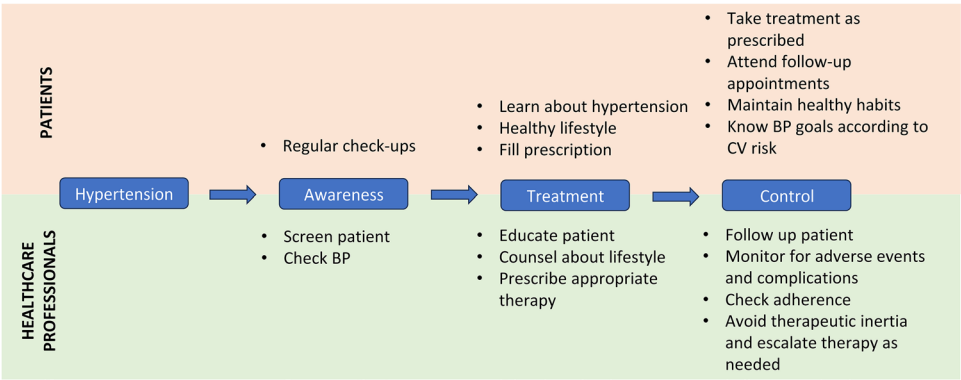

Fig. 1 The continuum of care in the management of hypertension, and the ways in which patients and healthcare professionals can positively impact outcomes. **A** For example, at screening sites, such as during May Measurement Month. **B** For example, with home BP monitors, if available. *BP* blood pressure, *CV* cardiovascular

and escalate antihypertensive therapy to achieve BP targets had a marked negative effect on maintaining short- and long-term BP control [26].

More than 70% of patients with hypertension do not achieve BP control on antihypertensive monotherapy [27]. Therefore, major regional and international hypertension guidelines now recommend starting treatment with a combination of antihypertensive agents and using an SPC to maximize adherence (Table 2) [28–35]. In contrast, the Colombian guidelines recommend starting combination antihypertensive therapy only in patients with SBP > 160 mmHg or diastolic BP (DBP) > 100 mmHg; in other patients, combination treatment is recommended only when BP goals have not been met on monotherapy [36]. The recommended initial monotherapy is a thiazide diuretic [36]. However, when combination therapy is indicated, Colombian guidelines recommend using an SPC to improve adherence [36].

Combination therapy not only results in greater antihypertensive efficacy compared with escalating the dose of monotherapy but also reduces some side effects [37]. For example, the renin–angiotensin–aldosterone system (RAAS) inhibitor-induced effects on post-capillary dilation and hydrostatic pressure ameliorate the development of ankle edema in patients taking calcium channel blockers (CCBs) [38, 39]. Therefore, many SPCs include an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor in combination with a CCB.

Specific combinations may be more suitable for some patients based on their comorbidity profile (Table 3) [29, 32, 34, 40], but in most cases initial treatment will be with a RAAS blocker (an ACE inhibitor or ARB), long-acting dihydropyridine CCB, and/or diuretic [28–32]. The availability of SPCs varies between countries, but four combinations are now included in the WHO essential medicines list, all of which include a RAAS inhibitor with either a diuretic or a CCB: lisinopril + amlodipine, lisinopril + hydrochlorothiazide (HCTZ), telmisartan + amlodipine, and telmisartan + HCTZ [41].

While ARBs and ACE inhibitors have a similar role in international hypertension guidelines, the two drug classes are not identical, and consideration should be given as to which class is best suited to individual patients [42]. ACE inhibitors are preferred for patients with chronic kidney disease because they have proven benefits over other classes of antihypertensive agents in this group [43]. Similarly, ACE inhibitors have shown more marked benefits than ARBs in reducing morbidity and mortality rates in patients who have established CVD or are at high risk of CVD [42]. ARBs are indicated in patients who develop adverse events during ACE inhibitor therapy and are favored in patients of African origin, who are at risk of developing angioedema with ACE inhibitors [31].

Women are a group that warrant particular consideration in Colombia because they comprise 70–80% of the population of patients with hypertension who attend subsidized primary care services (i.e., healthcare services for the most economically deprived portion of the population) [44]. While the prevalence of hypertension is not necessarily different in men and women, the trajectory of increasing BP over the lifespan is steeper in women than men from the third decade onwards [45]. In addition, the risk of cardiovascular outcomes is about 1.5 times higher in women than men with stage 1 or 2 hypertension, irrespective of age [45], and the significant risk of CVD, myocardial infarction, stroke, and heart failure begins at a lower BP threshold in women than in men [46].

Women are also more likely than men to show a BP drop of < 10% at night (non-dipper profile) [47], a profile that is associated with increased cardiovascular risk [48]. Therefore, women may benefit from a combination containing amlodipine (a long-acting CCB) to maintain 24-h BP control.

There are no solid data regarding patterns of hypertension management in Colombia. However, on a regular

Table 2 Colombian, regional, and international guideline recommendations related to the use of fixed-dose combinations for initial therapy of hypertension

Guideline	Recommendation	COR	LOE
Colombian guidelines 2017 [36]	Initiate combination antihypertensive therapy in patients with BP > 160/100 mmHg or with BP > 140/90 mmHg plus risk factors	NR	NR
	It is recommended that patients with hypertension undergoing pharmacological treatment who require combined therapy receive single daily doses and fixed combinations to increase adherence to antihypertensive treatment	NR	NR
Latin American guidelines 2017 [34]	Initiate combination therapy for individuals with grade 1 hypertension and high or very high cardiovascular risk, and in patients with grade 2 or 3 hypertension, independently of risk stratification	NR	NR
	When combination therapy is chosen, fixed-dose combination preparations should be used whenever possible as they are associated with higher adherence to treatment	NR	NR
	For patients with grade 2 hypertension (any level of cardiovascular risk) or grade 3 hypertension (moderate or high cardiovascular risk), start with SPC therapy at standard doses of ACE inhibitor or ARB + CCB or diuretic	NR	NR
US (ACC/AHA) guidelines 2017[a] [30]	Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mmHg above their BP target	I	C-EO
	Use of combination pills rather than free individual components can be useful to improve adherence to antihypertensive therapy	IIa	B-NR
	For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs	I	A^{SR}
	For secondary stroke prevention, treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful	I	A
European (ESC/ESH) guidelines 2018 [31]	Combination treatment is recommended for most patients with hypertension as initial therapy. Preferred combinations should comprise a RAAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used	I	A
	It is recommended that β-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g., angina, post-myocardial infarction, heart failure, or heart rate control	I	A
	It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg)	I	A
Interamerican Society of Cardiology (IASC) guidelines 2020 [35]	For patients with grade 1 hypertension and low cardiovascular risk, low-dose fixed-dose combination therapy is an option (along with monotherapy) as initial therapy, with ACE inhibitor or ARB + CCB or diuretic; combination therapy at standard doses can also be considered	NR	NR
	For patients with grade 2 hypertension (any level of cardiovascular risk) or grade 3 hypertension (moderate or high cardiovascular risk), start with SPC therapy at standard doses of ACE inhibitor or ARB + CCB or diuretic	NR	NR
International (ISH) guidelines 2020 [29]	Step 1 treatment is a dual low-dose combination, ideally SPC therapy; consider monotherapy in low-risk grade 1 hypertension or in very old (≥ 80 years) or frail patients	Optimal [b]	
	Step 1 treatment should be a RAAS blocker (ACE inhibitor or ARB) + CCB; consider RAAS blocker + diuretic in post-stroke, very elderly or Black patients, or those with incipient heart failure or CCB intolerance; consider CCB + diuretic in Black patients	Optimal [b]	
	Use free combinations if SPCs are not available or unaffordable	Essential [b]	

Table 2 (continued)

Guideline	Recommendation	COR	LOE
WHO guidelines 2021 [28]	For adults with hypertension requiring pharmacologic treatment, the WHO suggests combination therapy preferably with a SPC (to improve adherence and persistence) as an initial treatment. Antihypertensive medications used in combination therapy should be chosen from the following three drug classes: diuretics (thiazide or thiazide-like), ACE inhibitor/ARB, and long-acting dihydropyridine CCBs	Strong	High
	For adults with hypertension requiring pharmacologic treatment, the WHO recommends the use of drugs from any of the following three classes of pharmacologic antihypertensive medications as initial treatment: (1) thiazide and thiazide-like agents, (2) ACE inhibitors/ARBs, (3) long-acting dihydropyridine CCBs	Strong	High
Panamerican guidelines 2022 [33]	In adults with hypertension that require pharmacological treatment, it is recommended that patients are given a fixed combination in a single tablet (to improve compliance and therapeutic persistence) as initial treatment	Conditional	Moderate
	Antihypertensive medications administered in combination treatments must have a prolonged duration of effect that allows for once-daily administration and must be chosen from the following classes of medications: diuretics (thiazides or thiazide-like agents), ACE inhibitors or ARBs, and dihydropyridine CCBs	Conditional	Moderate
	Combination treatment may be especially valuable when baseline BP values are ≥ 20/10 mmHg higher than target values	Good practice	NR
	Combination treatment in a single tablet improves adherence and persistence and BP control	Good practice	NR
European (ESH) guidelines 2023 [32]	Initiation of therapy with a two-drug combination is recommended for most patients with hypertension. Preferred combinations should comprise a RAAS blocker (ACE inhibitor or ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used	I	A
	The use of SPCs should be preferred at any treatment step, i.e., during initiation of therapy with a two-drug combination and at any other step of treatment	I	B
	β-blockers should be used at initiation of therapy or at any treatment step in specific clinical situations (e.g., HFrEF), anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation, and younger hypertensive women of child-bearing potential or planning pregnancy	I	A

$A^{(SR)}$ high quality evidence (based on systematic review), *ACC* American College of Cardiology, *ACE* angiotensin converting enzyme, *AHA* American Heart Association, ARB angiotensin receptor blocker, *B-NR* moderate quality evidence from ≥ 1 well-designed well-executed nonrandomized studies observational studies registry studies and/or meta-analyses of such studies, *BP* blood pressure, *CCB* calcium channel blocker, *C-EO* consensus of expert opinion based on clinical experience, *COR* class of recommendation, *ESC* European Society of Cardiology, *ESH* European Society of Hypertension, *HFrEF* heart failure with reduced ejection fraction, *ISH* International Society of Hypertension, *LOE* level of evidence, *NR* not reported, *RAAS* renin-angiotensin-aldosterone system, *SBP* systolic blood pressure, *SPC* single-pill combination, *US* United States, *WHO* World Health Organization

[a]ACC/AHA/American Academy of Physician Assistants/Association of Black Cardiologists/American College of Preventive Medicine/American Geriatric Society/American Pharmacists Association/American Society of Hypertension/American Society for Preventive Cardiology/National Medical Association/Preventive Cardiovascular Nurses Association

[b]ISH guidelines do not provide COR or LOE but assign recommendations as "essential" or "optimal" standards of care

basis, it is observed that primary healthcare physicians and specialists in Colombia are still reluctant to start antihypertensive treatment with SPCs. The intent of this manuscript is to generate more co-responsibility, empowerment, and physician education to convince physicians to start combined therapy sooner.

4.2 Treatment Adherence

Antihypertensive therapy needs to be taken as prescribed to achieve BP control, but medication non-adherence rates are very high [49]. Globally, the prevalence of nonadherence with antihypertensive therapy is between 27 and 40%, with higher prevalence in low to middle-income countries

Table 3 First-line treatments and combinations based on patient characteristics or comorbidities [29, 32, 34, 40]

Characteristic	First-line recommendations
General population	ACE inhibitor or ARB
CAD	ACE inhibitor or ARB + β-blocker (irrespective of BP) or CCB
Post-MI	ACE inhibitor + β-blocker
Prior stroke	ACE inhibitor or ARB + CCB or diuretic
Heart failure (HFpEF)	ACE inhibitor or ARB or ARNI + β-blocker + MRA ± diuretic Add SGLT2 inhibitor
Chronic kidney disease	ACE inhibitor or ARB + CCB or diuretic
COPD	ACE inhibitor or ARB + CCB and/or diuretic β_1-selective β-blockers in selected patients (e.g., with CAD or heart failure)
Diabetes	ACE inhibitor or ARB + CCB and/or thiazide-like diuretic
Psychiatric disorders	ACE inhibitor or ARB and diuretic β-blocker (not metoprolol) if drug-induced tachycardia
Aortic valve stenosis	ACE inhibitor (+ β-blocker)
Atrial fibrillation	ACE inhibitor or ARB + β-blocker or non-dihydropyridine CCB[a] or ACE inhibitor or ARB + β-blocker + CCB or diuretic
Pregnant women	Methyldopa, β-blocker (labetalol), dihydropyridine CCB
HIV/AIDS	As per general population Consider drug interactions with CCBs
Lipid disorders	As per general population Add appropriate lipid-lowering therapy
Metabolic syndrome	As per general population Add appropriate additional therapy considering additional risk factors and overall cardiovascular risk
Inflammatory rheumatic disorders	As per general population (preferentially with RAAS blocker and CCB) Treat underlying inflammation effectively and avoid high doses of NSAIDs

ACE angiotensin converting enzyme, *AIDS* acquired immunodeficiency syndrome, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *BP* blood pressure, *CAD* coronary artery disease, *CCB* calcium channel blocker, *COPD* chronic obstructive pulmonary disease, *HFpEF* heart failure with preserved ejection fraction, *HIV* human immunodeficiency virus, *MI* myocardial infarction, *MRA* mineralocorticoid receptor antagonist, *NSAID* nonsteroidal anti-inflammatory drug, *RAAS* renin-angiotensin-aldosterone system, *SGLT2* sodium-glucose cotransporter 2

[a]Avoid combination of a β-blocker + non-dihydropyridine CCB (e.g., verapamil or diltiazem) because of the potential risk of heart block or bradycardia

compared with high-income countries, and in non-Western versus Western countries [49].

There are limited data on rates of adherence in Colombia, but one cross-sectional study conducted among 258 patients with hypertension aged 45–70 years in Medellín, Quibdó, and Bogotá reported that only 27% were compliant with treatment [50]. Higher socioeconomic status was associated with better adherence, and chronic stress was associated with worse adherence [50]. Similarly, a study in 500 Colombian patients with hypertension or type 2 diabetes found that adherence was worse among those with low socioeconomic status and those who had subsidized healthcare [51].

Parra-Gómez and colleagues identified a number of barriers to BP control in Latin America, including Colombia, several of which may directly or indirectly influence adherence with medication (Table 4) [52]. An important element identified in Colombia is the lack of knowledge about hypertension and its consequences by most patients [53]. Many patients perceive that there is no benefit to treatment because hypertension is asymptomatic, so it is important for healthcare professionals to educate patients about the role of BP in end-organ damage and cardiovascular events. There is now considerable evidence that effective patient education can have a significant impact on cardiovascular risk factors and outcomes [54]. Visual aids, such as risk charts, can help patients to see the personal impact of BP on risk [55].

The HOPE 4 randomized study, conducted in Malaysia and Colombia, used a multifaceted intervention in which non-physician healthcare workers conducted community screening, detection, and treatment of risk factors under the supervision of local physicians, using a simplified management algorithm, counselling, provision of free SPCs as needed, and engaging a patient-nominated support person to help maintain adherence and healthy behaviors [56]. Compared with patients who received standard care, those randomized to the multifaceted intervention had significantly better BP control rates (69% versus 30%; $p < 0.0001$), as well as significant reductions in other risk parameters (such

Table 4 Patient-related barriers to blood pressure control in Latin America [52]

Asymptomatic nature of hypertension
Lack of information about hypertension
Lack of knowledge about healthy lifestyles
Economic difficulties limiting access to medical center (e.g., transportation costs), drugs, tests, and healthy food
Lack of time and money for self-care
Lack of a support network for disease and treatment
Presence of comorbidities or other factors (e.g., age and obesity) that limits ability/motivation to undertake healthier lifestyles and habits
Poor doctor-patient relationship
Polypharmacy

Barriers identified in Colombia are shown in italics

as lipid levels) and overall cardiovascular risk status [56]. An important component of the successful intervention was that it was pragmatic and based on barriers that were specific to the populations under investigation. The inclusion of patient education, as well as ongoing follow-up and support from healthcare providers and the patient's nominated supporter addressed key barriers for patients in Colombia.

Telehealth offers a number of modalities to help improve BP control, including in Latin America [57]. Patients who forget to take the medication may benefit from reminders and cues, including via cell phone apps [55]. Telehealth can be used to reach patients who may not be able to access face-to-face health consultations, such as those in rural areas. Additionally, patients who measure their BP at home can transmit this information to their healthcare provider electronically [57]. While telehealth offers many benefits, middle-income countries like Colombia do not have equitable access to telecommunications across the whole population, and not all of the population has the digital literacy to use these technologies [57]. In addition, many practitioners need more education about how to implement and use telehealth modalities to improve hypertension management in clinical practice [57].

Polypharmacy is associated with worse adherence, so limiting the pill burden for patients is an important strategy to enhance adherence. When patients require combination therapy (as most with hypertension do), the use of SPCs is associated with significantly better adherence/persistence and greater BP reductions, compared with the same combination given as individual pills [58, 59]. SPCs were part of the active intervention arm in the HOPE 4 study and were likely an important component of the better BP control rates reported in the active treatment versus standard therapy group in that study [56].

SPCs are often underutilized in Latin America, and wider use of SPCs may have a positive effect on BP control in Latin America. As described earlier, SPCs are recommended in Colombian national guidelines for combination therapy, but combination therapy is not the recommended initial regimen for most patients [36].

4.3 Treatment Escalation

Reported BP control rates in Colombia vary from 37.1 to 66.4% (Table 1) [10, 11, 17, 19, 21, 44]. In a primary care study by Barrera and colleagues, 38.4% of treated patients with hypertension had BP controlled to recommended levels. BP control rates were higher in patients who attended a contributive primary care service than in those attending a subsidized service (43.9% versus 26.5%) [44], potentially related to better adherence among individuals in higher socioeconomic groups in Colombia reported by other researchers [50]. The study by Barrera and colleagues also showed that BP control was related to the number of visits the patient attended and the continuity of care they received [44], highlighting the importance of physician follow-up in the care of patients with hypertension. Among patients with hypertension in Colombia, follow-up is significantly worse in males, people without diabetes, employed people (versus those without a paying job), people insured under the subsidized health insurance scheme or those without any health insurance, and people reporting regular alcohol consumption [10].

While there are limited data on the rate of therapeutic inertia in Colombia, one study of 1142 consultations in 355 patients with hypertension found that 81.8% of cases of uncontrolled BP could be attributed to therapeutic inertia [60]. Use of concomitant antidiabetic medication was the only significant risk factor for therapeutic inertia, after adjustment [60], which is concerning because patients with diabetes are at increased risk of cardiovascular and renal adverse events and have more stringent BP goals [28–32].

There are three commonly cited reasons why physicians do not intensify antihypertensive therapy [61]. The first is overestimation of the care provided, whereby physicians overestimate their own adherence to treatment guidelines.

The second is the use of "soft" reasons to avoid intensifying therapy [61]. For example, physicians accept improvements in BP, rather than achievement of BP goals, as therapeutic success, or they assume (without asking them) that patients will be reluctant to escalate therapy. They may also avoid intensification because of concerns about potential side effects or interactions [61]. Some of these "soft" barriers to treatment intensification may be overcome by effective patient–physician communication, which can change patients' beliefs about medication, and enhance adherence and self-care among patients with hypertension [54, 62–64]. Qualitative research among Colombian patients with hypertension has shown that patients want to build a trusting relationship with their physician and to have better communication with them [53].

The third reason for not intensifying therapy is a lack of physician education/training or barriers associated with the organization of the practice, which do not facilitate the achievement of BP goals [61]. Resource-related or organizational barriers to BP control in Latin America include delays in getting appointments, brief appointments (not enough time to educate patients about their condition), poor communication between healthcare centers, and high turnover of healthcare professionals [52]. The HOPE 4 study and the study by Barrera and colleagues described earlier demonstrates that Colombian patients are more likely to achieve BP control when the practice they attend provides better follow-up and continuity of care [44, 56]. More regular follow-up may not only reduce therapeutic inertia but it may enhance patient adherence, as was shown in a separate study among urban residents of Medellin, Colombia [10].

5 Use of SPCs and BP Control in Latin America

Data show that the use of combination therapy (either as free combinations or SPCs) for hypertension is lower in low or middle-income countries than in high-income countries [65]. While limited prescribing data exist, it appears that SPCs are underutilized in Latin America, including in Colombia, despite evidence that SPCs improve adherence and BP control and reduce the overall costs of care [58, 59, 66].

Similarly, there is a paucity of research regarding reasons why SPCs may be underutilized in Latin America, but one potential reason may be the role of SPCs defined in national guidelines. Some countries lack national guidelines or have guidelines that are inconsistent with international recommendations on SPC use [67]. As described earlier, the 2017 Colombian hypertension guidelines recommend initial combination therapy only for patients with grade ≥ 2 hypertension or associated risk factors [36], which is inconsistent with international and regional guideline recommendations for early use of SPCs in most patients with hypertension [28–35].

Another potential reason for low use of SPCs is therapeutic inertia, whereby physicians continue to use monotherapy instead of intensifying treatment in patients who have not achieved target BP [60]. While data are limited, estimates suggest that therapeutic inertia is the major reason for non-achievement of BP control in urban centers in Colombia [60].

A third potential reason why SPCs are underused is affordability or cost [67, 68]. The cost of treatment with an SPC tends to be higher than with free-dose combinations [69], but the price will drop as more generic formulations become available and as the use of SPCs increases [70]. Current data suggest that the out-of-pocket costs related to hypertension are generally moderate and affordable for most patients in Colombia, and that only 23.3% of these costs were for pharmacological therapy; the rest of the out-of-pocket costs were for dietary requirements and transport to health appointments [71].

Availability of SPCs has been identified as an issue in low and middle-income countries [67, 68], but Colombia is one of the few that includes SPCs for hypertension on the national essential medicines list [67]. However, there are limited data describing the use of SPCs and the barriers to their use in Colombia [68].

Some physicians may be reluctant to prescribe SPCs because they are concerned about a lack of flexibility in dosing, if one or other agent needs to be titrated [70]. Choosing an SPC with a range of available dose combinations, or use of scored tablets that allow for use of partial doses, may limit this problem [70].

6 Regional and National Initiatives to Improve BP control

A number of global initiatives to improve BP control have been launched and are being implemented in Latin America, including Colombia. One of these is May Measurement Month, the global screening program initiated by the International Society of Hypertension. This program aims to raise awareness of, and provide education about, hypertension around the world and increase the number of adults who regularly have their BP checked. The first Colombian data (from May 2019) were published in 2021 and are included in Table 1 [11].

Another is the World Heart Foundation (WHF) roadmap, which was initiated in 2015. A joint initiative between the WHF and the Colombian Society of Cardiology and Cardiovascular Surgery (SCCC) was launched in

August 2020 to increase BP measurement in the population, certify allied healthcare professionals (e.g., physical therapists, nutritionists, respiratory therapists, and dentists) to measure BP, and offer lifestyle recommendations for the prevention and control of hypertension [72]. This was the first step in a range of joint initiatives between the WHF and SCCC, with further programs being planned. The HOPE 4 study showed that non-physician healthcare workers can provide effective screening and patient management/counselling when provided with the appropriate training and tools [56].

The community-based HEARTS in Americas program is designed to improve hypertension control and the secondary prevention of CVD [73, 74]. One of the strategic pillars in the HEARTS in Americas program is the treatment protocol and medication strategy, which aims to improve the availability, quality, and affordability of antihypertensive medications that patients can access, and to use treatment algorithms to simplify decision-making [73]. The use of combination therapy and SPCs is a core element of this strategy and is supported by the inclusion of SPCs on the WHO essential medicines list and on the Pan American Health Organization (PAHO) Strategic Fund list. Another core element is the development of a small and simple formulary of key antihypertensive medications based on four drug classes. The planning and implementation of this formulary is underway.

Researchers in Medellin, Colombia, are implementing a multi-component intervention to improve hypertension awareness and control among low-income communities [75]. This intervention uses an established chronic care model to redesign hypertension health services, train clinical staff, and engage patients and the community. The multi-interventional program will address many of the issues identified in this review as contributing to therapeutic inertia and poor adherence in Colombia, including active patient follow-up, standardized treatment algorithms, patient education by clinic staff and peers (specially trained "expert hypertension patients"), training to improve physician–patient communication, and availability of core antihypertensive medications through a central pharmacy [75]. The researchers have developed a protocol to formally study this intervention in 1160 patients (NCT05011838), with completion of the study expected in 2026.

7 Conclusions

Despite promising regional initiatives, BP control in Colombia remains suboptimal. Treatment initiation, adherence, and escalation can all be improved.

Wider use of evidence-based therapies, as well as an update of local guidelines to align more closely with international guidelines would be important steps toward improved hypertension control in Colombia, as would better engagement of patients in their self-care through improved physician–patient communication.

The use of SPCs from the first step of antihypertensive treatment in the majority of patients has proven to be a prime opportunity as it represents a cost-effective strategy to improve adherence, reduce inertia, and facilitate the achievement and maintenance of BP goals. This will help ensure the long-term benefit of the treatment in containing hypertensive damage and reducing its cardio-kidney-metabolism impact. Therefore, in Colombia, as in the rest of the world, using SPCs is the rule and monotherapy is the exception.

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Declarations

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