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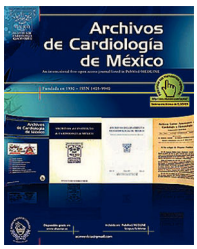

REVIEW ARTICLE

Fixed-dose combination therapy to improve hypertension treatment and control in Latin America

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Abstract Hypertension is a major risk factor for cardiovascular disease. Its prevalence is increasing worldwide, and is more common in low and middle-income countries. The effectiveness of hypertension treatment is determined by health cost, awareness, and patients' compliance with the treatment. People worldwide with an adequate control of hypertension correspond to a very small percentage in low and medium income countries as the Latin America ones. Between the causes to explain these are the low availability, affordability and adherence to treatment with multiple pills. It has been proposed that fixed dose combination therapy could improve the availability, affordability, adherence and control of hypertension. This article aims to review the evidence, showing that fixed dose combination can improve adherence, decrease health cost and improve control of hypertension. Improvement in hypertension control with fixed dose combination could make an important contribution to efforts to fight against the global cardiovascular morbidity and mortality.

PALABRAS CLAVE
Terapia combinada;
Hipertensión;
Cumplimiento de la medicación;
Colombia

Terapia de combinación a dosis fija para mejorar el tratamiento y el control de la hipertensión en América Latina

Resumen La hipertensión es un factor de riesgo importante para el desarrollo de enfermedades cardiovasculares. Su prevalencia está aumentando en todo el mundo, y es más común en los países de medianos a bajos ingresos. La eficacia del tratamiento de la hipertensión está determinada por el costo, el conocimiento y la adherencia de los pacientes con el tratamiento.

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El control adecuado de la hipertensión corresponde a un porcentaje muy pequeño en países de medianos a bajos ingresos como los países de América Latina. Entre las causas para explicar esto se encuentran la baja disponibilidad, asequibilidad y adherencia al tratamiento con múltiples medicamentos antihipertensivos. Se ha propuesto que la terapia combinada a dosis fija podría mejorar la disponibilidad, asequibilidad, adherencia y control de la hipertensión. Este artículo tiene como objetivo revisar la evidencia que demuestra que la combinación de dosis fija puede mejorar la adherencia, disminuir los costos de salud y mejorar el control de la hipertensión. La mejoría en el control de la hipertensión con terapia de combinación a dosis fija podría aportar una importante contribución a los esfuerzos para combatir la morbilidad y la mortalidad cardiovascular a nivel mundial.

Introduction

Hypertension is the most important risk factor for cardiovascular morbidity and mortality. It is estimated that hypertension is responsible for 9.4 million deaths per year[1] and has been associated with an increased risk of stroke, myocardial infarction, heart failure and renal failure.[2–4]

Recent projections suggest that the prevalence of hypertension will increase by 30% by 2025[5] with low- and middle-income countries (LMICs) accounting for three quarters of the world's hypertensive population. Currently more than 80% of the attributable burden of blood pressure-related diseases are in LMICs.[6] Recent meta-analyses showed that the prevalence of hypertension was the highest among Latin America and Caribbean populations. Moreover it is estimated that one of three individuals are hypertensive in these countries.[7] Rapid lifestyle changes has led to an increase in several modifiable risk factors associated with hypertension such as sugar consumption, overweight, obesity and physical inactivit.[8–10] In addition socioeconomic status (SES) influences hypertension rates with an increased prevalence among those with the lowest SES defined by income, occupation and education.[11–13] In Colombia, recently we reported that lower awareness, treatment and control of hypertension is observed between men younger than 50 years old, with low level of education, low income and living on rural areas.[14] Different reason has been proposed to explain the effects of SES on blood pressure (BP) such as level of education,[15] stress,[16] less quality of life,[17] working conditions,[18] healthcare and medicine access.[14]

The Cardiovascular Risk Factor Multiple Evaluation in Latin America study (CARMELA) conducted in seven capital cities reported that 24.3–46.9% of patients were unaware of their hypertensive condition, more than half of those with hypertension were untreated, and only 12.0% were controlled, findings associated with the poor communication between health staff and the community.[19] The average time taken to inform the patient is too lengthy and information regarding the implementation of healthy lifestyles and the need to take medicines to have a good control of hypertension and avoid complications is not well expressed.[20]

Among the 23,578 patients from Latin-America who participated in the Population Urban and Rural Epidemiology (PURE) study,[12] the prevalence of hypertension (defined as values of systolic blood pressure (SBP) $\geq$ 140 mmHg and diastolic blood pressure (DBP) $\geq$ 90 mmHg) was 50.8% in Argentina, 52.6% in Brazil, 46.7% in Chile and 37.5% in Colombia. Only 57% of the patients knew they had hypertension, 52.8% received treatment, but only 18.3% had adequate control of their high blood pressure (BP). In the results of the National Health Survey 2000 conducted in Mexico, the percentage of Mexicans with hypertension who were unaware of their condition was 61%, only 14.6% of hypertensive patients were controlled.[8] These findings demonstrated the importance of improving awareness, diagnosis, and adequate treatment that allows a good control of hypertension (SBP < 140 mmHg).

Hypertension treatment in low income settings is expensive because is a chronic risk factor that requires life-long medication therapy and most of the hypertensive patients need on average at least two antihypertensive medications for adequate BP control.[21] The PURE study demonstrated[22] that the use of cardiovascular medications as drugs to treated hypertension is affected by the negative impact of a low percentage of availability and affordability of cardiovascular disease medicines, especially in LMICs, where the capacity to pay these class of medications could demand more that the half of the family income. Maybe these factors can explain the recent report of Mills et al.[23] who demonstrated that the age adjusted prevalence of hypertension increased from 2000 to 2010 in LMIC, whereas control of hypertension in men decreased and the awareness and treatment increased only slightly.

Fixed dose combination therapy comes as a possible solution to improve treatment and control of high blood pressure in LMICs due to a simplify algorithm of treatment and by increasing adherence. Moreover, the combination of two or more antihypertensive drugs in one pill acts with a synergistic mechanism reflecting better results controlling BP levels. This article aims to review the evidence that support this proposal.

Barriers for hypertension treatment in Latin America

Most of the countries of the Americas have non communicable disease prevention and control programs aligned

with global mandates, with a large emphasis on the control of hypertension.[24] Health policies aimed to promote lifestyle changes that improve blood pressure levels such as a healthier diet, low sodium intake, low alcohol intake, increased physical activity and cessation of smoking have lowered cardiovascular diseases (CVDs) in some wealthy regions of the world,[25,26] but have had low impact in others, especially in LMIC.[27] Moreover, there are only few successful population-wide hypertension control programs and it has been shown that behavioral interventions to modify lifestyles are expensive, have low impact and are not sustainable over time.[28] Evidence suggests that education is the most important aspect of SES affecting hypertension control,[14,29–31] but this factor is not easy to improve in a short time. Modifying lifestyles may be difficult to achieve for some patients, making necessary the use of multiple pharmacological compounds to improve BP levels. As reviewed before, in LMICs there are a limited use of antihypertensive medicines because of their poor availability, a lack of affordability, poor prescription and a lack of patient adherence.[11] So, if we want to reach the 25 × 25 goal of the World Health Organization,[32] the call to action of the Lancet Commission on Hypertension[33] and the 20X20 strategy of the Latin American Society of Hypertension,[34] together with programs to implement changes in life style, we also need to implement programs that allow the improvement of the prescription of medications to treat hypertension. This therapy must be of high quality, affordable, available, with simplified indications to the patients permitting to improve the adherence and the BP control.

Fixed dose combination therapy for hypertensive treatment

A single dose of antihypertensive medication reduces SBP in average by 8–10 mmHg, but a largest effect can be achieved by increasing the dose of the medication.[35] Several studies have demonstrated that the combination of two agents from any two classes of antihypertensive drugs increases the BP reduction significantly more than increasing one agent dose.[36] Moreover, there are other advantages of initiating treatment with combination therapy in patients with high cardiovascular risk because there is a greater probability of achieving the target BP, and this lowers the probability of discouraging patient adherence with a multidrug therapy. Indeed, a survey showed that patients receiving combination therapy had a lower drop-out rate than patients with monotherapy.[37] European guidelines suggested fixed dose combination therapy over single drug therapy for hypertension treatment due to a higher compliance too.[38] The European experts noticed further advantage between physiological and pharmacological synergies among different classes of agents that may not only promote a greater BP reduction but also cause fewer side effects than a single agent.

The 2013 Latin America Society of Hypertension (LASH) consensus confirmed previous recommendations about hypertension treatment and highlighted the fact that diuretics, beta-blockers, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are all suitable for the initiation and maintenance of antihypertensive treatment.[39] This consensus favors the use of combinations of two antihypertensive drugs at fixed doses in a single tablet, because reducing the number of pills to be taken daily improves adherence, and increases the rate of BP control.[40] This approach is now facilitated by the availability of different fixed-dose combinations of the same drugs, which minimizes one of its inconveniences, namely the inability to increase the dose of one drug independently of the other.[39,41]

Clinical trials with fixed dose combination therapy

There is only indirect data available from randomized trials about fixed dose combination therapy for management of BP and cardiovascular outcomes. Among the trials using fixed dose combination therapy for hypertension, three studies compared two-drug combination in one arm versus one drug more placebo: the ADVANCE trial compared an ACE inhibitor plus a diuretic with a diuretic with placebo,[42] FEVER compared a calcium antagonist plus a diuretic versus a diuretic plus placebo[43] and ACCOMPLISH compared an ACE inhibitor in combination with either a diuretic or a calcium antagonist.[44] In all other trials, treatment was initiated by monotherapy in either arm and another drug (and sometimes more than one drug) was added in some patients. In some trials, the second drug was chosen by the investigator among those not used in the other treatment arms, as in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study.[45]

In trials comparing different regimens, all combinations have been used in a larger or smaller proportion of patients, without major differences in benefits. The only exceptions are two trials in which a large proportion of patients received either an angiotensin receptor blocker-diuretic combination or a calcium antagonist-ACE inhibitor combination,[46,47] both of which were superior to a beta-blocker-diuretic combination in reducing cardiovascular events. However, a beta-blocker-diuretic combination was as effective as other combinations in several other trials[45,48–50] and more effective than placebo in three trials.[51–53] However, the beta-blocker-diuretic combination appears to elicit more cases of new-onset diabetes in susceptible individuals, compared with other combinations.[54]

The ACCOMPLISH trial directly compared two combinations in all patients,[44] it found significant superiority of an ACE inhibitor-calcium antagonist combination over the ACE inhibitor-diuretic combination in cardiovascular outcomes despite no BP difference between the two arms. These unexpected results deserve to be repeated, because trials comparing a calcium antagonist-based therapy with a diuretic-based therapy have never shown superiority of the calcium antagonist. Nonetheless, the possibility that ACCOMPLISH results may be due to a more effective reduction of central BP by the association of a renin–angiotensin system blocker with a calcium antagonist deserves to be investigated. All these trials proved the effectiveness of fixed dose combination in hypertension therapy and thus in cardiovascular outcomes. Some of these studies results are summarized in Table 1.

Table 1 Major drug combinations used in trials of antihypertensive treatment.

Clinical trial	Intervention	Patients	SBP diff (mmHg)	Adherence	Outcomes
ADVANCE trial[42]	Fixed combination of Perindopril and indapamide or matching placebo	Patients with diabetes	−5.6	73%	−9% micro/macrovascular events ($p = 0.04$) 18% reduction in the risk of death from cardiovascular disease
FEVER[43]	Low-dose hydrochlorothiazide plus low dose felodipine extended release compared to only low-dose hydrochlorothiazide	Hypertensive patients	−4.2	85.9%	−27% cardiovascular events ($p < 0.001$)
ACCOMPLISH[44]	Benazepril plus amlodipine or benazepril plus hydrochlorothiazide	Hypertensive patients with risk factors	−1	Benazepril/amlodipine: 71.2% Benazepril–hydrochlorothiazide: 68.8%	−21% cardiovascular events ($p < 0.001$)
ALLHAT study[45]	Chlorthalidone, 12.5–25 mg/d; amlodipine 2.5–10 mg/d; or lisinopril	Hypertensive patients with risk factors	−2/−1	Adherence decreased over time from about 92% at 1 year to 84% to 87% at 5 years in all 3 treatment groups	Not significant in cardiovascular events

SBP diff: systolic blood pressure difference.

Evidence has shown that any of the drug classes blocking the renin–angiotensin system (ACEi and ARBs) combined with a dihydropyridine CCB, or combined with a thiazide diuretic, should be considered the preferred combination to initiate antihypertensive treatment for most patients, particularly in fixed-dose combination. Therefore, the selection of the individual components in each combination may be based mainly on the capacity of obtaining the lowest prizes of the original molecules in the different countries of Latin America.

In the review of Bautista et al.,[55] it was calculated that if in Latin-America a fixed dose combination therapy were given, the lifetime risk of cardiovascular events could be reduced by 15 percent in those in the high-risk group (those with a ten-year risk of cardiovascular disease greater than or equal to 15) or to those age fifty-five or older.

Recently, the results of the HOPE-3 study, in which Colombia participated including more than 1.500 patients, demonstrated that a combination therapy with a fixed dose of 16 mg/day of candesartan and 12.5 mg/of hydrochlorothiazide administered to individuals of intermediate-risk without CVD, with a SBP >144 mmHg (average 154 mmHg), produced an average decrease of 6/3 mmHg of SBP/DBP that was associated with a significant reduction of 27% in the relative risk of the composite outcome of cardiovascular death and non-fatal myocardial infarction and stroke (Fig. 1).[56]

In participants with BP in the highest tertile who also received rosuvastatin (10 mg/day) and the two antihypertensive medications, there was an increase in the relative

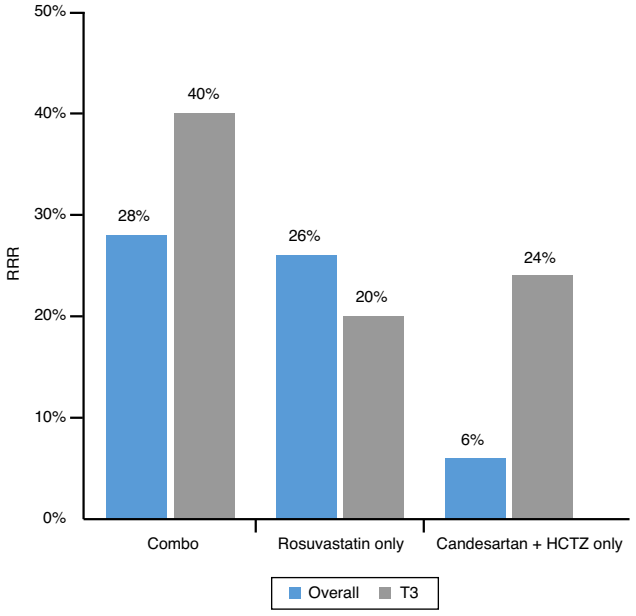

Figure 1 Reduction of cardiovascular outcomes in the HOPE 3 study of combination therapy in the overall group and in tertile 3 of systolic blood pressure (>143 mmHg). HCTZ: hydrochlorothiazide, RRR: relative risk reduction, T3: tertile 3 of systolic blood pressure.

risk reduction to 40%.[57] Treatment adherence in HOPE-3 was high: 88.2% were taking the prescribed regimen at 1 year, 83.6% at 3 years, 75.0% at 5 years, and 76.8% at the end of the trial. Moreover, HOPE-3 confirmed the results reported by the Anglo-Scandinavian Cardiac Outcomes Trial,[58] showing a potential synergy between lipid-lowering and blood pressure lowering in the management of CVDs. Importantly, the HOPE-3 study demonstrated that the beneficial effects in reducing the cardiovascular events of a fixed dose of two antihypertensive drugs is observed only in people with a SBP >144 mmHg, but not in people with lower levels of SBP.[56] The study also showed that cardiovascular protection is achieved when SBP falls below 140 mmHg. The HOPE-3 results suggest that combination therapy with statin and two antihypertensive agents must be indicated for primary prevention for those individuals with a systolic blood pressure >140 mmHg, while the statin alone must be used in those individuals without high systolic BP because the protective effects of statin were independent of the levels of BP.[59]

These results demonstrated for the first time that a combination of a statin with an ARB and a diuretic at low doses reduces LDL cholesterol, BP and cardiovascular events in patients with moderate risk and without cardiovascular disease. Moreover, the high adherence of these patients to the treatment support the proposal for the use of a combination of hypotensive drugs plus statin as an effective cardiovascular primary prevention strategy. However, the HOPE 3 study did not use the 3 medications in a single pill,[59] but currently several clinical trials are running to evaluate the efficacy of a polypill in primary and secondary prevention of CVDs.

All these studies proved that fixed dose combination therapy can control BP with an improvement of cardiovascular outcomes, the compliance was increased and the medications were well tolerated with few adverse events and non-relevant clinical changes in laboratory values. Thus, fixed dose combination could be a cheap solution improving the availability of medications, using generic medication of high quality for hypertension treatment in LMICs.

Fixed dose combination therapy cost

The mortality from CVDs has decreased in developed countries but it is increasing in LMIC.[60,61] It is estimated that more than half of the reduction in mortality may be attributable to medical therapy when medications are accessible and affordable.[22] Unfortunately, according to the World Health Organization in LMICs remains a low availability of effective pharmacological treatments in patients with hypertension and CVDs.[62] The cost of cardiovascular drugs used in secondary prevention becomes a greater challenge within the health system, since a one-month supply of generic drugs is equivalent to 1.5–18.4 days of the minimum income in LMICs.[63]

Inadequate health care systems are also implicated in poor hypertension control,[5] and the low level of government investment in healthcare systems is associated with the inadequate use of cardiovascular drugs in individuals with clear indications for them, including antihypertensive medications.[64] In most Latin-American countries, more than 50% of the population have difficulties in accessing healthcare and to cover expenses related to health.[65] We have identified that in Colombia the principal barriers to control of hypertension are related to the cost of transport to health care facilities and the copayment of medications.[66]

In a meta-analysis in which was compared fixed dose combination therapy versus free drug combination therapy, it was found that the annual cost in 2009 for hypertension or cardio-vascular related cost were lower in patients with fixed dose combination therapy.[67] Fixed dose combination therapy has shown also to decrease the number of visits to the hospital, to decrease emergency department visits and hospitalizations,[68] and with an increased adherence to treatment. Furthermore, low adherence is correlated with a higher risk of cardiovascular events and CVDs, resulting in greater healthcare costs. Fixed combination therapy comes as a solution to reach an adequate compliance in hypertensive patients. In Latin America it has been estimated that fixed dose combination therapy would be cost-effective even in countries with low gross national income,[55] making affordable the treatment for hypertension. However, more studies are needed in Latin-America proving the benefits of fixed dose combination in BP control, CVDs prevention and healthcare cost.

Problems of fixed dose combination therapy

Although fixed dose combination therapy is an effective, easy and attractive hypertensive way of treatment, the strategy cannot be applied to all the patients because it lacks of flexibility and certain individuals may present with contraindications or adverse effects for one of the components.[69] Also with a fixed dose combination therapy some patients may be exposed to unnecessary therapy. Another problem with fixed dose combination are the patents for the components of a single pill with multiple antihypertensive medications. In a study conducted to assess the availability of free patent cardiovascular drugs, it was found that from 48 cardiovascular medication in Canada and United States, only 19 drugs (40%) were totally patent free.[70] This can be a strong barrier for the marketing and worldwide distribution of an antihypertensive fixed dose combination. Although some generics companies, are already producing generic medication of fixed dose combination based on the requirements of the regulatory authorities, providing a temporary solution. Another solution is that the pharmaceutical companies who own the original patents bring the pills with fixed dose combination to the marked at an affordable price.

In conclusion, there is an increasing interest in the concept of prescribing a fixed dose of cardiovascular drugs such as antihypertensive medications. This is particularly interestedly in LMICs, where the burden of hypertension and cardiovascular diseases is high, resources for diagnostic are limited, and inexpensive and standardized treatments are more likely to be taken up in clinical practice than individualized therapeutic concepts. Fixed dose combination is effective controlling BP, because the administration of a single pill improves adherence, reduces CVDs and therefore decreases healthcare cost. However, there is the need to evaluate fixed dose combination in well-designed programs aimed to improve hypertension prevalence and cardiovascular prevention in Latin-America.

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Conflict of interest

The authors have no conflicts of interest whatsoever to declare with any pharmaceutical or medical device Company.

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