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The Effects of Single Pill Combinations on Adherence and Blood Pressure Control in Hypertensive Patients

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ABSTRACT

Background: Hypertension is the most important risk factor for cardiovascular morbidity and mortality. Blood pressure control rates are as low as 17% to 31% in patients diagnosed with hypertension in high-income countries; control rates are likely poorer in low- to middle- and low-income countries. Blood pressure control rates are as low as 17% to 31% in patients diagnosed with hypertension in high-income countries; control rates are likely poorer in low- to middle- and low-income countries. Overall, 43% to 66% of patients fail to adhere to their prescribed antihypertensive medications, and after 1 year, ≈40% of patients with hypertension may stop their initial drug treatment. **Objective:** The aim of the study was to evaluate the effects of single pill combination antihypertensive drugs on the adherence to treatment, blood pressure control and cardiovascular events vs. free-combination therapy. **Methods:** We enrolled 192 adult hypertensive patients not older than 79 years, with untreated or uncontrolled hypertension despite previously receiving free combination antihypertensive therapy, between November 2020 and March 2022. Patients treated with single pill combination (SPC) were compared with an arm of the same size (n = 96) and matched by age and gender who received a standard free combination (FC) antihypertensive therapy. **Results:** There were significant reductions from baseline to month 6 of follow-up in office SBP in the SPC group vs. reduction in FC group (21.9 vs. 13.1 mmHg; p < 0.0001). There were significant reductions from baseline to month 6 of follow-up in office DBP in the SPC group vs. group with free-combination therapy (13.7 vs. 8.0 mmHg; p < 0.0001). At 6 months, 94 participants (98%) were still prescribed the SPC therapy. At the final 6-month study visit, 84.2% of patients in the SPC therapy group were adherent to the prescribed antihypertensive therapy vs. 52% of patients in the FC group. Target BP values (mean 24h ambulatory systolic/diastolic BP < 130/80 mmHg) were reached by more recipients of SPC than free-combination therapy (78.2% vs. 46.3%, p < 0.05) at month 6 of follow-up. **Conclusion:** Treatment with single pill combinations (SPC), is the emerging best practice for safe, effective, rapid, and convenient hypertension control. It improves the affordability, adherence and control of arterial hypertension.

Keywords: Arterial hypertension, Single pill combination, Ambulatory blood pressure monitoring, Adherence.

1. BACKGROUND

Arterial hypertension remains the most important modifiable risk factor for cardiovascular disease, and according to the World Health Organization (WHO), it is still the world's leading cause of premature death. Hypertension is the most important risk factor for cardiovascular morbidity and mortality. It is estimated that hypertension is responsible for 10.8 million deaths in 2019 and has been associated with an increased risk of stroke, myocardial infarction, heart failure and renal failure. Among approximately 1.4 billion people with hypertension worldwide, only one in seven has their blood pressure successfully treated and adequately controlled. Despite an increased awareness of the importance of hypertension control and multiple treatment options and strategies available, many patients fail to reach their blood pressure targets. Rates of hypertensive control have plateaued worldwide over the last decade. Blood pressure control rates are as low as 17% to 31% in patients diagnosed with hypertension

in high-income countries; control rates are likely poorer in low- to middle- and low-income countries. Overall, 43% to 66% of patients fail to adhere to their prescribed antihypertensive medications, and after 1 year, ≈40% of patients with hypertension may stop their initial drug treatment. In addition, ≈10% of patients forget to take their medication on a daily basis. The relationship between poor adherence and high cardiovascular risk has been widely reported. The 2018 European Society of Cardiology (ESC) – European Society of Hypertension (ESH) guidelines identified that poor adherence to treatment and physician clinical inertia are important causes of poor blood pressure (BP) control. On July 9, 2019, WHO added single pill combination antihypertensive medications to the WHO Essential Medicines List. This inclusion aligns with the recommendations for single pill combinations in multiple national and international hypertension treatment guidelines.

2. OBJECTIVE

The aim of the study was to evaluate the effects of single pill combination antihypertensive drugs on the adherence to treatment and blood pressure control vs. free-combination therapy.

3. PATIENTS AND METHODS

We enrolled 192 adult hypertensive patients not older than 79 years, with untreated or uncontrolled hypertension despite previously receiving free combination antihypertensive therapy, between November 2020 and March 2022. Arterial hypertension was defined according to the 2018 ESC/ESH clinical practice guidelines for the management of arterial hypertension as office systolic BP ⩾140mmHg and/or diastolic BP ⩾90mmHg, daytime ambulatory BP or home BP mean systolic BP ⩾135mmHg and/or diastolic BP ⩾85mmHg, requiring initiation (untreated patients) or escalation (patients receiving free combination) of antihypertensive therapy. Exclusion criteria were patients ⩾79 years old, secondary hypertension, neoplastic or hepatic diseases, disabling diseases such as dementia or inability to cooperate, pregnancy or breast-feeding.

Ninety-six hypertensive patients treated with single pill combination were compared with a control group of the same size and matched by age and gender who received a standard free combination antihypertensive therapy. Office and 24h ambulatory blood pressure values were evaluated at baseline and at month 1 and at 6 months follow-up period. Office blood pressure (diastolic Korotkoff phase 5) was measured in the prone position using a mercury sphygmomanometer at 10-min intervals, and the average of the last two clinostat measurements was recorded as the blood pressure. Heart rate was also taken at the same time. Pulse pressure was the difference between SBP and DBP. In all patients, arterial hypertension was confirmed with 24h ambulatory blood pressure monitoring system devices (BOSO TM-2450, Germany and LABTECH EC-ABP, Czech Republic) which are clinically validated according to DIN EN ISO 81060-2. Adherence to medication was measured indirectly through patient self-reports and pill counts.

4. RESULTS

Ninety-six patients (52 men and 44 women, mean age 61.3 ± 10.9 years), age- and sex-matched by the case-to-case method with a control group of 96 patients, were evaluated. Consecutive patients had been screened and eligible patients enrolled between November 2020 and March 2022. Mean age was 61.4 ± 11.7 60.8 ± 12.1 years in all enrolled patients. Office BP at baseline was similar between study arms (SBP 153.5 ± 11.5 vs. 154.7 ± 12.8 mmHg; DBP 95.3 ± 5.7 vs. 94.4 ± 5.9 mmHg in single pill combination (SPC) vs free combination (FC) groups, respectively. The general characteristics of the two treatment groups at baseline are summarized in Table 1.

In the SPC patients arm how received fixed combination antihypertensive therapy, the distribution of dosages was as following: Perindopril/Amlodipine (4/5mg and 8/5mg, 8/10mg) in 27% of patients, Amlopdinpine/Valsartan (5/80mg, 5/160mg, 10/160mg) in 26%, Perindopril /Indapamide /Amlodipine (4/1.25/5mg, 4/1.25/10mg, 8/2.5/5mg, 8/2.5/10mg) in 43%, Nebivolol/HCTZ (5/12,5 mg, 10/25 mg) in 4%.

In the free-combination group, inhibition of renin-angiotensin-aldosterone system (RAAS) was accomplished with angiotensin-converting enzyme inhibitors (ACEIs): Lisinopril 10 & 20mg, Ramipril 2,5, 5 & 10mg, Perindopril 4 & 8 mg, Enalapril 10 & 20mg in 46% of patients, whereas angiotensin II receptor blockers (ARBs): Losartan 50 & 100 mg, Valsartan 80 & 160mg, Olmesartan 10 & 20mg) were used in 39%; Calcium channel blockers (Amlodipine 5 & 10mg) were used in 11% of patients, Beta blockers (Nebivolol 5 & 10mg) were used in 4% of patients, diuretics (hydrochlorothiazide 25mg or indapamide 2,5) in 1%. The distribution of antihypertensive potency was comparable in both groups.

In both treatment groups, significant reductions in ABPM values were observed at month 1 and month 6 of follow-up in SPC vs FC group (Tables 2 and 3). Significant

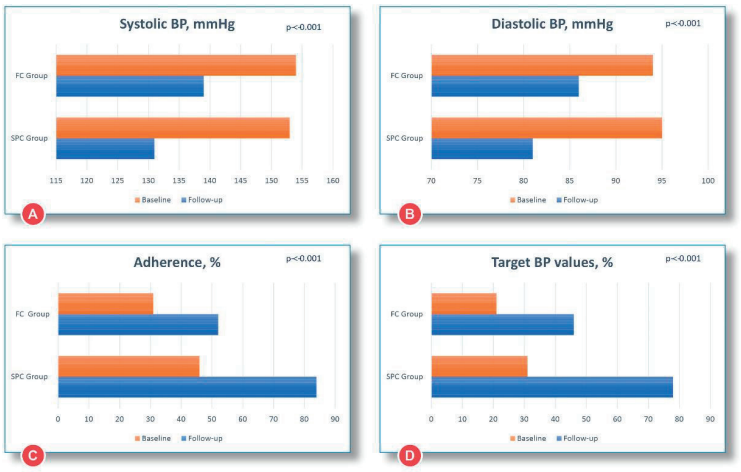

Figure 1. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), adherence and target blood pressure (BP) values from baseline and during follow-up period in both free-combination (FC) and single pill combination (SPC) group.

reductions in ambulatory 24-h, daytime, and nighttime systolic BP, and pulse pressure (PP) were found in the SPC group relative to reductions seen with free-combination therapy group. There were significant reductions from baseline to first month of follow-up in ambulatory 24h, daytime, and nighttime SBP were found in the SPC group (16.8 and 10.2 mmHg, respectively) relative to reductions seen with free-combination therapy (5.7 and 3.7 mmHg; $p < 0.0001$). There were significant reductions from baseline in 24 h ambulatory, daytime, and nighttime DBP were found in the SPC group (9.8 and 7.7 mmHg, respectively) relative to reductions seen with free-combination therapy (4.5 and 3.6 mmHg; $p < 0.0001$). However, at month 6 of follow-up, there were no significant differences in reductions from baseline between the two groups. Reductions from baseline in ambulatory 24-h, daytime, and nighttime pulse pressures were also significantly greater with SPC therapy (Figure 1).

In our study, a drop in nighttime blood pressure values was found during SPC treatment without any evening administration of drugs, suggesting that the drugs tested in this formulation had a long half-life and an antihypertensive effect sustained during the 24 h. Both office and ABPM-assessed heart rate values were essentially unchanged.

There were significant reductions from baseline to month 6 of follow-up in office SBP in the SPC group vs. reduction in FC group (21.9 vs. 13.1 mmHg; $p < 0.0001$). There were significant reductions from baseline to month 6 of follow-up in office DBP in the SPC group vs. group with free-combination therapy (13.7 vs. 8.0 mmHg; $p < 0.0001$). (Figure 1 A and B). At 6 months, 94 participants (98%) were still prescribed the SPC therapy. Of those receiving the SPC therapy, only 12 (12,7%) had been up titrated to the higher dose. However, at month 6 of follow-up, there were no significant differences in reductions from baseline between the two groups. At the final 6-month study visit, 84.2% of patients in the SPC therapy group were adherent to the prescribed antihypertensive therapy vs. 52% of patients in the FC group. (Figure 1 C). Target BP values (mean 24-h ambulatory systolic/diastolic BP < 130/80 mmHg) were reached by more recipients of SPC than free-combination therapy (78.2% vs. 46.3%, $p < 0.05$) at month 6 of follow-up. (Figur 1 D).

Demographics	All patients (n = 192)	SPC (n = 96)	FC (n = 96)
Age	61.4 ± 11.7	61.3 ± 10.9	60.7 ± 11.5
Male gender, %	54.7	54.2	55.2
Female gender, %	45.3	45.8	44.8
Risk factors			
Obesity or overweight	101 (53%)	51 (53%)	50 (52%)
Dyslipidemia	123 (64%)	62 (65%)	61 (64%)
Current Smoking	63 (33%)	33 (34%)	30 (31%)
Family history for CV disease	74 (39%)	38 (40%)	36 (38%)
Office BP values			
SBP, mmHg	154.6 ± 12.1	153.5 ± 11.5	154.7 ± 12.8
DBP, mmHg	94.9 ± 5.8	95.3 ± 5.7	94.4 ± 5.9
PP, mmHg	59.3 ± 11.3	58.2 ± 10.6	60.3 ± 11.9
24-h ABPM values			
24-h SBP, mmHg	145.0 ± 9.5	145.4 ± 8.4	144.6 ± 10.6
24-h DBP, mmHg	86.2 ± 7.1	85.7 ± 7.6	86.7 ± 6.6
24-h PP, mmHg	58.8 ± 8.2	59.7 ± 7.7	57.9 ± 8.6
Daytime SBP, mmHg	148.2 ± 9.2	148.5 ± 9.6	147.9 ± 8.8
Daytime DBP, mmHg	91.9 ± 6.4	92.7 ± 6.0	91.0 ± 6.7
Daytime PP, mmHg	56.3 ± 7.8	55.8 ± 7.8	56.9 ± 7.5
Nighttime SBP, mmHg	129.9 ± 9.6	129.5 ± 9.7	130.2 ± 9.4
Nighttime DBP, mmHg	77.0 ± 6.9	76.8 ± 7.7	77.2 ± 6.2
Nighttime PP, mmHg	52.9 ± 8.3	52.7 ± 8.7	53.0 ± 7.8
Lab. findings			
Cholesterol, mmol/L	5.3 ± 1.5	5.4 ± 1.4	5.2 ± 1.6
Triglycerides, mmol/L	1.5 ± 0.8	1.5 ± 0.7	1.6 ± 0.9
LDL-C, mmol/L	3.0 ± 0.7	3.1 ± 0.6	2.9 ± 0.7
Glucose, mmol/L	5.3 ± 0.5	5.3 ± 0.7	5.3 ± 0.2
Potassium, mmol/L	4.3 ± 0.4	4.2 ± 0.5	4.3 ± 0.2
Creatinine, µmol/L	84.0 ± 8.1	84.4 ± 7.9	83.7 ± 8.3
Comorbidities			
Coronary artery disease	54 (28%)	28 (29%)	26 (27%)
Cerebrovascular disease	40 (21%)	22 (23%)	18 (19%)
Diabetes Mellitus	45 (23%)	22 (23%)	23 (24%)
Chronic kidney disease	19 (10%)	9 (9%)	10 (10%)
Peripheral artery disease	25 (13%)	12 (13%)	13 (14%)

Table 1. Patient demographic, risk factors, office and ambulatory blood pressure values and clinical characteristics. ABPM ambulatory blood pressure monitoring, SBP systolic blood pressure, DBP diastolic blood pressure, SPC Single pill combination, FC free-combination, PP pulse pressure.

5. DISCUSSION

Despite the existence of effective and affordable antihypertensive treatment, hypertension is not always well detected, treated, or controlled in high-income countries but even less so in low- and middle-income countries (LMICs) (1, 2). JNC8, ESC, and ACC/AHA guidelines agree that for most patients, combination therapy should include angio-

	Baseline (n = 96)	1st month (n = 96)	6th month (n = 94)	p value
Office values				
SBP, mmHg	153.5 ± 11.5	139.4 ± 8.4	131.3 ± 5.4	0.0001
DBP, mmHg	95.3 ± 5.7	84.4 ± 5.9	81.6 ± 6.0	0.0001
PP, mmHg	58.2 ± 10.6	55.0 ± 7.2	49.7 ± 5.7	0.0001
HR, bpm	74.6 ± 6.4	73.5 ± 5.8	74.4 ± 4.9	0.3695
ABPM values				
24-h SBP, mmHg	145.4 ± 8.4	130.3 ± 7.5	124.8 ± 5.4	0.0001
24-h DBP, mmHg	85.7 ± 7.6	79.5 ± 4.4	77.3 ± 4.0	0.0001
24-h PP, mmHg	59.7 ± 7.7	53.0 ± 5.7	50.4 ± 3.3	0.0001
24-h HR, bpm	72.4 ± 6.4	72.5 ± 5.9	72.6 ± 5.0	0.9772
Daytime SBP, mmHg	148.5 ± 9.6	131.7 ± 7.9	128.3 ± 3.7	0.0001
Daytime DBP, mmHg	92.7 ± 6.0	82.9 ± 5.0	78.1 ± 4.1	0.0001
Daytime PP, mmHg	55.8 ± 7.8	52.4 ± 6.5	50.5 ± 3.6	0.0001
Daytime HR, bpm	75.4 ± 6.2	72.5 ± 6.1	73.0 ± 4.5	0.432
Nighttime SBP, mmHg	129.5 ± 9.7	119.3 ± 6.9	115.9 ± 4.2	0.0001
Nighttime DBP, mmHg	76.8 ± 7.7	69.1 ± 4.7	66.2 ± 3.9	0.0001
Nighttime PP, mmHg	52.7 ± 8.7	50.1 ± 5.7	50.2 ± 4.0	0.0074
Nighttime HR, bpm	66.9 ± 6.5	66.1 ± 5.8	67.9 ± 3.6	0.0763

Table 2. Baseline and follow up values of office and AMPB blood pressure in the SPC group. ABPM ambulatory blood pressure monitoring, SBP systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, HR heart rate.

tensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), calcium channel blockers and thiazide diuretic. They further agree that a patient should not take an ACEI and ARB simultaneously (3, 4). Therapy should be escalated at one-month intervals using any of the three accepted strategies.

The International Society of Hypertension 2020 guidelines recommend dual low dose SPCs as the optimal initial treatment for hypertension with the exception of 'low risk grade 1 hypertension or in very old (⩾ 80 years) or frailer patients' who should be considered for monotherapy (3). Similarly, the European Society of Cardiology 2018 guidelines recommend initial therapy with dual combination of ACEI or ARB with CCB or diuretic, preferably as SPC, with the same aforementioned recommendations of monotherapy in certain groups (4). The 2017 American College of Cardiology/American Heart Association guidelines support initiation of dual combination therapy as either separate agents or SPCs in adults with grade 2 hypertension (defined as SBP ⩾ 140mmHg and/or DBP ⩾ 90mmHg) and an average BP > 20/10mmHg above their BP target (5).

Compared with monotherapy, initial combination therapy achieves blood pressure control more quickly with similar tolerability. Although improved adherence to antihypertensive medications is expected to decrease morbidity and mortality. The 2013 ESH/ESC Guidelines favored the use of combinations of two antihypertensive drugs in a single pill, because reducing the number of pills to be taken daily improves adherence and increases the rate of BP control. This recommendation is endorsed by the current ESC 2018 Guidelines (4). First-line treatment with combination therapy has been associated with a significant (34%) risk reduction of cardiovascular events or all-cause death, when compared to those who received delayed combination treatment initiation due to initial monotherapy treatment This was primarily due to the more rapid and effective BP control. Combination therapy is also associated with lower healthcare resource use, which is particularly important for LMICs (6).

Patients with stage 2 hypertension and those with hypertension in the clinical setting of diabetes mellitus, obesity, or chronic renal disease, who constituted the bulk of our study population, have a very high likelihood of requiring multiple agents (7).

There is growing evidence that poor adherence to treatment in addition to physician inertia is the most important cause of poor BP control. Non-adherence to antihypertensive therapy correlates with higher risk of CV events. In order to decrease physician inertia and improve patients' adherence to treatment, several approaches have been proposed.

	Baseline (n = 96)	1st month (n = 96)	6th month (n = 95)	p value
Office values				
SBP, mmHg	154.7 ± 12.8	141.3 ± 7.1	139.2 ± 4.0	0.0001
DBP, mmHg	94.4 ± 5.9	89.3 ± 7.9	86.4 ± 6.0	0.0001
PP, mmHg	60.3 ± 11.9	52.0 ± 7.5	52.8 ± 5.0	0.0001
HR, bpm	74.1 ± 7.6	74.8 ± 6.6	75.0 ± 5.4	0.6123
ABPM values				
24-h SBP, mmHg	144.6 ± 10.6	138.0 ± 7.4	128.4 ± 6.5	0.0001
24-h DBP, mmHg	86.7 ± 6.6	82.1 ± 6.3	79.3 ± 5.0	0.0001
24-h PP, mmHg	57.9 ± 8.6	56.4 ± 6.1	49.3 ± 4.9	0.0001
24-h HR, bpm	79.0 ± 7.9	80.3 ± 6.7	79.8 ± 5.6	0.6853
Daytime SBP, mmHg	147.9 ± 8.8	142.2 ± 5.5	131.2 ± 5.0	0.0001
Daytime DBP, mmHg	91.0 ± 6.7	86.5 ± 5.9	81.6 ± 5.4	0.0001
Daytime PP, mmHg	56.9 ± 7.5	55.6 ± 6.9	49.0 ± 4.4	0.0001
Daytime HR, bpm	81.5 ± 6.5	79.6 ± 5.8	80.7 ± 6.0	0.5674
Nighttime SBP, mmHg	130.2 ± 9.4	126.5 ± 8.4	120.3 ± 7.3	0.0001
Nighttime DBP, mmHg	77.2 ± 6.2	73.6 ± 6.3	71.4 ± 7.9	0.0001
Nighttime PP, mmHg	53.0 ± 7.8	53.5 ± 4.1	49.0 ± 4.5	0.0001
Nighttime HR, bpm	71.0 ± 7.4	70.0 ± 6.3	71.4 ± 5.5	0.8246

Table 3. Baseline and follow up values of office and AMPB blood pressure in the FC group. ABPM ambulatory blood pressure monitoring, SBP systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, HR heart rate.

Educational and training programs seem to improve physician inertia although not as much as expected. On the other hand, improving patients' understanding regarding the goals of BP and the benefits of BP control could improve physician inertia, enhancing patient and physician interaction and collaboration). Current ESH/ESC guidelines encourage the distribution of informative material to both patients and health-related providers in order to inform and to improve motivation and clinical inertia, as well as adherence to treatment. Involving the patient in the assessment and treatment of BP (self-monitoring of blood pressure, self-management with a simple patient-guided system) could further improve BP assessment and control (4, 5, 11-14).

In a retrospective study which enrolled more than 80,000 hypertensive patients, adherence to treatment increased with the decrease in the number of pills prescribed. The use of fixed combinations significantly improves adherence to treatment (by 29%), reducing the risk of non-compliance by 24% relative to the free drug combinations (15). In addition, fixed combination enhances the BP-lowering effect with respect to free drug combinations, decreasing the incidence of adverse events while also lowering the costs of the therapy (16).

Nocturnal hypertension is a common complication of essential hypertension. The definition of nocturnal hypertension is night-time BP ≥120/70 mm Hg (>110/65 mm Hg by the new 2017ACC/AHA guidelines. Abnormal circadian blood pressure patterns associated with elevated sleep blood pressure include nondipping and reverse dipping, both of which are associated with increased target-organ damage and adverse cardiovascular outcomes. ABPM has historically been the gold standard for measuring night-time BP. Nocturnal hypertension can be treated with several approaches that include lifestyle changes, such as sodium restriction and potassium supplementation and pharmacotherapy. In clinical practice, the morning home BP-guided titration of antihypertensive drugs is the first step to achieve perfect 24-hour BP control, which consists of 3 components: lowering 24-hour BP; maintaining a normal circadian rhythm (dipper-type); and suppressing exaggerated BP variability, especially for morning and night-time surges (19, 20).

As discussed above achieving a BP target in most patients of <130/80 mmHg, the majority of patients will require combination therapy. Initial combination therapy is invariably more effective at BP lowering than monotherapy, indeed even low-dose combination therapy is usually more effective than maximal dose monotherapy (17). Furthermore, the combination of medications targeting multiple mechanisms, such as blocking the RAS as well as inducing vasodilatation and/or diuresis, reduces the heterogeneity of the BP response to initial treatment and provides a steeper dose response than is observed with escalating doses of monotherapy (18). Finally, two-drug combinations as initial therapy have been shown to be safe and well tolerated, with no or only a small increase in the risk of hypotensive episodes, even when given to patients with grade 1 hypertension, in which adverse events leading to treatment discontinuation are infrequent (3, 4, 17-20). But, at least, prevention measures in the treatment of hypertension are most important (21-25) and the role of primary health care workers in the family practice have great role (26-36).

6. CONCLUSION

The current ESC and ACC/AHA guidelines favored the use of combinations of two antihypertensive drugs in a single pill, because reducing the number of pills to be taken daily improves adherence and increases the rate of BP control. Treatment with single-pill combinations, is the emerging best practice for safe, effective, rapid, and convenient hypertension control. It improves the availability, affordability, adherence and control of arterial hypertension, which will reflect in reduction of the cardiovascular events and healthcare cost. There is the need to evaluate fixed dose combination in well-designed programs aimed to improve hypertension prevalence and cardiovascular prevention.

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