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 have 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, Amlopidpine/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

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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 24-h, 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 (21.9 vs. 13.1 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. 46.5%, p < 0.05) at month 6 of follow-up. (Figur 1 D).

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-

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**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.

| 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**

| Risk factors | All patients (n = 192) | SPC (n = 96) | FC (n = 96) |
|--------------|------------------------|-------------|-------------|
| 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**

| BP parameter | All patients (n = 192) | SPC (n = 96) | FC (n = 96) |
|--------------|------------------------|-------------|-------------|
| 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     | 59.5 ± 11.3            | 58.2 ± 10.6 | 60.3 ± 11.9 |

| 24-h ABPM values | All patients (n = 192) | SPC (n = 96) | FC (n = 96) |
|------------------|------------------------|-------------|-------------|
| 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**

| Lab parameter | All patients (n = 192) | SPC (n = 96) | FC (n = 96) |
|---------------|------------------------|-------------|-------------|
| 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 | All patients (n = 192) | SPC (n = 96) | FC (n = 96) |
|--------------|------------------------|-------------|-------------|
| 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%)   |
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Table 2. Baseline and follow up values of office and AMPB blood pressure in the SPC group.

|                      | 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  |
| Nighttime SBP, mmHg  | 129.5 ± 9.7       | 119.3 ± 6.9        | 115.9 ± 4.2        | 0.0001  |
| Daytime SBP, mmHg    | 148.5 ± 9.6       | 131.7 ± 7.9        | 128.3 ± 3.7        | 0.0001  |
| Daytime PP, mmHg     | 127.0 ± 6.0       | 82.9 ± 5.0         | 78.1 ± 4.1         | 0.0001  |
| Daytime HR, bpm      | 75.4 ± 6.2        | 72.5 ± 6.1         | 73.0 ± 4.5         | 0.432   |
| Nighttime SBP, mmHg  | 55.8 ± 7.8        | 52.4 ± 6.5         | 50.5 ± 3.6         | 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 3. Baseline and follow up values of office and AMPB blood pressure in the FC group.

|                      | 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        | 579 ± 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  |

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.
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 2017 ACC/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 hypertensive episodes, even when given to patients with grade 1 hypertension, in which adverse events leading to treatment discontinuation are infrequent (5, 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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REFERENCES
1. Geldsetzer P, Manne-Goehler J, Marcus ME et al. The state of hypertension care in 44 low-income and middle-income countries: A cross-sectional study of nationally representative individual-level data from 1.1 million adults. Lancet. 2019; 394: 652-662. doi.org/10.1016/S0140-6736(19)30955-9.
2. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries. Circulation. 2016; 134: 441-450. doi.org/10.1161/CIRCULATIONAHA.115.018912.
3. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75:1334-1357. doi.org/10.1161/HYPERTENSIONAHA.120.15026.
4. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Journal of Hypertension. 2018; 36: 1955-2041. doi.org/10.1097/HJH.0000000000001940.
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/ABC/ACPM/AGS/AGPhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Soc Hypertens. 2018; 12: 579-5713. doi.org/10.1516/jlash.2018.01.004.
6. Bruyn E, Nguyen L, Schutte AE, Murphy A, Perel P, Webster R. Implementing Single-Pill Combination Therapy for Hypertension: A Scoping Review of Key Health System Requirements in 30 Low- and Middle- Income Countries. Global Heart. 2022; 17(1): 6. doi.org/10.1053/j.gh.2018.02.007.
7. Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafuente M. H, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension, 2013; 61(2), 309-318. doi: 10.1161/HYPERTENSIONAHA.112.201566.
8. Salam A, Kanukula R, Atkins E, et al. Efficacy and safety of dual
combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens. 2019; 37(9): 1678-1774.

9. Gargiún J, Saiz LC, Azparren A, et al. First-line combination therapy versus first-line monotherapy for primary hypertension. Cochrane Database Syst Rev. 2017; (1): CD010316.

10. Gradman AH, Parisé H, Lefebvre P, et al. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension. 2013; 61(2): 309-318.

11. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly treated patients: a population-based study in Italy. J Hypertens. 2008 Apr; 26(4): 819-824. doi: 10.1097/ HJH.0b013e3282f4edd7.

12. Gale NK, Greenfield S, Gill P, Gutridge K, Marshall T. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. BMC Fam Pract. 2011 Jun 26; 12: 59. doi:10.1186/1471-2296-12-59.

13. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013 Apr;51(4):766-74. doi:10.1097/ HJH.0b013e3285e2286.

14. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2015 Aug; 62(2): 218-225. doi: 10.1161/HYPERTENSIONAHA.115.00687.

15. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007 Aug; 120(8): 713-719. doi:10.1016/j.amjmed.2006.08.033.

16. Tsiofus K, Kreutz R, Sykara G, van Vugt J, Hassan T. Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature. J Hypertens. 2020 Jun; 38(6): 1016-1028. doi: 10.1097/HJH.0000000000002381.

17. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009 Mar; 122(3): 290-300. doi:10.1016/j.amjmed.2008.09.038.

18. MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M et al. British Hypertension Society Programme of Prevention And Treatment of Hypertension With Algorithm-based Therapy (PATHWAY). Combination Therapy Is Superior to Sequential Monotherapy for the Initial Treatment of Hypertension: A Double-Blind Randomized Controlled Trial. J Am Heart Assoc. 2017 Nov 18; 6(11): e006986. doi:10.1161/JAHA.117.006986.

19. Naser N, Dzubur A, Durak A, Kulic M, Naser N. Blood Pressure Control and ECG Holter Monitoring in Detection of Cardiac Arrhythmias in Patients with Arterial Hypertension. Acta Inform Med. 2022 30(1):69-75. doi:10.5455/aim.2022.30.69-75.

20. Naser N, Pepic E, Avdlic S, The Diagnostic Value of Combined 24-h BP Measurements and Electrocardiogram Holter Monitoring in Detection of Cardiac Arrhythmias in Patients with Arterial Hypertension. Acta Inform Med. 2022 30(1):69-75. doi:10.5455/aim.2022.30.69-75.

21. Naser N, Pepic E, Avdlic S, The Diagnostic Value of Combined 24-h BP Measurements and Electrocardiogram Holter Monitoring in Detection of Cardiac Arrhythmias in Patients with Arterial Hypertension. Acta Inform Med. 2022 30(1):69-75. doi:10.5455/aim.2022.30.69-75.