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Research Article

The treatment of hypertension through Single-Pill Therapy, a present situation in Albania

Zamir DAMANI*

University of Medicine of Tirana, Faculty of Medical Sciences, Department of Diagnostics, QSUT, Tirana, Albania

**Corresponding author: zamird80@yahoo.com*

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Abstract-A significant cause of premature death globally, hypertension affects 1.28 billion adults between the ages of 30 and 79, two-thirds of whom live in low- and middle-income nations. Adults' blood pressure is affected by both controllable and non-modifiable factors. The primary risk factor for cardiovascular illnesses and death worldwide is high blood pressure. Due to poor treatment adherence brought on by its sometimes asymptomatic nature, many people go undetected, untreated, or receive subpar care. For the majority of patients, a two-drug regimen, consisting of either single-pill combos or free-equivalent monotherapy combinations, is advised for beginning hypertension treatment. A calcium channel blocker (CCB) or thiazide/thiazide-like diuretic is typically recommended in conjunction with a RAS blocker (ACE inhibitor or ARB). When compared to monotherapy, single-pill therapy lowers high blood pressure (BP), and this is supported by substantial data. This method reduces adverse drug reactions, enhances patient compliance, and facilitates faster blood pressure regulation. Keeping blood pressure under control is crucial to reducing cardiovascular morbidity and death. The European Society of Hypertension's (ESH) most recent guidelines suggest four major drug classes: beta blockers, thiazide medicines and thiazide-like diuretics, calcium channel blockers (CCBs), and renin-angiotensin-aldosterone system (RAS) blockers.
Albania lacks data regarding the hypertension load in adult populations and has insufficient knowledge of the benefits of single-pill combinations. It usually refers to Eastern Europe's group of states from WHO.

Keywords: Hypertension; Single-Pill Combination, Antihypertensives, ACE Inhibitor.

I. INTRODUCTION

Hypertension, commonly known as high blood pressure (HBP), plays a significant role in the early mortality of adults globally, impacting over 1.28 billion people aged 30 to 79, primarily in low- and middle-income countries (WHO, 2019). HBP elevates the likelihood of both micro- and macrovascular damage, leading to complications such as coronary heart disease, heart failure, strokes, chronic kidney diseases, and peripheral arterial diseases (Sarzani et al., 2022). Alarmingly, around 46% of those exhibiting HBP symptoms are unaware they have this condition, with only 42% obtaining diagnosis and treatment. Merely 1 in 5 adults, or 20%, effectively manage their blood pressure. Furthermore, the prevalence of hypertension among adults

surged from approximately 0.6 billion in 1975 to 1.13 billion in 2015, particularly in low- and middle-income nations, attributed to an increase in risk factors (WHO 2019).

High blood pressure (HBP) is characterized as any reading of 140/90 mmHg or above and is affected by both modifiable and non-modifiable factors. Modifiable risks include poor dietary choices, such as excessive salt intake and diets high in saturated and trans fats; lack of physical activity, smoking, alcohol consumption, and obesity. Environmental factors like air pollution and extreme temperatures also influence hypertension. Non-modifiable risk factors encompass family history, age over 65, and pre-existing health issues like diabetes or kidney disease. The primary goal is to maintain HBP levels under 140/90 mmHg, as elevated readings can lead to headaches, blurred vision, and chest pain. Lifestyle modifications can significantly enhance hypertension management, including adopting a healthy diet, reducing salt consumption, losing weight, engaging in physical activity, and avoiding smoking. (WHO, 2019).

Cardiovascular diseases (CVDs) rank as the top global cause of death (Wacker-Grossman Oberhoffer-Fritz, 2022). The World Health Organization (WHO) reported that in 2019, CVDs accounted for approximately 17.9 million fatalities, or 32% of all deaths worldwide. Most deaths related to CVDs occurred in low- and middle-income countries. CVDs encompass various conditions that affect the heart and blood vessels, including peripheral arterial disease, cerebrovascular disease, coronary heart disease, and pulmonary embolism (Garza, 2018). Many CVDs can be prevented by addressing behavioral and environmental risk factors such as tobacco use, poor diet, obesity, inactivity, harmful alcohol consumption, and air pollution (WHO, 2017). Key behavioral risk factors for heart disease and high blood pressure are commonly recognized and include an unhealthy diet, lack of physical activity, smoking, and excessive alcohol intake. Environmental risk factors play a significant role in the progression of these diseases as well. Government health policies promoting healthy lifestyles, including improving air quality and reducing pollution, are essential for encouraging positive behaviors related to CVDs. Moreover, managing hypertension, diabetes, and elevated blood lipids is crucial for reducing cardiovascular risk and preventing heart attacks and strokes (WHO, 2019).

II. CLINICAL TRIALS ON COMBINED THERAPIES

Hypertension represents a significant global health concern, impacting approximately 25% of the adult population. Among the two principal values, namely Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), SBP is identified as the primary risk factor contributing to morbidity and mortality in individuals at high risk of hypertension-related disease (Kiru et al., 2024). For adults diagnosed with hypertension who require pharmacological intervention, the World Health Organization (WHO) advocates for the employment of combined antihypertensive therapies. To enhance patient adherence, the administration of single-pill combinations is recommended. Antihypertensive medications should be derived from three distinct classes: diuretics (thiazide or thiazide-like agents), Angiotensin-Converting Enzyme (ACE) inhibitors/Angiotensin Receptor Blockers (ARBs), and long-acting calcium channel blockers.

The utilization of single-pill combinations is anticipated to enhance medication adherence, thereby facilitating improved management of hypertension and subsequently promoting health equity. An ideal antihypertensive strategy must take into account cardiovascular risk profiles, preventative measures, comorbidities, and the adherence of individual patients. This approach is supported by evidence-based medicine and randomized controlled trials that have assessed various fixed-dose combinations.

Global health studies focused on hypertension treatment have demonstrated that combination therapy is more effective in reducing blood pressure levels compared to monotherapy, resulting in fewer adverse events. A significant nonrandomized study conducted in Italy, involving 125,635 patients, found that initial treatment with a two-drug combination, whether in a single-pill or free combination format, reduced the risk of mortality by 20% and cardiovascular hospitalization by 16% in comparison to patients receiving monotherapy. Furthermore, combination therapy has the potential to reduce side effects through the use of lower doses of each individual drug.

The comparative analysis of two therapies highlights the efficacy of combined medications from three different drug classes. Several advantages have been identified, including enhanced treatment adherence and persistence among patients, with numerous studies concentrating on single-pill combinations, which complicate evaluations of monotherapy. A meta-analysis review revealed significant findings, such as an increase in adherence rates by 8–14% and a twofold increase in persistence for patients on single-pill combinations compared to those on monotherapy. Simplified dosing regimens have been shown to improve adherence rates by 6–20%.

The benefits associated with improved hypertension management and a reduction in major events outweigh the associated costs. Moreover, combination therapy frequently achieves blood pressure control in a more timely manner. Some modeling studies comparing fixed-dose combinations with monotherapy have not sufficiently addressed this particular issue. A Japanese model indicated that a low-dose combination exhibited greater efficacy and lower treatment costs in contrast to titrated monotherapy.

In comparison to free combinations, single-pill combinations of three antihypertensive medications have been shown to increase treatment adherence; however, less is known about the long-term costs and health implications of these single-pill combinations (Morabito et al., 2024).

The objective of this study was to evaluate the lifetime cost-effectiveness profile of a tri-drug Single-Pill Combination (SPC) comprising a diuretic, a calcium-channel blocker, and an angiotensin-converting enzyme inhibitor in comparison to the corresponding two-pill regimen (a two-drug SPC alongside an independently administered third drug) from the perspective of the Italian healthcare payer (Morabito et al., 2024).
In India, the prevalence of hypertension stands at approximately 30% (28% in rural areas and 34% in urban areas), making it a leading cause of mortality and disability (Kiru et al., 2024). Effective management of this condition often necessitates the use of at least two blood pressure-lowering medications, as monotherapy only achieves optimal control in roughly 30% of patients. Current clinical guidelines advocate for the initiation of combination therapy for most adults, particularly those with conditions that require rapid blood pressure reduction (Kiru et al., 2024). Typical combinations include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) paired with a calcium-channel blocker (CCB) or thiazide diuretic (Kiru et al., 2024). Fixed-dose single-pill combinations (SPCs) have been shown to enhance adherence to treatment regimens and improve blood pressure control's effectiveness when compared to monotherapy or two-pill combinations (Salam et al., 2019; Kiru et al., 2024).
There are several common blood pressure medicines:

- ACE inhibitors (e.g., enalapril, lisinopril),
- ARBs (e.g., losartan, telmisartan),
- calcium channel blockers (e.g., amlodipine, felodipine), and
- diuretics (e.g., hydrochlorothiazide, chlorthalidone)

All help lower blood pressure by relaxing blood vessels or eliminating excess water.

III. FINDINGS AND ANALYSIS

In India, over 300 million individuals are experiencing rising hypertension (Kiru et al., 2024). Recommended single pill combinations (SPCs) consist of three classes: a calcium channel blocker (amlodipine), an ACE inhibitor (perindopril), and a thiazide-like diuretic (indapamide) (Kiru et al., 2024). The trial can identify a 3-mmHg difference in 24-hour ambulatory systolic blood pressure (ASBP) among the groups with 85% power (Kiru et al., 2024).
The WHO recommends initiating pharmacological antihypertensive treatment for anyone with a confirmed hypertension diagnosis and a systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg.

Strong recommendation with moderate to high certainty evidence

WHO recommends antihypertensive treatment for individuals at high cardiovascular risk who do not have cardiovascular disease, including those with diabetes or chronic kidney disease, particularly when their systolic blood pressure is between 130 and 139 mmHg. Both patients and healthcare providers value antihypertensive therapy. Patients emphasize the importance of preventing cardiovascular events, yet some may not seek care, become lost to follow-up, or stick to their treatment plans. Asymptomatic patients might perceive treatment as less valuable unless they grasp the trade-off between short-term side effects and long-term benefits.

Assessment of cardiovascular disease risk as a guideline for initiating antihypertensive medications

Evidence and rationale

The most compelling evidence comes from a meta-analysis by Karmali et al. (2018), which assessed major adverse cardiovascular events (MACE) over five years. This analysis utilized a cardiovascular disease (CVD) risk assessment method that included factors such as age, sex, BMI, blood pressure, antihypertensive treatment, smoking status, diabetes, and history of CVD, comparing it to using blood pressure levels alone. The findings suggested a prevention of 310 MACE incidents per 1,000 individuals over five years, a benefit classified as moderate-to-large by the Guideline Development Group (GDG) (WHO, guideline, 2021). Consequently, the WHO advises that hypertensive adults should initiate treatment with one of three categories of antihypertensive medications:

1. thiazide and thiazide-like agents
2. angiotensin-converting enzyme inhibitors (ACEs)/angiotensin-receptor blockers (ARBs)
3. long-acting dihydropyridine calcium channel blockers (CCBs).

The appropriate selection of the single-pill FDC based on BP levels and objectives

High-normal blood pressure (BP) and grade 1 hypertension, particularly in patients with low cardiovascular risk, are frequently underdiagnosed and inadequately treated. To avert the advancement of hypertension and lower cardiovascular risk, lifestyle modifications should be the main strategy for these patients. Essential changes encompass reducing sodium intake to less than 5 grams per day, moderating alcohol consumption, boosting fruit and vegetable intake, achieving and maintaining a healthy body weight, exercising regularly, and quitting smoking. With their low cardiovascular risk, patients may benefit from antihypertensive supplements or nutraceuticals that assist in lowering BP, usually without serious side effects, in conjunction with lifestyle adjustments. Although many nutraceuticals do not demonstrate proven advantages, those containing nitrates, such as red beets, exhibit vasodilatory effects and can effectively lower BP. If lifestyle changes and supplements are insufficient, antihypertensive medications, including angiotensin receptor blockers (ARBs) or ACE inhibitors, might be warranted for grade 1 hypertension or high-normal BP when cardiovascular risk escalates, with the goal of achieving a BP below 130/80 mmHg (Sarzani et al., 2022).

Hypertension in patients uncontrolled by monotherapy

The 2018 ESC/ESH Guidelines advocate for the implementation of initial monotherapy in instances of grade 1 hypertension coupled with a low cardiovascular risk factor or in elderly, frail patients. Should monotherapy not suffice in meeting the targeted blood pressure goals, it is advisable to explore alternative pharmacological options that target mechanisms such as renin-angiotensin system (RAS) inhibition, vasodilation, and diuresis. The utilization of a Fixed-Dose Combination (FDC) has been shown to enhance 24-hour blood pressure management and improve patient adherence to prescribed treatments. Moreover, combination therapy involving two drugs has demonstrated greater efficacy relative to monotherapy, even when the latter is administered at double the dosage. Additionally, low-dose combinations are associated with a reduced

incidence of adverse effects in comparison to higher doses of individual agents. The recommended initial choice for FDC consists of either ACE inhibitors or ARBs in conjunction with a calcium channel blocker or diuretic, resulting in four viable fixed-dose combinations (Sarzani et al., 2022).

Table 1. Current single-pill FDC for hypertension and hypertension-dyslipidemia management.

Two-drug single-pill FDC of antihypertensive drugs
ACEi + TD
ACEi + TLD
ACEi + Loop diuretic
ARB + TD
Direct renin inhibitors + TD
ACEi + CCB
ARB + CCB
MRA + TD
MRA + Loop diuretic
Potassium-sparing diuretic + TD
Potassium-sparing diuretic + Loop diuretic
Three-drug single-pill FDC of antihypertensive drugs
ACEi + TLD + CCB (perindopril/indapamide/amlodipine)
ARB + CCB + TD (Olmesartan/amlodipine/hydrochlorothiazide)
FDC of lipid-lowering and antihypertensive drugs
Statin + ACEi + CCB (atorvastatin/perindopril/amlodipine)
Statin + CCB
Statin + ARB

ACEi, Angiotensin-Converting-Enzyme inhibitor; ARB, Angiotensin II type 1 Receptor Antagonist; BB, beta-blocker; CCB, Calcium Channel Blocker; FDC, Fixed-Dose Combination; MRA, mineralocorticoid receptors antagonist; TD, thiazide diuretic; TLD, thiazide-like diuretic.

Combination of single pills and comorbid conditions

High blood pressure and abnormal lipid levels

Dyslipidemia and LDL-C levels are frequently overlooked in hypertensive patients, particularly those at increased cardiovascular risk. Familial hypercholesterolemia, the most severe form of monogenic hyperlipidemia, occurs in about 1 in 250–300 births. Patients are often diagnosed only after experiencing a cardiovascular event. According to the 2019 ESC/EAS Guidelines, achieving an LDL-C target below 70 or 55 mg/dL is necessary, but this goal is rarely met with single-drug therapy. Early detection and combination therapies are essential for reducing cardiovascular risk.

Hypertension and overweight/obesity

The overweight or obese phenotype is commonly seen in clinical settings, impacting around 75% of individuals with essential hypertension. Increased body fat significantly elevates blood pressure through several mechanisms. Overweight or obese patients with hypertension are encouraged to lose weight, although maintaining current weight can also be a practical objective. This phenotype leads to salt and water retention due to elevated activity in the renin-angiotensin system (RAS), decreased levels of natriuretic peptides, and persistent sympathetic overactivity. As blood pressure rises, sodium filtration increases to prevent edema, aligning with the pressure/natriuresis relationship. Therefore, diuretic therapy is essential for managing blood

pressure in these patients, although it may cause hypokalemia if RAS is not blocked, especially considering their high average salt intake of up to 12 g/day. Consequently, blood pressure control in overweight and obese individuals is often inadequate due to these factors and associated comorbidities. In patients with metabolic syndrome, thiazide diuretics (TD) and beta-blockers (BB) can worsen insulin resistance, while ACE inhibitors and angiotensin receptor blockers (ARB) may enhance insulin sensitivity.

IV. CONCLUSIONS

Arterial hypertension represents a predominant cause of cardiovascular disease and mortality on a global scale. Effective and sustained reduction of blood pressure is essential for minimizing individual cardiovascular risk. Fixed-dose combinations of various pharmaceutical classes, which target multiple pathophysiological pathways, serve as vital therapeutic tools that can enhance treatment adherence and facilitate cardiovascular risk management in standard clinical practice. The trial is designed with an 85% power to detect a 3 mmHg difference in 24-hour Ambulatory Systolic Blood Pressure (ASBP) among the groups. In comparison to monotherapy, a two-drug single-pill or free combination has demonstrated a reduction in the risk of death (20%) and cardiovascular hospitalization (16%). Furthermore, combination therapy has the potential to mitigate adverse effects by allowing for the administration of lower doses of each medication.

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