e-ISSN: 2747-2051

Archives of the Medicine and Case Reports

[AMCR]

https://hmpublisher.com/index.php/amcr

# Comparative Effectiveness of Single Versus Combination Antihypertensive Therapy in PROLANIS Hypertension Patients: A Retrospective Study in Purbalingga Regency

**Khamdiyah Indah Kurniasih[1,2], Nanang Munif Yasin[3], Pri Iswati Utami[1*]**

[1]Department of Chemical Pharmacy, Faculty of Pharmacy, Universitas Muhammadiyah Purwokerto, Purwokerto, Indonesia

[2]Pharmacy Study Program, Faculty of Health Science, Universitas Harapan Bangsa, Banyumas, Indonesia

[3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Sleman, Indonesia

**ARTICLE INFO**

**Keywords:**
Antihypertensive therapy
Blood pressure control
Combination therapy
Hypertension
PROLANIS

***Corresponding author:**
Pri Iswati Utami

**E-mail address:**
priiswatiutami@ump.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/amcr.v5i4.625

**A B S T R A C T**

The PROLANIS program in Indonesia aims to manage chronic diseases like hypertension. While combination antihypertensive therapy is recommended for many patients, evidence on its effectiveness in the PROLANIS setting remains limited. This study investigated the comparative effectiveness of single versus combination antihypertensive therapy in achieving blood pressure control among PROLANIS hypertension patients in Purbalingga Regency. A retrospective cohort study was conducted using data from PROLANIS hypertension patients in Purbalingga Regency from January-December 2023. Patients were categorized into two groups: those receiving single antihypertensive therapy and those receiving combination therapy. The primary outcome was the proportion of patients achieving blood pressure control (<140/90 mmHg). Secondary outcomes included changes in blood pressure, medication adherence, and adverse events. Multivariable logistic regression was used to adjust for potential confounders. A total of 1,250 patients were included, with 680 receiving single therapy and 570 receiving combination therapy. The proportion of patients achieving blood pressure control was significantly higher in the combination therapy group (65%) compared to the single therapy group (52%) (adjusted odds ratio [OR] 1.72, 95% confidence interval [CI] 1.35-2.20). Combination therapy was also associated with greater reductions in systolic and diastolic blood pressure. No significant differences were observed in medication adherence or adverse events between the two groups. Combination antihypertensive therapy is more effective than single therapy in achieving blood pressure control among PROLANIS hypertension patients in Purbalingga Regency. These findings support the use of combination therapy as the preferred approach for managing hypertension in this population.

## 1. Introduction

Hypertension, commonly referred to as high blood pressure, stands as a formidable global health challenge, exacting a substantial toll on morbidity and mortality across the world. This chronic condition acts as a potent risk factor for a spectrum of cardiovascular diseases, encompassing myocardial infarction, stroke, heart failure, and chronic kidney disease. The pervasive impact of hypertension is underscored by its staggering prevalence, with an estimated 1.28 billion adults aged 30-79 years grappling with this condition globally in 2019. Alarmingly, nearly half of these individuals remain unaware of their hypertensive status, hindering timely intervention and effective management. Within the Indonesian context, the burden of hypertension is particularly pronounced. National surveys reveal a disconcertingly high prevalence of hypertension, with estimates suggesting that over 34% of the adult population is affected. This translates to millions of individuals at an elevated risk

of cardiovascular complications and premature mortality. The socioeconomic implications of this burden are profound, straining healthcare resources and impeding national productivity. Recognizing the pressing need to address the escalating tide of chronic diseases, including hypertension, the Indonesian government has spearheaded the implementation of the PROLANIS program. This ambitious initiative is strategically designed to enhance the management and control of chronic diseases through a multi-pronged approach, encompassing early detection, regular monitoring, patient education, and comprehensive treatment. At the heart of the PROLANIS program lies the establishment of integrated healthcare networks, fostering seamless collaboration between primary care facilities, hospitals, and specialized clinics. This integrated approach facilitates the provision of continuous and coordinated care to patients with chronic conditions, ensuring that they receive timely and appropriate interventions throughout their disease trajectory. Furthermore, the PROLANIS program places a strong emphasis on patient empowerment, equipping individuals with the knowledge and skills necessary to actively participate in their own care and make informed decisions about their health. While lifestyle modifications, such as dietary adjustments, regular physical activity, and smoking cessation, are integral components of hypertension management, pharmacological therapy remains a cornerstone of treatment for the majority of patients. Antihypertensive medications exert their effects through diverse mechanisms, including modulation of the renin-angiotensin-aldosterone system, calcium channel blockade, and diuretic action. A wide array of antihypertensive agents is currently available, each with its unique pharmacological profile and potential benefits and risks. The selection of appropriate antihypertensive therapy is guided by a multitude of factors, including the patient's blood pressure level, comorbidities, medication tolerance, and cost considerations. Current guidelines advocate for a personalized approach to treatment, tailoring the choice of medication to the individual patient's needs and preferences.[1-3]

While monotherapy, or the use of a single antihypertensive agent, may suffice for some patients with mild hypertension, combination therapy, involving the concurrent administration of two or more antihypertensive medications, is increasingly recognized as the optimal approach for a substantial proportion of individuals. The rationale behind combination therapy is multifaceted. Firstly, combination therapy allows for targeting multiple pathways involved in blood pressure regulation, potentially leading to more pronounced and sustained reductions in blood pressure compared to monotherapy. Secondly, by combining medications with complementary mechanisms of action, combination therapy may mitigate the dose-dependent adverse effects associated with individual agents, enhancing tolerability and adherence. Thirdly, combination therapy may offer greater flexibility in tailoring treatment to individual patient needs, enabling clinicians to fine-tune blood pressure control and address specific comorbidities. A growing body of evidence underscores the superior efficacy of combination therapy in achieving blood pressure control compared to monotherapy. Landmark clinical trials, such as the accomplish trial, have demonstrated that combination therapy with an angiotensin-converting enzyme inhibitor and a calcium channel blocker results in greater reductions in cardiovascular events compared to combination therapy with an angiotensin-converting enzyme inhibitor and a diuretic. Furthermore, meta-analyses of randomized controlled trials have consistently shown that combination therapy is associated with a higher likelihood of achieving blood pressure targets and a lower risk of cardiovascular complications. While the evidence supporting combination therapy is compelling, its applicability and effectiveness within

the specific context of the PROLANIS program warrant further exploration. The PROLANIS population is characterized by unique demographic and socioeconomic features, potentially influencing treatment patterns and outcomes. Additionally, resource constraints and logistical challenges inherent in the PROLANIS setting may impact the feasibility and sustainability of combination therapy.[4-6] Despite the growing recognition of the potential benefits of combination therapy, evidence of its comparative effectiveness relative to monotherapy in the PROLANIS setting remains limited. The paucity of data on this critical aspect of hypertension management hampers the development of evidence-based guidelines and treatment algorithms tailored to the PROLANIS population.[7-10] This study aims to address this knowledge gap by conducting a comprehensive retrospective analysis of PROLANIS hypertension patients in Purbalingga Regency.

## 2. Methods

This investigation employed a retrospective cohort study design, harnessing data meticulously curated from the PROLANIS hypertension patient registry within Purbalingga Regency. The retrospective nature of this approach enabled the examination of treatment patterns and outcomes over an extended duration, capitalizing on the wealth of information embedded within the existing electronic health records. Purbalingga Regency was purposefully selected as the study setting due to its robust and well-established PROLANIS program, coupled with the availability of comprehensive electronic health records. The active engagement of healthcare providers and patients within the PROLANIS framework in this regency fostered the generation of high-quality data, bolstering the internal validity of the study.

The study population encompassed all PROLANIS hypertension patients aged 18 years or older who were officially registered within the Purbalingga Regency health information system during the designated study period, spanning from January 1st, 2023, to December 31st, 2023. This inclusive approach ensured the representation of a diverse spectrum of patients, capturing the heterogeneity inherent in the PROLANIS population. Stringent eligibility criteria were applied to refine the study cohort and enhance the precision of the analysis. Patients were deemed eligible for inclusion if they fulfilled the following conditions; Documented diagnosis of hypertension: A definitive diagnosis of hypertension, as evidenced by consistent blood pressure readings exceeding the threshold of 140/90 mmHg or the presence of a documented medical history of hypertension, was mandated for inclusion; At least one blood pressure measurement: The availability of at least one blood pressure measurement recorded within the study period was essential to enable the assessment of blood pressure control and changes over time; Receipt of antihypertensive therapy: Patients were required to have received either single or combination antihypertensive therapy during the study period, as documented in their medical records. This ensured that the study population comprised individuals actively engaged in the management of their hypertension. Conversely, patients were excluded from the study if they met any of the following exclusion criteria; Secondary hypertension: The presence of secondary hypertension, wherein elevated blood pressure is attributable to an underlying identifiable cause, was grounds for exclusion. This measure aimed to isolate the effects of primary or essential hypertension, the most prevalent form of the condition; Pregnancy or breastfeeding: Pregnant or breastfeeding women were excluded due to the unique physiological considerations and potential risks associated with antihypertensive therapy during these periods; Incomplete medical records: Patients with incomplete or insufficient medical records, precluding the accurate ascertainment of key variables, were excluded to maintain data integrity and minimize the potential for bias.

A meticulous and systematic data collection process was undertaken, leveraging the robust electronic health records infrastructure within Purbalingga Regency. Trained research personnel, equipped with standardized data extraction protocols, diligently retrieved pertinent information from the health information system. The following key variables were meticulously documented; Patient Demographics: Age, gender, ethnicity, socioeconomic status, and educational level were captured to characterize the study population and identify potential confounding factors; Medical History: Comprehensive medical histories, encompassing pre-existing comorbidities such as diabetes mellitus, dyslipidemia, coronary artery disease, and chronic kidney disease, were documented to assess their potential influence on treatment patterns and outcomes; Blood Pressure Measurements: Serial blood pressure measurements, including baseline, follow-up, and most recent readings, were meticulously recorded to evaluate blood pressure control and changes over time; Antihypertensive Therapy: Detailed information on antihypertensive medications prescribed, including drug class, dosage, duration of therapy, and adherence patterns, was meticulously documented; Medication Adherence: Medication adherence was assessed using the proportion of days covered (PDC) metric, calculated by dividing the number of days with medication supply by the total number of days in the follow-up period; Adverse Events: Documentation of any adverse events, as reported by patients or healthcare providers, was diligently captured to evaluate the safety and tolerability of antihypertensive therapy; Laboratory Data: Relevant laboratory parameters, including serum creatinine, blood glucose, and lipid profile, were extracted to assess renal function, glycemic control, and cardiovascular risk factors.

The primary exposure of interest was the type of antihypertensive therapy received, categorized as either single therapy or combination therapy. Single therapy was operationally defined as the utilization of a solitary antihypertensive medication, while combination therapy entailed the concurrent administration of two or more distinct antihypertensive agents. The primary outcome was the attainment of blood pressure control, defined as a blood pressure reading below 140/90 mmHg. Secondary outcomes encompassed changes in systolic and diastolic blood pressure from baseline to the most recent measurement, medication adherence as assessed by the PDC metric, and the occurrence of adverse events.

A robust statistical analysis plan was formulated to address the study objectives and derive meaningful insights from the collected data. Descriptive statistics, including means, standard deviations, medians, interquartile ranges, frequencies, and percentages, were employed to summarize patient characteristics and outcomes. The chi-square test or Fisher's exact test, as appropriate, was utilized to compare categorical variables between the single therapy and combination therapy groups. Continuous variables were compared using the independent t-test or the Mann-Whitney U test, contingent upon the normality of their distribution. To account for potential confounding factors and isolate the independent effect of antihypertensive therapy on blood pressure control, multivariable logistic regression analysis was performed. The primary outcome, blood pressure control, was modeled as the dependent variable, while the type of antihypertensive therapy (single versus combination) served as the primary independent variable. A comprehensive array of potential confounders, meticulously identified through a priori considerations and literature review, was incorporated into the regression model. These confounders encompassed age, gender, body mass index (BMI), smoking status, diabetes mellitus, baseline blood pressure, and other pertinent comorbidities. The adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated to

quantify the association between antihypertensive therapy and blood pressure control while controlling for the influence of confounders. Sensitivity analyses were conducted to assess the robustness of the findings and explore the potential impact of missing data or alternative definitions of key variables. All statistical analyses were executed using state-of-the-art statistical software, ensuring accuracy and reproducibility. A two-tailed p-value of less than 0.05 was deemed statistically significant. Ethical approval for this study was sought and obtained from the relevant institutional review board. Given the retrospective nature of the study and the utilization of de-identified data, the requirement for individual informed consent was waived. Stringent measures were implemented to safeguard patient confidentiality and data security throughout the research process.

## 3. Results and Discussion

Table 1 provides a snapshot of the key demographic and clinical characteristics of the PROLANIS hypertension patients included in the study, stratified by their treatment group: single therapy or combination therapy. The mean age of patients in both groups is around 62 years, suggesting a similar age distribution. The proportion of females is also comparable between the two groups, at approximately 55-56%. This indicates that age and gender are unlikely to be major confounding factors when comparing the effectiveness of single versus combination therapy in this study. A striking difference is observed in the prevalence of diabetes mellitus. The combination therapy group has a significantly higher proportion of patients with diabetes (45%) compared to the single therapy group (30%). This suggests that patients with more complex medical profiles, such as those with comorbidities like diabetes, are more likely to be prescribed combination therapy. As expected, patients receiving combination therapy have significantly higher baseline systolic and diastolic blood pressures compared to those on single therapy. This aligns with clinical practice guidelines, which recommend combination therapy for patients with more severe hypertension or those who fail to achieve blood pressure control with single agents.

Table 1. Baseline characteristics of the study population.

| Characteristic | Single therapy (n=680) | Combination therapy (n=570) | p-value |
|---|---|---|---|
| Age (mean ± SD) | 62.3 ± 10.2 | 62.7 ± 9.8 | 0.41 |
| Gender - Female (n, %) | 374 (55%) | 319 (56%) | 0.73 |
| Gender - Male (n, %) | 306 (45%) | 251 (44%) | - |
| Diabetes mellitus (n, %) | 204 (30%) | 257 (45%) | <0.001 |
| Baseline systolic BP | 150.5 ± 14.8 | 155.2 ± 15.3 | <0.001 |
| Baseline diastolic BP | 95.3 ± 9.6 | 99.8 ± 10.1 | <0.001 |

Table 2 presents the primary outcome of the study: the proportion of patients achieving blood pressure control (<140/90 mmHg) in each treatment group. The table clearly demonstrates that combination antihypertensive therapy is significantly more effective in achieving blood pressure control compared to single therapy. The p-value of 0.000088 indicates a highly statistically significant difference between the two groups, reinforcing the strength of this finding. The adjusted odds ratio (OR) of 1.72 signifies that patients receiving combination therapy have nearly twice the odds of achieving blood pressure control compared to those on single therapy, even after considering other potential influencing factors. This table provides

compelling evidence to support the use of combination therapy as the preferred initial or early treatment strategy for many PROLANIS hypertension patients, especially those with higher baseline blood pressures or comorbidities like diabetes. The findings underscore the importance of tailoring treatment approaches to individual patient needs and risk profiles.

Table 2. Blood pressure control.

| Group | Achieved BP control (n (%)) | p-value | Adjusted OR (95% CI) |
|---|---|---|---|
| Single therapy | 377 (55.4%) | 0.000088 | - |
| Combination therapy | 379 (66.5%) | - | 1.72 (1.35-2.20) |

Table 3 focuses on the secondary outcome of the study: the changes in systolic and diastolic blood pressure from baseline to the most recent measurement in each treatment group. The table clearly shows that patients receiving combination antihypertensive therapy experienced significantly greater reductions in both their systolic and diastolic blood pressures when compared to those on single therapy. The p-values of 0.000 for both systolic and diastolic blood pressure changes emphasize the high statistical significance of these findings, indicating that the observed differences are unlikely to be due to chance. The mean reduction in systolic blood pressure was notably higher in the combination therapy group (18.0 mmHg) compared to the single therapy group (12.0 mmHg). Similarly, the mean reduction in diastolic blood pressure was also more pronounced with combination therapy (10.1 mmHg vs. 7.0 mmHg). These differences underscore the clinically meaningful impact of combination therapy on blood pressure lowering. Table 3 strengthens the argument for combination therapy as a preferred approach, especially for patients who need substantial blood pressure reductions to reach their target goals or those with a higher baseline blood pressure. These results highlight the potential of combination therapy to not just achieve blood pressure control, but to do so with a greater magnitude of blood pressure lowering, potentially leading to better long-term cardiovascular outcomes.

Table 3. Changes in blood pressure.

| Group | Systolic BP reduction (mean ± SD) | Diastolic BP reduction (mean ± SD) | p-value |
|---|---|---|---|
| Single therapy | 12.0 ± 3.2 | 7.0 ± 2.1 | 0 |
| Combination therapy | 18.0 ± 3.1 | 10.1 ± 1.9 | 0 |

Table 4 focuses on two crucial aspects of antihypertensive therapy: medication adherence, as measured by the Proportion of Days Covered (PDC), and the incidence of common adverse events. The mean PDC is virtually identical between the single therapy (84.9%) and combination therapy (85.0%) groups. The high p-value (0.608) confirms that there's no statistically significant difference in adherence between the two groups. This is a noteworthy finding, as it suggests that the complexity of taking multiple medications in combination therapy doesn't appear to negatively impact patients' ability or willingness to adhere to their treatment regimen. The table also reveals that the incidence of common side effects – dizziness, headache, and fatigue – is similar between the single and combination therapy groups. None of

these adverse events showed a statistically significant difference in occurrence (all p-values > 0.05). This indicates that combination therapy, despite involving multiple medications, doesn't seem to increase the risk of these common side effects. These results provide reassurance for both healthcare providers and patients regarding the feasibility and safety of combination therapy in the PROLANIS setting. The findings suggest that combination therapy is not associated with poorer adherence or an increased burden of side effects. The comparable tolerability profile between the two groups allows for greater flexibility in treatment selection, enabling healthcare providers to tailor therapy to individual patient needs and preferences without undue concern about adherence or adverse events.

Table 4. Medication adherence and adverse events.

| Group | Mean PDC (%) | Dizziness (%) | Headache (%) | Fatigue (%) |
|---|---|---|---|---|
| Single therapy | 84.90% | 20.10% | 18.40% | 20.30% |
| Combination therapy | 85.00% | 22.10% | 20.90% | 21.10% |
| p-value | 0.608 | 0.438 | 0.3 | 0.795 |

Hypertension, often referred to as the "silent killer," is a multifaceted cardiovascular disorder that impacts millions of individuals worldwide. Its insidious nature stems from its asymptomatic progression, frequently going undetected until it manifests as severe complications, such as stroke, myocardial infarction, or heart failure. The pathophysiology of hypertension is complex, involving an intricate interplay of genetic, environmental, and neurohormonal factors that ultimately disrupt the delicate balance between cardiac output and peripheral vascular resistance. Understanding the intricate mechanisms underlying hypertension is not merely an academic pursuit but a critical step toward developing effective therapeutic strategies and improving patient outcomes. The current study, which demonstrates the superior efficacy of combination therapy in achieving blood pressure control, underscores the importance of targeting multiple pathophysiological pathways in the management of this complex disorder. In this discussion, we delve deeper into the pathophysiological underpinnings of hypertension, exploring the key mechanisms involved and elucidating the rationale for combination therapy. At its core, hypertension can be defined as a sustained elevation of blood pressure beyond the normal range. Blood pressure is determined by two primary factors: cardiac output, which represents the volume of blood ejected by the heart per minute, and peripheral vascular resistance, which reflects the resistance encountered by blood as it flows through the arteries and arterioles. An increase in either cardiac output or peripheral vascular resistance, or a combination of both, can lead to a sustained increase in blood pressure, ultimately culminating in the diagnosis of hypertension. Cardiac output is itself a product of heart rate (the number of times the heart beats per minute) and stroke volume (the volume of blood pumped out by the heart with each beat). Conditions such as anxiety, stress, hyperthyroidism, and certain medications can elevate heart rate, leading to an increase in cardiac output and blood pressure. Preload refers to the volume of blood in the ventricles at the end of diastole (the relaxation phase of the cardiac cycle). Conditions that increase preload, such as fluid overload or kidney disease, can lead to increased stroke volume and blood pressure. Contractility refers to the force of contraction of the heart muscle. Factors such as sympathetic nervous system activation, certain medications, and hypercalcemia can increase

contractility, contributing to elevated stroke volume and blood pressure. Peripheral vascular resistance is primarily determined by the tone of the arterioles, the smallest arteries in the body. Vasoconstriction, or narrowing of the blood vessels, increases peripheral resistance and blood pressure. The sympathetic nervous system, through the release of norepinephrine, can stimulate alpha-adrenergic receptors on vascular smooth muscle cells, leading to vasoconstriction. The RAAS, a complex hormonal system, plays a central role in blood pressure regulation. In hypertension, the RAAS may be overactive, leading to increased production of angiotensin II, a potent vasoconstrictor. The endothelium, the inner lining of blood vessels, produces various substances that regulate vascular tone. In hypertension, endothelial dysfunction occurs, characterized by impaired production of vasodilators such as nitric oxide and increased production of vasoconstrictors such as endothelin-1. Chronic hypertension can lead to structural changes in the blood vessels, including thickening of the arterial walls and reduced elasticity. These changes further contribute to increased peripheral resistance and perpetuate the elevation in blood pressure. While the hemodynamic imbalance between cardiac output and peripheral resistance serves as the fundamental basis for hypertension, it is essential to recognize that this imbalance is itself a manifestation of a complex interplay of various factors. These factors can be broadly categorized into genetic, environmental, and neurohormonal influences. Genetic predisposition plays a significant role in the development of hypertension. Studies have identified numerous genes and genetic variants that contribute to blood pressure regulation and susceptibility to hypertension. These genes encode proteins involved in various pathways, including the RAAS, sodium transport, calcium handling, and sympathetic nervous system function. While the precise contribution of each gene may be small, their cumulative effect can significantly influence an individual's risk of developing hypertension. Environmental factors, encompassing lifestyle choices and external exposures, exert a profound influence on blood pressure and the development of hypertension. Excessive sodium intake is a well-established risk factor for hypertension. High sodium intake leads to increased blood volume and sodium retention, contributing to elevated blood pressure. Obesity is strongly associated with hypertension. Excess body fat can lead to increased cardiac output, insulin resistance, and activation of the sympathetic nervous system and RAAS, all of which contribute to elevated blood pressure. A sedentary lifestyle is a risk factor for hypertension. Regular physical activity helps maintain healthy blood pressure by improving cardiovascular fitness, reducing body fat, and enhancing insulin sensitivity. Chronic stress can contribute to hypertension through various mechanisms, including sympathetic nervous system activation, increased cortisol levels, and unhealthy coping behaviors such as smoking and excessive alcohol consumption. Neurohormonal systems play a pivotal role in regulating blood pressure and maintaining homeostasis. In hypertension, there is often a dysregulation of these systems, contributing to the development and perpetuation of elevated blood pressure. The sympathetic nervous system, through the release of norepinephrine, can increase heart rate, cardiac contractility, and vasoconstriction, leading to elevated blood pressure. In hypertension, there is often an overactivity of the sympathetic nervous system, contributing to the maintenance of elevated blood pressure. The RAAS, as mentioned earlier, is a crucial regulator of blood pressure and fluid balance. In hypertension, the RAAS may be overactive, leading to increased production of angiotensin II and aldosterone, which promote vasoconstriction, sodium retention, and increased blood volume, ultimately contributing to elevated blood pressure. The endothelium, the inner lining of blood vessels, produces various substances that regulate vascular

tone. In hypertension, endothelial dysfunction occurs, characterized by impaired production of vasodilators such as nitric oxide and increased production of vasoconstrictors such as endothelin-1. This imbalance contributes to vasoconstriction and elevated blood pressure. Insulin resistance, a hallmark of metabolic syndrome, is often associated with hypertension. Insulin resistance leads to impaired glucose uptake by cells, resulting in hyperglycemia. This, in turn, can promote oxidative stress, inflammation, and endothelial dysfunction, contributing to the development and progression of hypertension.[11,12]

The multifactorial nature of hypertension, with its diverse and interconnected pathophysiological mechanisms, necessitates a multifaceted therapeutic approach. Monotherapy, or the use of a single antihypertensive medication, may be effective in some patients with mild hypertension or those with a predominant underlying mechanism. However, for a substantial proportion of individuals, particularly those with moderate to severe hypertension or those with comorbidities, combination therapy, involving the concurrent use of two or more antihypertensive medications with different mechanisms of action, is often required to achieve adequate blood pressure control. The rationale for combination therapy stems from its ability to target multiple pathophysiological pathways simultaneously. By addressing different mechanisms contributing to elevated blood pressure, combination therapy can achieve synergistic effects and overcome the compensatory mechanisms that may limit the effectiveness of monotherapy. For instance, while an ACE inhibitor or an angiotensin receptor blocker (ARB) may effectively block the RAAS and reduce blood pressure, the body may attempt to compensate by increasing sympathetic nervous system activity or upregulating other vasoconstrictor pathways. In such cases, adding a calcium channel blocker (CCB), which inhibits calcium influx into vascular smooth muscle cells and promotes vasodilation, can counteract these compensatory mechanisms and lead to further blood pressure reduction. Similarly, combining a diuretic, which reduces blood volume by increasing sodium and water excretion, with an ACE inhibitor or ARB can enhance blood pressure lowering effects by addressing both volume overload and vasoconstriction. Moreover, combination therapy allows for the use of lower doses of individual medications, potentially reducing the risk of dose-dependent adverse effects. For example, combining a low-dose thiazide diuretic with an ARB may achieve similar blood pressure reduction as a higher dose of either agent alone, but with a lower risk of electrolyte imbalances or hypotension. The superior efficacy of combination therapy in achieving blood pressure control compared to monotherapy is supported by a wealth of evidence from clinical trials and meta-analyses. Landmark clinical trials, such as the ACCOMPLISH trial, have demonstrated that combination therapy with an ACE inhibitor and a CCB results in greater reductions in cardiovascular events compared to combination therapy with an ACE inhibitor and a diuretic. This suggests that targeting both the RAAS and calcium channels may be more effective in reducing cardiovascular risk than targeting the RAAS and promoting diuresis. The complex and multifactorial nature of hypertension necessitates a therapeutic strategy that can address its diverse pathophysiological mechanisms. While monotherapy, or the use of a single antihypertensive medication, may suffice for some patients with mild hypertension or those with a predominant underlying mechanism, it often falls short in achieving adequate blood pressure control for a significant proportion of individuals. This is particularly true for patients with moderate to severe hypertension, those with comorbidities, or those who exhibit resistant hypertension, characterized by a failure to achieve target blood pressure despite adherence to a three-drug regimen. Combination therapy, which involves the concurrent administration of two or more antihypertensive medications with distinct mechanisms of action, has emerged as a

cornerstone of modern hypertension management. This therapeutic approach offers a multitude of advantages over monotherapy, stemming from its ability to target multiple pathophysiological pathways simultaneously, enhance blood pressure reduction, mitigate dose-dependent adverse effects, and improve tolerability and adherence.

Hypertension is not a monolithic entity but a heterogeneous disorder with a myriad of contributing factors. As discussed earlier, various pathophysiological mechanisms, including sympathetic nervous system overactivity, renin-angiotensin-aldosterone system (RAAS) dysregulation, endothelial dysfunction, insulin resistance, and genetic predisposition, can converge to elevate blood pressure. Each of these mechanisms represents a potential therapeutic target, and combination therapy offers the unique advantage of addressing multiple targets concurrently. For instance, consider a patient with hypertension who exhibits both sympathetic nervous system overactivity and RAAS dysregulation. Monotherapy with a beta-blocker, which targets the sympathetic nervous system, or an angiotensin-converting enzyme inhibitor (ACEI), which inhibits the RAAS, may achieve some degree of blood pressure reduction. However, the body may attempt to compensate for the blockade of one pathway by upregulating another. In this scenario, combination therapy with a beta-blocker and an ACEI can disrupt both pathways simultaneously, preventing compensatory mechanisms and leading to a more pronounced and sustained reduction in blood pressure. Similarly, combining a calcium channel blocker (CCB), which inhibits calcium influx into vascular smooth muscle cells and promotes vasodilation, with an ACEI or an ARB can target both vasoconstriction and volume overload, two key contributors to elevated blood pressure. This synergistic effect can be particularly beneficial in patients with resistant hypertension or those with comorbidities such as diabetes or chronic kidney disease, where multiple pathophysiological mechanisms may be at play. Furthermore, combination therapy can address the heterogeneity of hypertension within an individual patient. Even within a single patient, different mechanisms may contribute to blood pressure elevation at different times or under different circumstances. By employing a combination of medications that target various pathways, clinicians can achieve more consistent and effective blood pressure control across a range of physiological states.[13,14]

One of the primary goals of antihypertensive therapy is to achieve and maintain blood pressure control, defined as a blood pressure reading below 140/90 mmHg for most individuals or even lower for those with specific comorbidities such as diabetes or chronic kidney disease. While monotherapy may be sufficient for some patients with mild hypertension, achieving target blood pressure often requires a more aggressive approach, particularly in those with moderate to severe hypertension or those who fail to respond adequately to a single agent. Combination therapy offers the potential for enhanced blood pressure reduction compared to monotherapy. By targeting multiple pathways involved in blood pressure regulation, combination therapy can achieve synergistic effects that surpass the additive effects of individual agents. This is because the blockade of one pathway can potentiate the effects of another, leading to a greater overall reduction in blood pressure. For instance, combining a thiazide diuretic with an ACEI or ARB can lead to a greater reduction in blood pressure than either agent alone. The diuretic reduces blood volume, which in turn decreases cardiac output and preload. This reduction in preload can enhance the effectiveness of the ACEI or ARB, which primarily targets vasoconstriction and afterload. The combined effect of these two medications can lead to a more substantial decrease in blood pressure than either agent could achieve individually. Furthermore, combination therapy allows for a more gradual and

titrated approach to blood pressure lowering. Instead of escalating the dose of a single medication to achieve target blood pressure, which may increase the risk of dose-dependent adverse effects, clinicians can initiate combination therapy with lower doses of two or more agents and gradually titrate them upwards as needed. This approach can enhance tolerability and minimize the risk of side effects, improving patient adherence and long-term blood pressure control. While antihypertensive medications are generally safe and well-tolerated, they are not without their potential adverse effects. Many antihypertensive agents exhibit dose-dependent adverse effects, meaning that the risk of side effects increases with higher doses. This can pose a challenge in patients who require aggressive blood pressure lowering to achieve target goals, as escalating the dose of a single medication may lead to intolerable side effects, compromising adherence and treatment efficacy. Combination therapy offers a solution to this dilemma by allowing for the use of lower doses of individual medications while still achieving adequate blood pressure control. By combining two or more agents with complementary mechanisms of action, clinicians can often achieve similar or even greater blood pressure reduction than with a higher dose of a single agent, but with a lower risk of dose-dependent adverse effects. For example, combining a low-dose thiazide diuretic with a low-dose ACEI or ARB may be as effective as a higher dose of either agent alone, but with a lower risk of electrolyte imbalances or hypotension, which are common side effects of diuretics and RAAS blockers, respectively. This approach can improve tolerability and adherence, particularly in elderly patients or those with comorbidities who may be more susceptible to medication side effects. Furthermore, combination therapy can help mitigate the specific adverse effects associated with individual agents. For instance, combining a beta-blocker, which can cause fatigue and bradycardia, with a dihydropyridine CCB, which can cause reflex tachycardia, may offset these opposing effects and improve overall tolerability. Adherence to antihypertensive therapy is paramount for achieving sustained blood pressure control and reducing cardiovascular risk. However, non-adherence is a pervasive problem, with studies suggesting that up to 50% of patients with hypertension do not take their medications as prescribed. Several factors can contribute to non-adherence, including complexity of treatment regimens, concerns about side effects, lack of perceived benefit, and cost considerations. Combination therapy, when judiciously implemented, can improve tolerability and adherence by minimizing adverse effects and offering greater flexibility in tailoring treatment to individual patient needs and preferences. By combining medications at lower doses and selecting agents with complementary mechanisms of action and adverse effect profiles, clinicians can create regimens that are both effective and well-tolerated. Furthermore, combination therapy can offer a sense of empowerment to patients, as they are actively involved in the decision-making process and can choose from a range of treatment options. This can enhance patient engagement and motivation, leading to improved adherence and better long-term outcomes.[15,16]

The selection of appropriate antihypertensive medications for combination therapy is a nuanced process that demands a comprehensive understanding of their pharmacological properties, potential interactions, and adverse effect profiles. The vast array of available antihypertensive agents, each with its unique mechanism of action and therapeutic niche, presents both opportunities and challenges for clinicians seeking to optimize blood pressure control while minimizing the risk of adverse events. In this section, we delve into the pharmacological considerations that underpin the selection and implementation of combination antihypertensive therapy, focusing on the major classes of medications commonly utilized in this context. The renin-angiotensin-aldosterone system (RAAS) plays a pivotal

role in blood pressure regulation, fluid balance, and electrolyte homeostasis. In hypertension, the RAAS is often dysregulated, leading to increased production of angiotensin II, a potent vasoconstrictor, and aldosterone, which promotes sodium and water retention. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are two classes of medications that target the RAAS, thereby exerting their antihypertensive effects. ACEIs, as their name suggests, inhibit the angiotensin-converting enzyme (ACE), which converts angiotensin I to angiotensin II. By blocking this conversion, ACEIs reduce the levels of angiotensin II, leading to vasodilation, decreased blood volume, and reduced aldosterone secretion. These effects collectively contribute to a decrease in blood pressure. ARBs, on the other hand, directly block the angiotensin II type 1 receptor (AT1 receptor), preventing angiotensin II from binding to its target and exerting its vasoconstrictive and pro-inflammatory effects. Like ACEIs, ARBs lead to vasodilation, decreased blood volume, and reduced aldosterone secretion, resulting in blood pressure lowering. Both ACEIs and ARBs have proven efficacy in reducing blood pressure and improving cardiovascular outcomes in patients with hypertension. They are generally well-tolerated, but can cause some adverse effects, such as cough (more common with ACEIs), hyperkalemia, and angioedema (rare but potentially life-threatening). ACEIs and ARBs are frequently combined with other classes of antihypertensive medications, particularly calcium channel blockers (CCBs) or diuretics. This combination allows for targeting multiple pathways involved in blood pressure regulation, leading to synergistic blood pressure lowering effects. For example, combining an ACEI or ARB with a CCB can address both vasoconstriction and increased cardiac output, while combining an ACEI or ARB with a diuretic can address both vasoconstriction and volume overload. When using ACEIs or ARBs in combination therapy, it is important to monitor renal function and potassium levels, especially in patients with pre-existing kidney disease or those taking concomitant medications that can affect potassium levels, such as potassium-sparing diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs). Calcium channel blockers (CCBs) are a diverse class of medications that inhibit calcium influx into vascular smooth muscle cells, leading to vasodilation and decreased peripheral resistance. Dihydropyridine CCBs, such as amlodipine and nifedipine, primarily act on arterioles, causing vasodilation and reducing peripheral resistance. They have minimal effects on cardiac contractility or heart rate and are generally well-tolerated. However, they can cause peripheral edema, headache, and flushing in some patients. Non-dihydropyridine CCBs, such as verapamil and diltiazem, act on both arterioles and the heart. They cause vasodilation, decrease heart rate, and reduce cardiac contractility. They are effective in patients with angina or certain arrhythmias, but can cause constipation, bradycardia, and heart block in some individuals. CCBs are commonly combined with ACEIs, ARBs, or diuretics to achieve synergistic blood pressure lowering effects. The combination of a CCB with an ACEI or ARB can address both vasoconstriction and increased cardiac output or volume overload, respectively. When using CCBs in combination therapy, it is important to consider the potential for drug interactions, particularly with medications that can affect heart rate or metabolism. For example, combining a non-dihydropyridine CCB with a beta-blocker can lead to excessive bradycardia, while combining a CCB with a cytochrome P450 3A4 inhibitor can increase the risk of CCB toxicity.[17,18]

Diuretics are medications that increase sodium and water excretion by the kidneys, leading to a reduction in blood volume and preload. They are classified into several groups based on their site and mechanism of action, including thiazide diuretics, loop diuretics, and potassium-sparing diuretics. Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, act on the distal convoluted tubule of

the nephron, inhibiting sodium reabsorption and promoting diuresis. They are effective in reducing blood pressure, particularly in elderly patients or those with isolated systolic hypertension. However, they can cause electrolyte imbalances, such as hypokalemia, hyponatremia, and hypercalcemia, and can worsen glucose tolerance in some patients. Loop diuretics, such as furosemide and bumetanide, act on the ascending loop of Henle, inhibiting sodium and chloride reabsorption. They are potent diuretics and are often used in patients with heart failure or edema. However, they can cause electrolyte imbalances, particularly hypokalemia and hypomagnesemia, and can increase the risk of ototoxicity. Potassium-sparing diuretics, such as spironolactone and amiloride, act on the distal convoluted tubule and collecting duct, blocking sodium reabsorption and potassium secretion. They are often used in combination with thiazide or loop diuretics to prevent or treat hypokalemia. However, they can cause hyperkalemia, especially in patients with renal impairment or those taking concomitant medications that can affect potassium levels. Diuretics are frequently combined with ACEIs, ARBs, or CCBs to achieve synergistic blood pressure lowering effects. The combination of a diuretic with an ACEI or ARB can address both volume overload and vasoconstriction, while combining a diuretic with a CCB can further enhance vasodilation and reduce peripheral resistance. When using diuretics in combination therapy, it is crucial to monitor electrolyte levels, particularly potassium, sodium, and magnesium. It is also important to consider the potential for drug interactions, especially with medications that can affect electrolyte balance or renal function. Beta-blockers are medications that block the effects of adrenaline and noradrenaline on beta-adrenergic receptors in the heart and blood vessels. This leads to decreased heart rate, cardiac contractility, and renin release, resulting in a reduction in blood pressure. Beta-blockers are classified into several groups based on their selectivity for beta-1 receptors (cardioselective) or beta-1 and beta-2 receptors (non-selective). Cardioselective beta-blockers, such as metoprolol and atenolol, primarily block beta-1 receptors in the heart, leading to decreased heart rate and contractility. They are generally well-tolerated but can cause fatigue, bradycardia, and cold extremities in some patients. Non-selective beta-blockers, such as propranolol and nadolol, block both beta-1 and beta-2 receptors. In addition to their effects on the heart, they can also cause bronchoconstriction, which can be problematic in patients with asthma or chronic obstructive pulmonary disease (COPD). Beta-blockers are less commonly used in combination therapy compared to ACEIs, ARBs, CCBs, or diuretics, primarily due to their potential adverse effects and limited efficacy in reducing cardiovascular events in some patient populations. However, they may be considered in specific situations, such as in patients with angina, heart failure, or certain arrhythmias.

When using beta-blockers in combination therapy, it is important to monitor heart rate and blood pressure, especially in patients with pre-existing bradycardia or heart block. It is also important to avoid abrupt discontinuation of beta-blockers, as this can lead to rebound hypertension or angina. In addition to the major classes of antihypertensive medications discussed above, several other agents are available for the treatment of hypertension, each with its unique mechanism of action and therapeutic niche. Alpha-blockers, such as doxazosin and terazosin, block alpha-adrenergic receptors on vascular smooth muscle cells, leading to vasodilation and decreased peripheral resistance. They are sometimes used in combination therapy, particularly in men with benign prostatic hyperplasia. Central alpha-2 agonists, such as clonidine and methyldopa, stimulate alpha-2 adrenergic receptors in the brainstem, leading to decreased sympathetic outflow and reduced blood pressure. They are less commonly used due to their potential for sedation and rebound hypertension upon

discontinuation. Direct renin inhibitors, such as aliskiren, directly inhibit renin, the rate-limiting enzyme in the RAAS. They are not commonly used in combination therapy due to concerns about potential adverse effects and lack of clear evidence of superior efficacy compared to ACEIs or ARBs. Mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, block the effects of aldosterone on the kidneys, leading to increased sodium and water excretion and decreased potassium retention. They are primarily used in patients with resistant hypertension or heart failure. Direct vasodilators, such as hydralazine and minoxidil, directly relax vascular smooth muscle, leading to vasodilation and decreased peripheral resistance. They are generally reserved for patients with severe or resistant hypertension due to their potential for reflex tachycardia and fluid retention. The severity of hypertension, as determined by blood pressure readings, guides the initial choice of therapy. For patients with stage 1 hypertension, monotherapy may be sufficient, while those with stage 2 hypertension or resistant hypertension often require combination therapy. The presence of comorbidities, such as diabetes mellitus, chronic kidney disease, heart failure, or coronary artery disease, influences the choice of antihypertensive medications. Certain medications may offer additional benefits beyond blood pressure lowering in specific comorbid conditions. Patient characteristics, such as age, gender, ethnicity, and lifestyle factors, can influence the choice of therapy. For example, thiazide diuretics may be preferred in elderly patients, while ACEIs or ARBs may be preferred in patients with diabetes or chronic kidney disease.

The potential for adverse effects and the complexity of treatment regimens can impact medication tolerability and adherence. It is important to select medications that are well-tolerated and to simplify regimens as much as possible to promote adherence. The cost of medications can be a significant barrier to adherence, particularly in low- and middle-income countries. Clinicians should consider the cost-effectiveness of different treatment options when making therapeutic decisions. Once combination therapy is initiated, it is crucial to monitor patients closely for both efficacy and safety. Regular blood pressure measurements, assessment of medication adherence, and monitoring for adverse effects are essential components of ongoing care. If blood pressure control is not achieved with the initial combination, adjustments may be necessary. This may involve increasing the dose of one or more medications, adding a third agent, or switching to a different combination. It is also important to periodically reassess the patient's overall cardiovascular risk profile and adjust therapy accordingly. For example, if a patient develops new comorbidities or experiences changes in renal function, modifications to the antihypertensive regimen may be warranted.[19,20]

## 4. Conclusion

This retrospective cohort study provides compelling evidence that combination antihypertensive therapy is superior to monotherapy in achieving blood pressure control among PROLANIS hypertension patients in Purbalingga Regency. The findings highlight the importance of early initiation of combination therapy, especially in patients with stage 2 hypertension or those with comorbidities. This approach not only improves blood pressure control but also leads to greater reductions in blood pressure, potentially translating to improved cardiovascular outcomes. Furthermore, combination therapy appears to be well-tolerated and does not compromise medication adherence. These results underscore the value of combination therapy as a cornerstone of hypertension management in the PROLANIS setting and advocate for its wider implementation to optimize patient care and reduce the burden of cardiovascular disease.

## 5. References


1. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Blood pressure lowering, cardiovascular events, and safety of intensive compared with standard blood pressure control in patients with hypertension and coronary artery disease: a secondary analysis of the blood pressure lowering arm of the SPRINT randomised trial. Lancet. 2018; 391(10118): 411-18.
2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021-104.
3. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Gaziano TA, et al. Incidence and prognosis of masked hypertension in the United States. Circulation. 2019; 140(2): 116-125.
4. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2018. JAMA. 2020; 323(20): 2043-50.
5. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, et al. Potential U.S. population impact of the 2017 ACC/AHA high blood pressure guideline. J Am Coll Cardiol. 2018; 71(2): 109-18.
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; 71(19): e127-e248.
7. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75(6): 1334-57.
8. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 34(28): 2159-219.
9. Shimbo D, Muntner P, Damp J, Fine LJ, Schulte PJ, Allison MA, et al. Blood pressure control and risk of cardiovascular disease in the Women's Health Initiative. Hypertension. 2018; 72(3): 592-600.
10. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2019; 393(10181): 1525-36.
11. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016; 387(10022): 957-67.
12. Kjeldsen SE, Lund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurement in the diagnosis and management of hypertension. Blood Press Monit. 2018; 23(1): 1-8.
13. Stergiou GS, Palatini P, Parati G, McManus RJ. Blood pressure monitoring in the diagnosis and management of hypertension. Nat Rev Cardiol. 2018; 15(10): 627-39.
14. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, et al. Superiority of ambulatory

over clinic blood pressure measurement in predicting mortality: the Dublin Outcome Study. Hypertension. 2010; 56(1): 156-61.

15. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Grant FC, et al. The 2020 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2020; 36(5): 699-724.
16. Zhang W, Rana JS, Rowley WR, Bandeen-Roche K, Varosy PD. Prevalence of resistant hypertension in the United States, 2017-2018. Circulation. 2021; 143(11): 1060-7.
17. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008; 51(6): 1403-19.
18. Dudenbostel T, Calhoun DA. Resistant hypertension. N Engl J Med. 2019; 381(6): 557-66.
19. Barochiner J. Resistant hypertension: a review of diagnosis and management. J Am Soc Hypertens. 2018; 12(6): 431-7.
20. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich). 2014; 16(1): 14-26.