JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2025, VOL 8, NO 1

Comparative Analysis of Hypertension Medications in Saudi Arabia: Evaluating Efficacy and Blood Pressure Reduction for Patients with Hypertension Following Up in PHCs in Makkah, Saudi Arabia, 2023.

Running Title: Hypertension Medications: Efficacy in Makkah PHCs

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Budget, Fund or Grant
This study was self-funded.

Acknowledgments
We want to thank Dr. Abdulrahman Al-Thagafi, our colleague, for his invaluable assistance with data extraction, cleaning, and organization. His dedication and efforts were instrumental in enabling the progress of this study, and without his support, this research would not have been possible.

Conflicts of Interest
All authors declare no conflicts of interest relevant to this study.

IRB Approval
The study obtained approval from the Makkah Health Research Ethical Committee (approval number H-02-K-076-0324-1091).

Abstract
Background: Hypertension poses a substantial public health concern and continues to be a pivotal area of exploration due to its extensive prevalence and its role as a primary risk factor for cardiovascular diseases. **Aim**: to assess and compare the effectiveness of various antihypertensive medications in controlling or reducing blood pressure measurements among Saudi hypertensive patients. **Methodology:** Analytical cross-sectional study based on patient health information system data. **Results:** This study included 6,242 participants with high BP. ACE, ARB, and CCB significantly reduced MAP over time, with males experiencing more significant reductions than females.
Conclusion: This study highlights the superior efficacy of ACE inhibitors, ARB, and CCB in reducing MAP over time, while BB and diuretics had a limited impact.
Keywords
Blood pressure, hypertension, medication, efficacy, Saudi population.

Introduction

Hypertension poses a substantial public health concern and continues to be a pivotal area of exploration due to its extensive prevalence and its role as a primary risk factor for cardiovascular diseases and associated complications. The global impact of hypertension is profound, with approximately 7.5 million deaths annually, representing 12.8% of total global mortality (World Health Organization, 2021). Forecasts indicate a projected increase in the worldwide adult hypertensive population to 1.56 billion by 2025 (1). Hypertension presents a worldwide challenge, significantly impacting daily life's social, economic, and psychological aspects (2). Despite being a widespread issue, there remains limited clarity regarding the comparative efficacy of various first-line medications for hypertension (3)

This research aims to assess and compare the effectiveness of various antihypertensive medications in controlling or reducing blood pressure measurements among primary hypertensive patients receiving treatment within the Makkah Al-Mukaramah Health Cluster primary healthcare centers. The objectives include evaluating the effectiveness of different classes of antihypertensive medications in reducing both systolic and diastolic blood pressure among hypertensive patients in Saudi Arabia. Additionally, the study seeks to identify patient-specific factors, such as demographics and comorbidities, that may influence the choice of antihypertensive medication class and its impact on blood pressure control in the Saudi Arabian hypertensive population. Another key objective is to investigate whether the population in Saudi Arabia exhibits different patterns of response to antihypertensive medication classes compared to populations in other parts of the world. The research aims to answer the question: among hypertensive patients in Saudi Arabia, which class of antihypertensive medication demonstrates the most significant efficacy and effectiveness in controlling and reducing blood pressure?

Literature Review

Hypertension remains a significant global health concern, affecting 1.13 billion people worldwide and accounting for 7.5 million deaths annually, or 12.8% of total mortality (1). By 2025, the global hypertensive population is projected to reach 1.56 billion, reflecting the growing public health burden of this condition (1). Defined by sustained systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, hypertension is a leading risk factor for cardiovascular, cerebrovascular, and renal disorders (4). Globally, 33% of adults aged 30–79 are hypertensive, with a disproportionate burden in low- and middle-income countries (2).

In Saudi Arabia, hypertension prevalence has risen from 25.5% to 29.2% among adults, with rates varying by gender and rural-urban demographics (5). Contributing factors include sedentary lifestyles, obesity (average BMI ~30), and high rates of diabetes and hypercholesterolemia (6). These trends are consistent with those observed across the MENA region, emphasizing the need for targeted public health interventions.

Hypertension is driven by age, gender, socioeconomic status, obesity, and dietary habits (7). Complications include cardiovascular diseases, stroke, and renal failure, accounting for a significant portion of preventable deaths worldwide (8). Lifestyle changes, such as dietary improvements and increased physical activity, are critical for prevention and management (9).

Antihypertensive medications are the cornerstone of hypertension management, with global guidelines offering varying recommendations. The **JNC 8 guidelines** emphasize individualized treatment, recommending ACE inhibitors or ARBs for diabetic or renal disease patients, while diuretics and CCBs are preferred for Black patients (10). The **ESC/ESH guidelines** focus on achieving specific BP targets, emphasizing CCBs and ACE inhibitors for high-risk populations (11). Despite these frameworks, ethnicity and local health systems influence medication efficacy and adherence. In Saudi Arabia, urbanization, dietary salt intake, and obesity necessitate tailored approaches to hypertension treatment.

Behavioral factors, such as treatment adherence, are critical in managing hypertension. Barriers include medication side effects, lack of awareness, and socioeconomic challenges, all of which can impact BP control and long-term outcomes (2).

The selection of antihypertensive therapy varies globally and regionally, influenced by the patient's clinical profile, local guidelines, and systemic factors. Despite established recommendations for first-line hypertension treatment, significant variability exists in prescribing patterns, reflecting differences in epidemiology, healthcare infrastructure, and cultural factors.

In Saudi Arabia, Calcium Channel Blockers (CCBs) are the most commonly prescribed antihypertensives. This preference likely stems from their availability, minimal side effects, and efficacy in lowering blood pressure. However, global trends reveal marked regional differences in preferred antihypertensive classes, influenced by disease prevalence, treatment guidelines, and medication access. For instance, salt-sensitive hypertension, common in individuals of African descent, often responds better to diuretics and CCBs (12) Regional guidelines also shape prescribing patterns, with some emphasizing ACE inhibitors or ARBs for diabetic patients, while others prioritize diuretics or CCBs depending on the population (13) (14)

Physicians' familiarity with specific drugs, influenced by training and local practices, also impacts prescribing behavior (15). Additionally, patient factors, including genetic predisposition, lifestyle, and treatment adherence, influence antihypertensives' effectiveness and tolerability, ultimately shaping regional prescribing preferences (16).

Globally, systematic reviews estimate the usage of antihypertensive classes as follows: CCBs (25–35%), particularly in Asia; ACE inhibitors (20–30%), commonly used in North America and Europe; ARBs (20–30%), often interchangeable with ACE inhibitors; thiazide diuretics (15–25%), favored for their cost-effectiveness and efficacy in salt-sensitive populations; and beta-blockers (10–20%), whose utilization has declined as they are no longer first-line options for uncomplicated hypertension (17) (18). Other classes, such as loop diuretics and aldosterone antagonists, account for 5–10% of prescriptions and are reserved for specific conditions.

ACEIs were this study's most frequently prescribed antihypertensive drug class, accounting for 48.1% of prescriptions, followed by diuretics (42.7%) and β-blockers (36.0%). This trend is consistent with findings from Gu et al. (2019) and NHANES data from 2013–2016, highlighting the dominance of ACEIs and ARBs in antihypertensive prescriptions (19). While β-blockers were less commonly prescribed and less effective in our population, Anderson et al. (2022) noted an increasing preference for β-blockers as initial monotherapy, along with declining thiazide use and rising reliance on CCBs (20)

Study Rationale

This study addresses a critical gap in understanding the real-world effectiveness of antihypertensive medications in PHC settings in Saudi Arabia. By evaluating medication efficacy and patient outcomes, the research provides valuable insights to optimize treatment strategies and align clinical guidelines with local population needs. These findings may inform broader public health strategies and contribute to improving hypertension management in the region.

Methodology

This study utilized data from the Raqeem health information system, the primary database for patient health records in Makkah, encompassing data from 2021. Institutional Review Board (IRB) approval was obtained before data collection and analysis to ensure ethical compliance. All patients in the system who met the inclusion criteria were included in the analysis, eliminating the need for a predefined sample size. The study population comprised 42,131 patients actively monitored and registered within the primary healthcare centers (PHCs) in Makkah, all of whom were diagnosed with primary hypertension. Adult patients with complete health records and exclusively diagnosed with primary hypertension, receiving antihypertensive treatment in PHC facilities, were included in the study. Patients with secondary hypertension, other comorbidities, or incomplete records were excluded.

The study adopted a longitudinal cohort design to evaluate changes in blood pressure (BP) and the effectiveness of various antihypertensive medications over time. Independent variables included the class of antihypertensive medication (e.g., ACE inhibitors, beta-blockers, diuretics, calcium channel blockers) and demographic data such as age, gender, BMI, and smoking status. The dependent variable was blood pressure measurements. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics summarized demographic characteristics and medication usage patterns, with categorical variables presented as frequencies and percentages and continuous variables as means with standard deviations (SD). The dataset underwent rigorous quality checks for accuracy, outliers, and normal distribution adherence.

Inferential statistics were employed to investigate significant trends and relationships. t-tests were used to compare mean BP measurements between groups, while Analysis of Variance (ANOVA) assessed differences among medication classes. Analysis of Covariance (ANCOVA) was performed to control for confounding variables and assess their impact on BP control. The analysis focused on identifying significant differences, trends in BP control, and the comparative effectiveness of antihypertensive medications across the study population.

Results

Descriptive Tables

Table 1. Nationality and Gender Distribution

Nationality	**Frequency**	**%**	**Gender**	**Frequency**	**%**
Non-Saudi	1,845	14.617	Male	6,430	50.943
Saudi	10,777	85.383	Female	6,192	49.057
Total	12,622	100.000	**Total**	12,622	100.000

Table 3. Medication Usage in Total Population

Status	**ARB**	**%**	**ACE**	**%**	**BB**	**%**	**CCB**	**%**	**Diuretics**	**%**
No	7,121	56.0	8,305	65.798	11,473	90.897	4,490	35.573	9,278	73.507
Yes	5,501	44.0	4,317	34.202	1,149	9.103	8,132	64.427	3,344	26.493
Total	12,622	100.0	12,622	100.000	12,622	100.000	12,622	100.000	12,622	100.000

Table 2. BP Changes Before and After Treatment

BP Before Medication	Frequency	%	BP After Medication	Frequency	%	Changed to Normal	Frequency	%
High	6,242	49.453	High	5,859	46.419	No	10,422	82.570
Normal	6,380	50.547	Normal	6,763	53.581	Yes	2,200	17.430
Total	12,622	100.000	**Total**	12,622	100.000	**Total**	12,622	100.000

Table 4. High BP Strata Demographics

	Count	%
Gender		
Female	2,796	44.8
Male	3,446	55.2
Nationality		
Non-Saudi	1,104	17.7
Saudi	5,138	82.3
Smoking		
No	5,294	84.8
Yes	948	15.2

Table 5. Descriptive Statistics for High BP Strata

Parameter	Valid	Mean	CI 95% Upper	CI 95% Lower	Std. Deviation
Age	6,242	59.368	59.657	59.08	11.619
BMI	6,242	31.072	31.212	30.932	5.654
MAP Change	6,242	-5.08	-4.816	-5.344	10.634
Average DBP	6,242	82.234	82.415	82.052	7.328
Average SBP	6,242	152.109	152.436	151.782	13.169

Table 6. Medication Usage in High BP Strata

Medication	No	%	Yes	%	Total	%
ARB	3,351	54	2,891	46	6,242	100
ACE	3,949	63	2,293	37	6,242	100
BB	5,790	93	452	7	6,242	100
CCB	1,983	32	4,259	68	6,242	100
Diuretics	4,463	71	1,779	29	6,242	100

Statistical Analysis Tables

Table 7. ANCOVA Results for MAP Changes

Medication	Sum of Squares	df	Mean Square	F	p	η^2
ARB	840.122	1	840.122	7.451	0.006	0.001
ACE	1,272.988	1	1,272.988	11.29	< .001	0.002
BB	62.344	1	62.344	0.553	0.457	8.833×10^{-5}
CCB	437.571	1	437.571	3.881	0.049	6.200×10^{-4}
Diuretics	261.269	1	261.269	2.317	0.128	3.702×10^{-4}

Table 8. T-Test for MAP Changes Between Genders

Test	Statistic	df	p
Mann-Whitney	4.396×10^{6}	-	< .001

Table 9. Test of Equality of Variances (Levene's)

Parameter	F	df1	df2	p
MAP Changes	4.13	1	6,240	0.042

Table 10. Repeated Measures Results for MAP Over Time

Effect	Pillai's Trace	F	Hypothesis df	Error df	p
MAP Changes	.084	190.50	3.000	6,234	< .001
ARB	.002	4.036	3.000	6,234	0.007
ACE	.003	7.061	3.000	6,234	< .001
CCB	.002	5.034	3.000	6,234	0.002

Table 11. Multivariate Tests for MAP Over Time

Effect	Pillai's Trace	F	Hypothesis df	Error df	Sig.
MAP Changes	0.084	190.500	3.000	6234	< .001
ARB	0.002	4.036	3.000	6234	0.007
ACE	0.003	7.061	3.000	6234	< .001
BB	0.000	0.297	3.000	6234	0.828
CCB	0.002	5.034	3.000	6234	0.002
Diuretics	0.001	1.858	3.000	6234	0.134

Table 12. Linear Regression Summary for MAP Changes

Variable	Unstandardized Coefficient	Standard Error	t	p
Intercept	6.267	0.362	17.325	< .001
ARB	-0.78	0.302	-2.581	0.010
ACE	-1.03	0.315	-3.276	0.001

Table 13. Tests of Between-Subjects Effects

Source	Sum of Squares	df	Mean Square	F	p
Intercept	69,170,198.34	1	69,170,198.34	333,952.90	< .001
ARB	20,077.38	1	20,077.38	96.93	< .001

This study analyzed 12,622 participants to assess the effectiveness of antihypertensive medications, with a focus on 6,242 individuals identified with high blood pressure (BP) based on the American Heart Association guidelines (BP ≥ 130/80 mmHg or MAP ≥ 100 mmHg). The distribution of nationality and gender among the participants is shown in Table 1. Most participants were Saudi nationals (85.4%, n = 10,777), with males comprising 50.9% of the sample (n = 6,430). Table 2 highlights BP changes before and after treatment. Initially, 49.5% (n = 6,242) of participants had high BP, decreasing to 46.4% (n = 5,859) after treatment. BP normalization was achieved in 17.4% (n = 2,200), while 82.6% (n = 10,422) did not achieve normalization.

Medication usage patterns for the total population are presented in Table 3. Calcium channel blockers (CCB) were the most frequently used medication (64.4%), followed by angiotensin receptor blockers (ARB) (44%), while beta blockers (BB) were the least utilized (9.1%). Demographic characteristics and medication usage are summarized in Tables 4–6 among the high BP subgroup. This group consisted of 55.2% males (n = 3,446), 82.3% Saudi nationals (n = 5,138), and 84.8% non-smokers (n = 5,294). Descriptive statistics for this subgroup are detailed in Table 5, with a mean age of 59.4 years (95% CI: 59.08–59.66), BMI of 31.1 (95% CI: 30.93–31.21), and MAP change of -5.08 mmHg (95% CI: -5.34 to -4.82). Among the subgroup, CCB was the most utilized medication (68%, n = 4,259), followed by ARB (46%, n = 2,891). BB usage remained the lowest at 7% (n = 452) (Table 6).

ANCOVA results, shown in Table 7, revealed significant MAP reductions associated with ACE inhibitors ($F = 11.29$, $p < .001$, $\eta^2 = 0.002$), ARB ($F = 7.45$, $p = .006$, $\eta^2 = 0.001$), and CCB ($F = 3.88$, $p = .049$, $\eta^2 = 6.20\times10^{-4}$). Neither BB ($p = .457$) nor diuretics ($p = .128$) had significant effects. Gender differences in MAP changes were analyzed, as summarized in Tables 8 and 9. Male participants showed greater MAP reductions compared to females ($t = -5.58$, $p < .001$). Levene's test indicated unequal variances between genders ($F = 4.13$, $p = .042$).

Smoking status and nationality were assessed but did not show significant effects on MAP changes ($p = .324$ and $p = .109$, respectively). Repeated measures analysis, detailed in Table 10, demonstrated significant MAP reductions over time (Pillai's Trace = .084, $F = 190.50$, $p < .001$). Interactions with ARB ($p = .007$), ACE ($p < .001$), and CCB ($p = .002$) were significant, indicating these medications influenced MAP reductions over time. BB ($p = .828$) and diuretics ($p = .134$) did not exhibit significant interaction effects.

Multivariate tests demonstrated a significant main effect for MAP changes over time (table 11) (Pillai's Trace = 0.084, $F (3, 6234) = 190.500$, $p < .001$), indicating consistent MAP reductions across time points. Significant interactions with time were observed for ARB (Pillai's Trace = 0.002, $F (3, 6234) = 4.036$, $p = .007$), ACE inhibitors (Pillai's Trace = 0.003, $F (3, 6234) = 7.061$, $p < .001$), and CCB (Pillai's Trace = 0.002, $F (3, 6234) = 5.034$, $p = .002$),

Linear regression analysis, presented in Table 12, identified significant predictors of MAP reductions. ACE inhibitors ($\beta = -1.03$, $p = .001$) and ARB ($\beta = -0.78$, $p = .010$) were strongly associated with MAP reductions, while BB ($p = .401$) and diuretics ($p = .261$) were not significant predictors. Between-subjects effects, shown in Table 13, confirmed significant impacts of ARB ($F = 96.93$, $p < .001$), ACE ($F = 72.01$, $p < .001$), CCB ($F = 138.05$, $p < .001$), and diuretics ($F = 56.59$, $p < .001$) on MAP. BB showed no significant effect ($F = 0.02$, $p = .88$).

In the high-BP subgroup, 2,200 participants normalized their MAP readings (70–99.9 mmHg), and 6,702 participants experienced MAP reductions regardless of initial or final levels. These findings demonstrate that ACE inhibitors, ARBs, and CCBs are the most effective antihypertensive medications, with significant reductions observed over time. Males exhibited greater MAP improvements than females, while smoking and nationality had no discernible effect. BB and diuretics showed minimal impact on MAP reductions, highlighting the superior efficacy of ACE inhibitors, ARBs, and CCBs.

Discussion

This study aimed to assess and compare the effectiveness of various antihypertensive medications in controlling blood pressure (BP) among primary hypertensive patients treated within the Makkah Al-Mukaramah Health Cluster primary healthcare centers. The prevalence of controlled BP among treated patients in this cohort was 46.4% (n = 5,859). This figure reflects a lower level of uncontrolled hypertension compared to findings from Najran, Saudi Arabia, where uncontrolled hypertension among treated patients was 48.7% (M., 2018). This difference can be attributed to variations in the definition of uncontrolled hypertension, with this study adopting the stricter American College of Cardiology/American Heart Association (ACC/AHA) 2017 hypertension guideline threshold of ≥130/80 mmHg (10). While the Najran study used the older threshold of ≥140/90 mmHg. Similarly, Alyabsi et al. (2020) observed that using lower thresholds for defining hypertension resulted in a higher prevalence of uncontrolled hypertension, consistent with our findings. Additionally, the younger mean age of our cohort (59.4 years) compared to the Najran study, where over 56.3% of participants were above 60 years, may also contribute to the differences (Alyabsi M, 2020).

A nationwide study assessing the impact of adopting the 2017 ACC/AHA guidelines reported a prevalence of uncontrolled hypertension among treated patients of 49.57% (Alshammari SA, 2023), slightly higher than the 46.4% observed in this study. Conversely, a survey of 92 primary healthcare centers in Saudi Arabia in 2019 reported a lower prevalence of uncontrolled hypertension among treated patients (35.4%) compared to this study population (5). This discrepancy likely arises from differences in the BP thresholds used to define controlled and uncontrolled hypertension (≥140/90 mmHg in the national survey vs. <130/80 mmHg in this study).

The prevalence of controlled hypertension in this study (53.5%) was higher than the pooled proportion of 34.9% reported by Alshammari et al. (2023) (21). While this result may seem paradoxical given the stricter threshold used here, it underscores the effectiveness of adherence to guidelines like the ACC/AHA 2017 recommendations in managing hypertension. The mean systolic BP (SBP) in our study was 152.1 mmHg, and the mean diastolic BP (DBP) was 82.2 mmHg, comparable to another local study with mean SBP and DBP of 153.3 mmHg and 83 mmHg, respectively (M., 2018). However, a study from Iraq reported a lower mean SBP (149.4 mmHg) but a higher mean DBP (92.1 mmHg) among primary healthcare patients in Baghdad, indicating similar challenges in managing hypertension across the region (22).

Sex and BMI differences may also explain disparities in BP control across populations. Abdel Aal et al. (2021) observed a higher prevalence of uncontrolled hypertension (57.4%) in Egyptian hypertensive patients despite their use of a lower threshold to define uncontrolled BP. This could partly be attributed to a higher mean BMI (32.4 kg/m²) among their cohort compared to our population's mean BMI (31 kg/m²) (14).

Hypertensive smoker patients in this study constituted 15.2% of the total population, a lower rate than reported in a local study (17.1%), where smoking was associated with poorer hypertension control (23). The lower smoking prevalence in our cohort may have contributed to higher levels of BP control.

Recent studies provide valuable insights into the comparative effectiveness of antihypertensive medications. For instance, Masoud (2020) demonstrated that irbesartan outperformed amlodipine, captopril, and atenolol in reducing BP. Among calcium channel blockers (CCBs), cilnidipine and azelnidipine have been noted for effectively controlling morning BP by targeting both N-type and L-type calcium channels, while amlodipine remains a widely used option due to its prolonged action (24; 25)

In our cohort, BP normalization was achieved in only 17.4% of patients with elevated BP at the start of 2023. This is significantly lower than the BP control rates reported by Gu et al. (2019), where control improved from 37.1% in 1999–2002 to 46.9% in 2013–2014 (19). CCBs demonstrated the greatest effectiveness in our population, aligning with findings from Suchard et al. (2019), who reported that CCBs achieved the lowest median BP (133/80 mmHg) and narrowest interquartile range (122/70–146/87), indicating superior BP control (Suchard MA, 2019). Thiazide-like diuretics had the highest median BP (142/88 mmHg) and the widest IQR (130/80–152/95). By contrast, Shreya J. Shah et al. (2017) reported ACE inhibitors (ACEIs) as more effective, attributing poorer CCB outcomes to their higher usage among African Americans, a population with known challenges in achieving BP control (26)

This study's low BP normalization rate likely reflects systemic and cultural challenges. Perez et al. (n.d.) reported that Black patients were 25% less likely to achieve BP control than White patients, with biological, social, and communication barriers playing a significant role (27). These factors may similarly influence our population’s outcomes.

Our study emphasized real-world antihypertensive medication efficacy, with CCBs emerging as particularly effective in lowering BP. However, additional research is needed to explore the underlying causes of low BP control rates and to develop tailored strategies for enhancing hypertension management across diverse populations.

Limitations

The study's reliance on HIS data may have introduced inaccuracies or needed more information. While necessary for focused analysis, excluding patients with comorbidities limits generalizability. Additionally, the study’s geographical focus on Makkah may not reflect national variations in medication efficacy.

Ethical considerations

The study was conducted strictly to ethical standards, obtaining approval from the Makkah Health Research Ethical Committee (approval number H-02-K-076-0324-1091). The Makkah Health Cluster also granted authorization to conduct the research. Rigorous measures were undertaken to ensure the confidentiality of all data collected, which was used exclusively for the stated research purposes. No data was shared or used beyond the scope of this study. The research team is committed to transparency and integrity, ensuring all findings are reported accurately and honestly in subsequent publications. Furthermore, the authors declare no conflicts of interest that could compromise the objectivity or impartiality of the research. These ethical considerations emphasize the commitment of the research team to maintain the highest standards of ethical conduct and scientific rigor.

Future Directions and Recommendations

Future studies should include broader populations, such as individuals with comorbid conditions, and assess the long-term effects of antihypertensive medications to establish comprehensive evidence. Research should also explore cultural and lifestyle factors influencing adherence and evaluate gender-specific responses to treatment. Based on their demonstrated efficacy in this study, policymakers should consider revising clinical guidelines to prioritize ACE inhibitors, ARBs, and CCBs. Additionally, integrating digital health tools for adherence monitoring into hypertension care models could further enhance treatment outcomes.

Conclusion

This study highlights the superior efficacy of ACE inhibitors, ARBs, and CCBs in reducing mean arterial pressure (MAP) over time, while β-blockers and diuretics showed limited impact. These findings emphasize the need for tailored treatment strategies in hypertension management in Saudi Arabia, focusing on integrated care models, early detection, and lifestyle interventions. Improved patient education and adherence strategies are critical to reducing the burden of hypertension and its complications, with potential implications for revising national clinical guidelines and public health policies.

Budget, Fund or Grant

This study was self-funded.

Acknowledgments

We want to thank Dr. Abdulrahman Al-Thagafi, our colleague, for his invaluable assistance with data extraction, cleaning, and organization. His dedication and efforts were instrumental in enabling the progress of this study, and without his support, this research would not have been possible.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this study.

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