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Research Article

Medication Adherence and Antihypertensive Treatment Intensification on Blood Pressure Control at Bali Mandara Hospital

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ABSTRACT

Controlling blood pressure (BP) in patients with hypertension can reduce cardiovascular events. Efforts to improve BP control include enhancing medication adherence and intensifying antihypertensive treatment. This study aims to analyze the association of adherence and treatment intensification of antihypertensives with therapeutic outcomes among outpatients and assess the role of additional contributing factors. This retrospective cohort study at Bali Mandara Regional Hospital used patient medical records from April 2023 to March 2024. Subjects included outpatients on antihypertensive therapy, meeting inclusion and exclusion criteria. The independent variables were adherence, measured by Medication Possession Ratio, and treatment intensification, assessed based on the Treatment Intensification (TI) score. The dependent variable is a therapeutic outcome, BP, at the end of the study period. This study found a strong relationship between treatment intensification and improved BP control (p<0.05). However, there was no correlation between medication adherence and BP status. Patients with higher TI scores generally achieved better control over their BP. Individuals with TI scores < 0 had a 24 times higher chance of experiencing uncontrolled blood pressure compared to patients with higher TI scores. These findings highlight the critical role of treatment intensification in managing BP effectively.

INTRODUCTION

Hypertension therapy aims to lower arterial blood pressure (BP) and reduce all modifiable risk factors, preventing target organ damage and adverse cardiovascular events (Tasić *et al*., 2020). One approach to achieving optimal blood pressure targets is antihypertensive drug treatment intensification. Treatment intensification is a critical factor in BP control. If the BP target is not achieved with two antihypertensive drugs, a third drug may be added. If three drugs still do not achieve the blood pressure target, with or without contraindications, antihypertensive drugs from other classes may be considered. Healthcare providers should monitor BP or adjust therapy management until the target is achieved (Suhadi *et al*., 2016).

Given that hypertension is a chronic disease with long-term drug treatment, adherence is one crucial aspect to consider (Simatupang *et al*., 2022). Nonadherence to antihypertensive treatment among hypertensive patients is associated with an increased risk of cardiovascular disease (CVD)(Lee *et al*., 2017). Based on these factors, it is necessary to examine adherence and the management of hypertension therapy intensification among outpatients. This study aims to determine the correlation between adherence and treatment intensification on BP targets as therapeutic outcomes. Knowing the correlation between levels of adherence and treatment intensification, there will likely be improvements in the management of hypertension therapy.

The research was conducted in the province of Bali, where the prevalence rate of hypertension is 29.97% (Kemenkes RI, 2018). One of the hospitals that handles many referral and outpatient cases in Bali is Bali Mandara

General Hospital, which is a model of a secondary-level healthcare facility serving as a referral center.

METHODS

This study was conducted using a retrospective cohort design based on medical record data of patients diagnosed primarily with hypertension at RSUD Bali Mandara from April 2023 to March 2024. The inclusion criteria are patients undergoing antihypertensive therapy, aged ≥45 years (an age group vulnerable to hypertension), with none or less than two comorbidities, and attending outpatient visits in ≥3 months. We also excluded patients not prescribed antihypertensive medications throughout the study period.

The independent variables in this study are therapy adherence and treatment intensification level of adherence measured by the Medication Possession Ratio (MPR), which is a ratio of the number of days of medication supply from all prescription refills within a specified time interval. The MPR is calculated by dividing the total number of days the medication was available to the patient during the specified period by the total number of days in that period (Sperber *et al*., 2017). For patients who had either no antihypertensive medication prescriptions filled or just one filled, their MPR was deemed unavailable (Roumie *et al*., 2015). Participants were categorized into two groups based on the MPR value. We defined adherence as an MPR of ≥80% and nonadherence as an MPR of <80%.

Treatment intensification was defined as switching to a different medication in a different therapeutic class within 3 and 6 months after the initial observation of inadequate control, increasing the number of pharmacological classes provided, or increasing the dosage of at least one medication (Selby *et al*., 2009). Several studies on treatment intensification focus on chronic diseases, such as hypertension, diabetes, and hyperlipidemia (Chiu *et al*., 2023; Farnier *et al*., 2022; Fontil *et al*., 2022; Suhadi *et al*., 2013; Tan *et al*., 2023). Suboptimal control of a variety of chronic diseases has been associated with the failure to initiate or intensify treatment in accordance with clinical guidelines (Usherwood, 2024).

Antihypertensive treatment intensification is evaluated using the Standard-Based Method (Rose *et al*., 2009). The qualitative assessment of therapy intensification relies on the Treatment Intensification Score (TI Score). This score is determined by taking the number of visits where medication changes were made, subtracting the number of visits that recorded an increase in blood pressure, and then dividing this result by the total number of clinical visits, as outlined in the formula below (Kim *et al*., 2021a):

$$\frac{\text{(Frequency of observed medication changes – Frequency of predicted medication changes based on given standard)}}{\text{Frequency of clinic visits}}$$

Medication changes were identified as prescription orders for new classes of antihypertensive drugs or increases in dosage, either at a visit where elevated BP was recorded or between that visit and the following one (Fontil *et al*., 2022). The range of the TI score is -1.0 to 1.0. A score of 0 means that for every visit where a rise in blood pressure was noted, treatment was intensified once. A TI score larger than zero means that more visits were made when the treatment was escalated than when the blood pressure rose. On the other hand, a negative score (TI score < 0) means that more visits with elevated blood pressure occur than visits with more intensive therapy or treatment (Levy *et al*., 2016).

The dependent variable in this study is therapy outcome, assessed by BP control. For patients under 65, the target systolic blood pressure (SBP) is ≤130 mmHg, except for patients with chronic kidney disease, where the target SBP is <140 mmHg. The target diastolic blood pressure (DBP) is 70-79 mmHg. For patients 65 years and older, the target SBP is 130-139 mmHg, and the DBP target is 70-79 mmHg (Perhi, 2019). Quantitative analysis was performed using IBM SPSS version 29 for Windows to achieve the research objectives. Univariate analysis was used to examine the characteristics of the study subjects. In contrast, bivariate analysis, specifically the chi-square test, assessed the impact of independent variables on the dependent variable at a 95% confidence level and a significance level of 0.05. This study also employed the prevalence odds ratio (OR) as a measure of association.

RESULTS AND DISCUSSION

Details of patients with hypertension were extracted from patients who had clinical visits from April 2023 to March 2024 (n = 966). A total of 129 patients met the inclusion criteria. Table 1 shows the descriptive characteristics of the patients who met these criteria and their relationship with BP status. 51.2% were male, and 48.8% were female. The number of male and female patients did not differ significantly. The

Table 1. Patient demographics and BP status

Characteristics	Subject (N=129)		BP status		*p*-value
	N	%	Controlled	Uncontrolled	
Gender					0.463
Male	66	51.2	39	28	
Female	63	48.8	40	22	
Age					
45 – 59	60	46.5	32	27	0.274
60 - 69	38	29.5	25	14	
≥ 70	31	24.0	22	9	
Comorbid Status					
With Comorbid	95	73.6	62	32	0.072
Without Comorbid	34	26.4	17	18	
Antihypertensive Therapy					
Monotherapy	62	48.1	43	19	0.097
Dual therapy	52	40.3	26	26	
Triple therapy or more	15	11.6	10	5	

*$p < 0.05$ indicates a significant relationship.

proportion of controlled BP was similar between genders, with 39 males and 40 females having controlled BP. The difference in BP status between genders was not statistically significant (p>0.05).

Based on age, the most common age range was 45 to 59 years, which is categorized as pre-elderly. As age increases, susceptibility to hypertension also increases. The likelihood of developing hypertension rises with age, with nearly three times higher chances in individuals aged 40-55 years (Defianna *et al*., 2021). The difference in BP status across age groups in this study was not statistically significant (p>0.05).

Of the participants, 95 (73.6%) had comorbid conditions, while 34 (26.4%) did not. Among those with comorbidities, 62 had controlled BP, and 32 had uncontrolled BP. In contrast, among those without comorbidities, 17 had controlled BP, and 18 had uncontrolled BP. The association between comorbidity status and BP status was not statistically significant (p>0.05).

The participants were treated with different antihypertensive regimens. 62 (48.1%) of the patients received monotherapy, 52 (40.3%) received dual therapy, and 15 (11.6%) received triple or more therapy. Monotherapy is considered for patients with grade 1 hypertension with low risk (SBP <150 mmHg), patients with high-normal BP (130–139/85–89 mmHg) who have very high cardiovascular risk, and very elderly patients (≥80 years) or frail individuals. In these conditions, a limited reduction in BP is sufficient to achieve the recommended BP target (<130/80 mmHg) (Mancia *et al*., 2019; Perhi, 2019).

Patients on monotherapy received one antihypertensive pill and medication category. Patients on dual and triple therapy received pills in different medication categories. The difference in BP status based on the type of antihypertensive therapy approach did not reach statistical significance (p>0.05). The prescription of antihypertensive drugs refers to the *Formularium Nasional* (*Fornas*). The proportion of the antihypertensive drugs administered is included in Table 2.

As shown in Table 2, the five main classes of antihypertensive drugs routinely recommended are ACE inhibitors (ACEi), angiotensin II receptor blockers (ARB), beta-blockers, calcium channel blockers (CCB), and diuretics. The most commonly prescribed antihypertensive drugs are ARBs and CCBs. Few patients begin treatment with a combination of two medications. The frequently used two-drug combination is the Renin-Angiotensin System (RAS) blocker, such as an ACEi or ARB, combined with a CCB or diuretic. Combining two RAS inhibitors is not recommended (Perhi, 2019). Compared to initial monotherapy, starting treatment with a combination of two medications can effectively avoid therapeutic inertia (Mancia *et al*., 2019). Two-drug therapy outperforms monotherapy for BP control, especially in patients with moderate to severe hypertension (Marinier *et al*., 2019). The predominant second-line drug used is the β-blocker class, with bisoprolol being the most common choice for patients with coronary artery

Table 2. The percentage of antihypertensive medications used by patients compared to the total number of patients

Class	Drug name	Total (%)
ACE inhibitor	Captopril	4.7
	Lisinopril	5.4
	Ramipril	14.7
Angiotensin Receptor Blocker (ARB)	Candesartan	31.8
	Valsartan	15.5
Calcium Channel Blocker (CCB)	Amlodipine	53.5
	Nifedipine (Adalat OROS®)	3.9
α2 receptor antagonist	Clonidine	2.3
β-blocker	Bisoprolol	30.2
	Nebivolol	0.8
	Propranolol	0.8
Diuretics	Hydrochlorothiazide	5.4
	Spironolactone	1.6

Table 3. Medication Possession Ratio (MPR) values based on patient characteristics

Characteristics	Non-adherent (MPR <80%)	Adherent (MPR≥80%)	*p*-value
Gender			
- Male	11	55	0.271
- Female	15	48	
Age			
- 45-59	8	52	0.110
- 60-69	8	30	
- >70	10	21	
Comorbid			
- With Comorbid	17	78	0.337
- Without Comorbid	9	25	
Antihypertensive Therapy			
- Monotherapy	7	55	0.036*
- Dual Therapy	16	36	
- Triple therapy or more	3	12	

*$p < 0.05$ indicates a significant relationship.

disease (CAD) and those with type II diabetes mellitus. Combining β-blockers with diuretics or other drug classes is recommended when there are specific indications, such as angina, post-myocardial infarction (MI), heart failure, or heart rate control (Perhi, 2019). Diuretic drugs are used in patients with comorbid heart conditions.

Medication adherence refers to how closely patients follow their healthcare provider's recommendations regarding the dosage and frequency of prescribed medications (Tang *et al*., 2017). MPR is defined as the proportion of time during which medication supply is available. MPR usually requires at least two refill dates to be calculated (Tang *et al*., 2017; Zhu *et al*., 2014). Adherence to antihypertensive medication was estimated as the cumulative medication adherence. In this study, participants were divided into two groups: the adherent group if MPR ≥80% and the non-adherent group if MPR <80%) (Jung *et al*., 2023; Lee *et al*., 2017). Table 3 displays the results of MPR measurements in patients.

In this study, we found that the proportion of adherent subjects is 103 (79.8%). These findings reflect easy access to healthcare facilities and widespread insurance coverage, which could contribute to adherence. Additionally, outpatient visits provide opportunities to monitor medication effectiveness, address other complaints or side effects, and educate patients about medication adherence. The Medication Possession Ratio (MPR) is a measure of medication compliance. Lower scores indicate that the patient is less compliant with medication therapy (Mathew *et al*., 2018). An MPR exceeding 100% suggests that the patient has taken more medication than

prescribed, while an MPR below one indicates that the patient has taken less medication than required within a specified period (Asamoah-Boaheng *et al*., 2021; Sperber *et al*., 2017).

There is no significant difference between men and women regarding MPR values (p>0.05). Other studies have also indicated no relationship between gender and adherence to antihypertensive medication (Mayefis *et al*., 2022; Pratiwi *et al*., 2024). In several studies, definitive evidence regarding gender differences in adherence to antihypertensive therapy cannot be established (Biffi *et al*., 2020). Similarly, there *is* no significant difference across age groups (p>0.05) or in comorbid status (p>0.05). Overall, gender, age, and comorbid status do not significantly affect patient adherence to antihypertensive medication based on the data obtained.

However, we found that the chi-square test results indicate a significant relationship between the type of antihypertensive therapy and patient adherence levels (p<0.05). The analysis demonstrates that the different antihypertensive treatment types impact patient adherence to their medication regimens. Monotherapy refers to the use of a single antihypertensive medication to manage BP. This traditional approach is easy to administer and monitor, making it a practical option for patients (Zaman *et al.*, 2023). However, the drawback of monotherapy is its limited effectiveness in controlling BP, even at the highest prescribed doses. This finding suggests that monotherapy may not be sufficient for all patients, especially those with more severe hypertension (Egan *et al*., 2022).

According to prior research, patients on multiple medications were observed to have lower chances of adhering to their treatment. This relationship may be linked to the fact that those with polypharmacy and more comorbidities often face challenges in following their medication regimens due to their complexity and the potential for adverse effects from drug interactions. The loss of medication administration time may also result from taking more medications (Kassaw *et al.*, 2024). Both dual and triple-drug combination therapies can be designed using a single-pill approach (or two pills) to minimize the pill burden and promote better adherence. Furthermore, one advantage of triple medication combination therapy is its improved effectiveness compared to standard monotherapy (Zaman *et al.*, 2023).

A meta-analysis confirms that Fixed-Dose Combinations (FDC) are linked to better medication adherence and persistence in patients with hypertension than free-equivalent combinations (Du *et al*., 2018). In some studies, FDC therapy was linked to a significantly reduced risk of composite clinical outcomes, likely due to improved medication adherence. FDCs improve adherence and persistence with antihypertensive treatments among patients who are beginning therapy compared to single-drug therapy (Mazza *et al.*, 2017; Verma *et al*., 2018). In this study, patients receive their medications through multi-pill combinations. The *Fornas* does not currently include antihypertensive drugs in FDC forms. Furthermore, the available FDC do not always align with the specific antihypertensive therapies that physicians might choose for their patients (Wang *et al*., 2015).

The Treatment Intensification (TI) measure has been recognized as the most consistently linked to BP control compared to other commonly used approaches for treatment intensification (Egan *et al.,* 2021; Tang *et al*., 2017). The relationship between the TI score and patients' characteristics is shown in Table 4.

The analysis reveals that gender, age, and comorbid conditions do not significantly impact the TI score (p>0.05), suggesting that these factors do not influence treatment intensification. However, it reveals a significant relationship between the type of antihypertensive therapy and treatment intensification. The Chi-square test result indicates that differences in antihypertensive therapy types significantly impact the TI score (p<0.05). Patients receiving monotherapy have a lower TI score because they are only using one medication. In monotherapy and dual therapy, patients experienced changes to their most recent medication regimen within six months. For their patients, doctors frequently choose monotherapy or a mix of two drug classes, resulting in fewer overall treatment regimen modifications (Siga *et al*., 2019).

As shown in Table 5, there is no association between medication adherence and antihypertensive treatment intensification (p>0.05). The odds ratio (OR=0.632) suggests the adherence group may have lower odds of having a TI score ≥0. However, the wide confidence interval (CI(95%)= 0.189-2.021), which includes the number 1, indicates that there is not substantial evidence to support the existence of this difference in the population (Egbuchulem, 2022; Tenny and Hoffman, 2024). (Egbuchulem, 2022; Tenny and Hoffman, 2024). The average MPR value does not significantly contribute to

Table 4. TI score breakdown by patient characteristic

Patient Characteristics	TI score		*p*-value
	<0	≥0	
Gender			
- Male	53	14	0.992
- Female	49	13	
Age			
- 45-59	49	10	0.571
- 60-69	30	9	
- >70	23	8	
Comorbid			
- With comorbid	73	21	0.519
- Without comorbid	29	6	
Antihypertensive Therapy			
- Monotherapy	49	13	0.021*
- Dual Therapy	45	7	
- Triple therapy or more	8	7	

*$p < 0.05$ indicates a significant relationship.

Table 5. Association between adherence levels and TI score

Adherence Level	TI score		*p* value	OR (95%CI)
	<0	≥0		
Adherence	80	23	0.437	0.632 (0.189-2.021)
Nonadherence	22	4		

*$p < 0.05$ indicates a significant relationship; CI, confidence interval; OR, odds ratio.

Table 6. Relationship between adherence and treatment intensification in BP status

Variable		BP status		*p*-value	OR (95%CI)
		Controlled BP	Uncontrolled BP		
Adherence Level	Adherence	66	37	0.188	1.784 (0.749-4.248)
	Nonadherence	13	13		
TI score	< 0	53	49	0.000*	24.038 (3.142-183.891)
	≥ 0	26	1		

*$p < 0.05$ indicates a significant relationship; CI, confidence interval; OR, odds ratio; TI, treatment intensification.

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hanges in the TI score. These results align with previous study findings, yet providers often overlook or fail to assess adherence when considering treatment intensification (Roumie *et al*., 2015). Other previous research highlights the importance of TI scores relative to medication adherence; our study suggests that TI scores can reflect the performance or attentiveness of physicians (Kim *et al*., 2021a).

The results of cross-tabulating the research data for the independent and dependent variables in Table 6 show no significant relationship between medication adherence and BP status ($p>0.05$). This finding is consistent with several other studies showing that adherence levels have no significant relationship with BP control (Setiawan *et al*., 2024).

In this study, data on pharmacy refills are sourced directly from pharmacies. The pharmacy filling data from the hospital is accessible to clinicians through their electronic health records, including information on prescriptions paid for by cash and insurance. The assessment of adherence to antihypertensive medication in this study was based on prescription records. Consequently, adherence may have been overestimated, since we cannot confirm whether the medication was consumed. Adherence to antihypertensive medication is an essential but underrecognized aspect of the management of hypertension (Kim *et al*., 2021b).

This value indicates that individuals with higher adherence levels have approximately 1.784 times greater odds of experiencing the studied outcome compared to those with lower adherence (OR (95%CI) = 1.784(0.749-4.248)). It suggests a positive trend but does not reflect a strong relationship. The confidence interval (CI) includes 1, indicating that the result is not statistically significant (Tenny and Hoffman, 2024). Since no relationship was found between patient adherence to medication and BP control, more than simply adhering to the medication schedule is required to ensure that patients' BP is well controlled.

The bivariate analysis indicates a highly significant relationship between antihypertensive treatment intensification and BP control (p<0.05). This finding suggests that treatment intensification has a significant impact on BP status. Based on the available data, higher TI scores are associated with better BP control. Specifically, individuals with TI scores <0 had a 24 times higher chance of experiencing uncontrolled blood pressure compared to patients with TI scores ≥0 (OR (95%CI) = 24.038 (3.142-183.891)). This striking difference underscores the importance of TI scores in predicting and improving BP outcomes.

Therefore, increasing TI scores could be an essential strategy for enhancing BP management. Higher TI scores have been linked to improved BP control in follow-up studies of patients with coronary artery disease. A low TI score, which reflects physicians' therapeutic inertia in blood pressure management, was related with an increased risk of recurrent stroke (Kim *et al*., 2021a; Roumie *et al*., 2015). Longer delays in initiating treatment intensification are linked to a higher risk of a composite outcome. This composite outcome is defined as the first occurrence of acute cardiovascular events, MI, stroke, acute heart failure, peripheral vascular disease, or death. The baseline for comparison starts at the lowest time frame (0–1.4 months). Patients with a follow-up time exceeding 2.7 months have a higher risk of the composite outcome. Lower thresholds for increasing SBP are related to a lower risk of the composite outcome. Additionally, shorter intervals before treatment intensification are associated with a reduced risk of cardiovascular events or death (Xu *et al.*, 2015). Furthermore, a recent direct meta-analysis which was limited to 19 trials where adults with hypertension were randomly assigned to a different blood pressure target, found that those assigned to more intensive treatment had a significantly lower risk of major CVD events, MI, and stroke. Additionally, subgroup analysis revealed that a blood pressure target of less than 130/80 mmHg was the best for protecting against CVD (Sakima *et al.*, 2019).

There are limitations to our study. Since this retrospective study relies on medical records to assess treatment history, we cannot access medication data from other healthcare facilities. Information from the patients' medical records at Bali Mandara Hospital is the only source of data used in this study. Consequently, information about a patient receiving care or treatment at other medical institutions, including hospitals or health centers is not included. As a result, there is insufficient information available about the patient's care at other medical facilities, particularly if the same drugs were prescribed there. To address the limitations found in this study, several strategies could enhance the robustness and completeness of future research. Refining data collection methods is essential. Broadening the scope to include information from multiple healthcare facilities will provide a fuller picture of patients' treatment histories.

Additionally, incorporating patient surveys or interviews can offer valuable insights into treatments received outside of the primary healthcare system. Implementing prospective or longitudinal studies could also significantly improve data accuracy. By monitoring treatments and outcomes in real time, these studies can provide a more detailed and current understanding of patient care, thus addressing some of the challenges associated with retrospective analysis.

CONCLUSIONS

This study did not find a significant relationship between medication adherence and blood pressure control. The difference in therapy regimens affects adherence and the TI score. On the other hand, the study revealed a highly significant relationship between treatment intensification and blood pressure control. The data suggest that patients with higher TI scores tend to have better blood pressure control. Individuals with TI scores <0 had a 24 times higher chance of experiencing uncontrolled blood pressure compared to patients with TI scores ≥0. This difference highlights the importance of treatment intensification in achieving optimal blood pressure outcomes. Furthermore, factors such as gender, age, and comorbidities did not significantly impact blood pressure control in this study. It seems that these

variables do not significantly impact the results obtained.

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CONFLICT OF INTEREST

The author states that there are no conflicts of interest.

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