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Association of antihypertensive therapy intensification on blood pressure control and atherosclerotic cardiovascular disease (ASCVD) risk: a retrospective cohort study in Bali, Indonesia

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ABSTRACT

Background: Hypertension is a major ASCVD risk factor, especially among elderly and diabetic patients. Appropriately intensifying antihypertensive therapy may improve blood pressure (BP) control and reduce ASCVD risk.

Objective: This study evaluated the effect of antihypertensive therapy intensification on BP outcomes and 10-year ASCVD risk among hypertensive patients in Bali, Indonesia.

Methods: A retrospective cohort study included hypertensive patients aged 40–74 years receiving outpatient care at regional public hospitals in Bali (January–December 2024). Therapy intensification was assessed using a guideline-based treatment intensification (TI) score; primary outcomes were final BP and estimated 10-year ASCVD risk.

Results: Of 191 patients (median age 62 years; 75.9% with type 2 diabetes mellitus), those with appropriate therapy intensification achieved significantly lower systolic BP than those with inappropriate intensification (122.77 vs. 143.28 mmHg; $p < 0.001$) and were more likely to attain controlled BP (OR = 63.462; 95%CI: 8.017–502.354; $p < 0.001$; estimate based on a small reference cell). Each 0.1-unit increase in the TI score was associated with a 0.35% reduction in estimated ASCVD risk ($p < 0.001$).

Conclusion: Appropriate antihypertensive therapy intensification was associated with significantly better blood pressure control, with a non-significant tendency toward below-target BP among patients receiving appropriate intensification.

Keywords: antihypertensive therapy, ASCVD risk, blood pressure, hypertension, treatment intensification

Introduction

Hypertension is often referred to as the "silent killer" because it is strongly associated with complications such as stroke, heart disease, and kidney failure, which are major global health problems [1,2]. The global burden of hypertension accounts for up to 9.4 million deaths annually and contributes to approximately 7% of all disability cases. High blood pressure is a significant risk factor for both atherosclerotic cardiovascular diseases (ASCVD) and non-atherosclerotic cardiovascular diseases, including coronary artery disease, stroke, and heart failure [3].

According to the WHO Global Report on Hypertension (2023), hypertension is estimated to affect 33% of adults aged 30–79 years worldwide, with prevalence rising substantially with age, reaching approximately 49% among adults aged 50–79 years [4]. In Indonesia, 30.8% of the population has hypertension, with a higher prevalence among the elderly, according to the 2023 Indonesian Health Survey [5]. This condition is further exacerbated by unhealthy lifestyle factors such as smoking, stress, and obesity, posing a serious challenge to the Indonesian healthcare system [6,7].

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Atherosclerosis is a pathological process characterized by lipid accumulation, inflammation, and plaque formation within the arterial walls, which disrupts blood flow and leads to various cardiovascular diseases, including ASCVD [8,9]. Hypertension contributes to the initiation and progression of atherosclerosis by causing endothelial injury, promoting vascular inflammation, and increasing arterial wall stress. These changes accelerate plaque formation and instability, thereby increasing the risk of ASCVD [10,11]. Uncontrolled blood pressure may also lead to left ventricular hypertrophy and vascular remodeling, further elevating the risk of heart failure, arrhythmias, stroke, and sudden cardiac death [12]. Previous studies have shown that adequate blood pressure control can significantly reduce ASCVD risk and slow the progression of atherosclerosis [13,14].

Epidemiological data also demonstrates a strong association between hypertension and ASCVD risk across different populations. Although hypertension is a major risk factor for ASCVD, variations in population size, assessment techniques, and comorbidities may influence estimated risk levels [15–17]. In the United States, individuals with stage 1 hypertension have an average 10-year ASCVD risk of 5.4%, with 16% having a risk ⩾10% [18,19]. In India, 37.8% of individuals with type 2 diabetes mellitus and hypertension are at intermediate risk (10–20%), while 27.9% are at high risk (21–95%) for ASCVD [16]. In Saudi Arabia, 10.4% of the population has a high (⩾20%) average 10-year ASCVD risk, many of whom have hypertension [17].

Intensification of antihypertensive therapy is a proven method for achieving better blood pressure control. It is defined as increasing treatment either by raising the dose or frequency of existing medications or by adding new antihypertensive agents [20–22]. Previous studies have shown that therapy intensification effectively reduces systolic blood pressure and major cardiovascular events, such as recurrent myocardial infarction and stroke [22–25]. However, evidence directly linking therapy intensification to reductions in ASCVD risk remains limited. Most studies have focused on the effects of blood pressure control and medication adherence on cardiovascular outcomes [24–28].

Most previous studies have classified antihypertensive therapy intensification only as a binary outcome (intensified vs. not intensified), without quantifying the degree of appropriateness relative to guideline recommendations, and few have directly linked this measure to a quantitative 10-year ASCVD risk estimate. To date, no study conducted in Indonesia has combined a guideline-based treatment intensification (TI) score with WHO Cardiovascular Disease Risk Chart-based ASCVD estimation among hypertensive patients.

Local data on the effectiveness of therapy intensification in reducing ASCVD risk remain limited, given the high prevalence of hypertension in Indonesia, particularly in Bali, which reaches 21.7% [5]. Therefore, this study aims to examine the impact of intensifying antihypertensive therapy on blood pressure outcomes and ASCVD risk in hypertensive patients treated at regional public hospitals in Bali.

Methods

Research design

This retrospective cohort study was conducted at regional public hospitals in Bali, Indonesia. Ethics approval was obtained from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University (Ethics Approval Letter Reference Number: KE/FK/1807/EC; December 2, 2024). The objective of this study was to assess the effect of antihypertensive therapy intensification on blood pressure outcomes and the projected 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in hypertensive patients.

Population and sample

This study employed a non-probability purposive sampling technique, selecting patients aged 40–74 years with hypertension who met the inclusion and exclusion criteria and received outpatient care between January and December 2024 at regional public hospitals in Bali, Indonesia. The inclusion criteria comprised patients diagnosed with hypertension who had at least three outpatient visits during the study period, to ensure data completeness. The exclusion criteria included hypertensive patients with end-stage renal disease, pregnant patients, individuals with a history of cardiovascular disease, cancer patients, and those with incomplete medical records. Sample selection was performed through a review of medical records to identify patients who met the eligibility criteria.

Instrument

Data extracted from computerized and paper-based medical records included demographic

information (age, sex, weight, height, smoking status), clinical parameters (systolic and diastolic blood pressure), type 2 diabetes mellitus status, lipid profile (total cholesterol), and detailed information on antihypertensive medications received during the study period. Patients' blood pressure was measured during outpatient visits in accordance with standard clinical procedures. Data extraction from medical records was conducted by dedicated data collectors at each site using a standardized data extraction template, with all subsequent data processing performed centrally by the authors according to the same standardized criteria. Given the retrospective nature of the study and the use of de-identified medical records, the ethics committee granted a waiver of individual informed consent.

The assessment of antihypertensive therapy intensification was calculated using a standardized model that compares changes in the antihypertensive therapy regimen, either increasing the dose or frequency of medication or adding a new agent, with the patient's blood pressure, in accordance with established treatment protocols. The therapy intensification (TI) score was calculated using the following formula:

$$\text{TI score} = \frac{(F\_observed - F\_predicted)}{F\_visits}$$

where:

F_observed = frequency of observed medication changes made by the clinician during the observation period

F_predicted = frequency of predicted medication changes based on blood pressure measurements and guideline recommendations (2019 Indonesian Hypertension Consensus)

F_visits = total frequency of clinic visits during the observation period

Observed medication changes refer to the number of antihypertensive drug adjustments made by clinician during the observation period, whereas predicted medication changes refer to the number of therapy adjustments that should have been made based on blood pressure measurements and guideline recommendations. Predicted medication changes were determined according to the 2019 Consensus on Hypertension Management from the Indonesian Hypertension Association, which recommends therapy escalation when target blood pressure is not achieved despite ongoing treatment. The resulting TI score could be either positive (⩾0) or negative (<0). A positive TI score indicates appropriate therapy intensification, meaning that therapy adjustments are consistent with clinical indications. In contrast, a negative TI score reflects inappropriate intensification or clinical inertia, indicating that therapy modifications were less frequent than recommended. Therapy changes included dose escalation, addition of a new antihypertensive drug, or both. Therefore, a patient could receive a therapy modification (e.g., dose increase or addition of a new medication) and still have a negative TI score if the frequency of adjustment was lower than expected based on their blood pressure level [23].

Blood pressure and ASCVD risk scores were the primary outcomes of this study. Patients' blood pressure status was assessed using medical record data obtained during outpatient visits. For each patient, the most recent blood pressure measurements before and after therapy intensification were recorded and used to determine outcomes. Target blood pressure was defined according to age group, based on the 2019 Consensus on Hypertension Management from the Indonesian Hypertension Association. For patients aged 18–64 years, the target was a systolic blood pressure (SBP) of ⩽130 mmHg if tolerated (but not <120 mmHg), and a diastolic blood pressure (DBP) of 70-79 mmHg. For patients aged 65–79 years, the target was an SBP of 130–139 mmHg (if tolerated) and a DBP of 70–79 mmHg. For patients aged ⩾ 80 years, the same target range (SBP 130–139 mmHg and DBP 70–79 mmHg) was applied if tolerated. Patients were categorized into three blood pressure groups: controlled (within the target range), below-target (lower than the target range), and hypertensive (above the therapeutic target) [29]. Assessment of the 10-year ASCVD risk projection was conducted using the World Health Organization (WHO) Cardiovascular Disease Risk Chart for the Southeast Asia Region. The risk calculation incorporated age, sex, systolic blood pressure (SBP), smoking status, diabetes mellitus status, body mass index, and total cholesterol. The most recent SBP value recorded during the observation period was used for ASCVD risk calculation, consistent with the blood pressure data used to determine treatment outcomes. WHO CVD Risk Chart for Southeast Asia provides two validated versions depending on data availability: a lipid-based version utilizing total cholesterol data, and a BMI-based version for settings where lipid data are

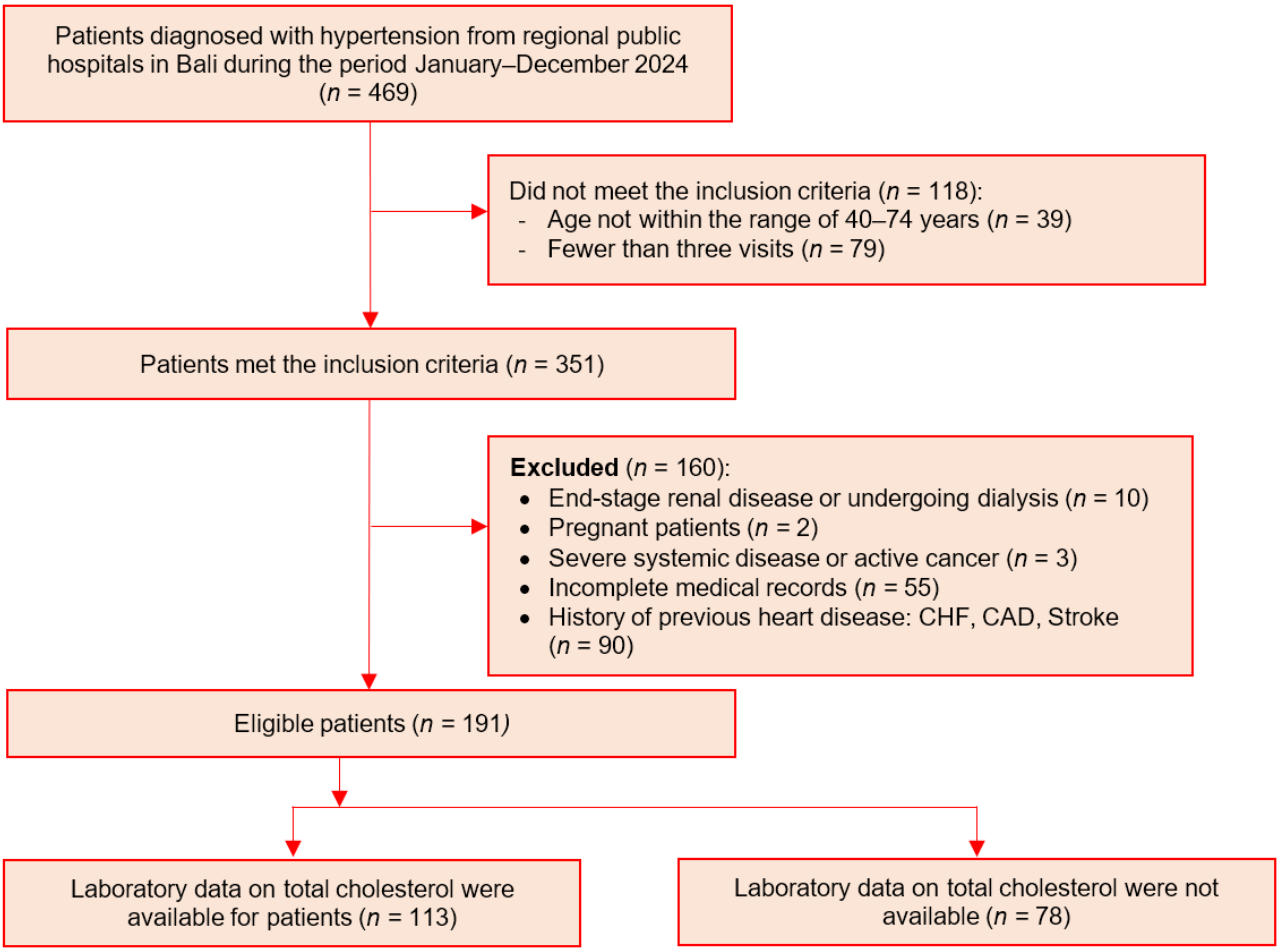

Figure 1. Sample selection flowchart. Patients were screened and selected from regional public hospitals in Bali based on pre-specified inclusion and exclusion criteria, yielding a final analytic cohort of 191 patients from 469 candidates initially screened. CHF: Congestive Heart Failure; CAD: Coronary Artery Disease.

unavailable. In this study, the lipid-based version was applied to patients with available total cholesterol data, while the BMI-based version was used as a validated substitute for patients with incomplete lipid data. Both versions are components of the same WHO risk estimation framework and have been developed for use in resource-limited clinical settings [30].

Analysis

In this study, categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means ± standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Data analysis was conducted using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro-Wilk test. As blood pressure data were not normally distributed, the Mann–Whitney U test was used to compare systolic and diastolic blood pressure between patients who received appropriate and inappropriate treatment intensification. The chi-square test was used to assess the association between treatment intensification and blood pressure category (controlled vs uncontrolled). The strength of this association was expressed as an odds ratio (OR) with a 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. The association between treatment intensification (TI) scores and 10-year ASCVD risk was analyzed using multiple linear regression. Prior to analysis, the assumptions of linearity, normality of residuals, homoscedasticity, and multicollinearity were examined to ensure model validity. Independent variables included TI score, age, smoking status, type 2 diabetes mellitus status, sex, and calculation method (total cholesterol or body mass index), while the ASCVD risk score served as the dependent variable. A p-value <0.05 was considered

Table 1. Baseline characteristics of the study patients with blood pressure outcome

Variables	Total (*N* = 191)	Blood pressure outcome		
		Below-target blood pressure	Controlled blood pressure	Hypertension
Age (year)	62(57 — 62.5); n=191	64(56 — 69); n=39	60(53 — 66); n=41	59.5(51.25 — 66.75); n=111
Sex				
- Male	79(41.36)	20(51.28)	16(39.02)	43(38.74)
- Female	112(58.64)	19(48.72)	25(60.98)	68(61.26)
BMI (kg/m²)	23.83(22.47 — 26.67); n=132	24.44(23.31 — 26.37); n=30	23.25(21.25 — 25.08); n=24	25.72(23.06 — 28.67); n=78
Total cholesterol (mg/dL)	194(170 — 231); n=113	196(171 — 232); n=28	185(156 — 211); n=26	196(168 — 238.5); n=59
Smoking				
- No	171(89.53)	36(92.30)	37(90.25)	98(88.29)
- Yes	20(10.47)	3(7.7)	4(9.76)	13(11.71)
T2DM				
- No	46(24.08)	7(17.95)	14(34.15)	25(22.52)
- Yes	145(75.92)	32(82.05)	27(65.85)	86(77.48)
SBP (mmHg)	139(128 — 150.5); n=191	116(109.5 — 120.5); n=39	129(125 — 135); n=41	154(141.5 — 168.5); n=111
DBP (mmHg)	76(69 — 80); n=191	69(63.25 — 75.75); n=39	72.5(59.75 — 80.25); n=41	78(68 — 90); n=111
TI score	[-0.55] ([-0.83] — [-0.21]); n=191	[-0.23] ([-0.39] — [-0.02]); n=39	[-0.31] ([-0.58] — [-0.09]); n=41	[-0.63] ([-0.82] — [-0.42]); n=111

Values are presented as median (interquartile range) or numbers (%). Blood pressure outcome was classified according to the 2019 Consensus on the Management of Hypertension by the Indonesian Society of Hypertension [29]. BMI, body mass index; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; TI, treatment intensification

statistically significant. Because the observed treatment intensification (TI) score in this cohort had a narrow distribution (see Results), regression-based effect estimates are additionally expressed per clinically-relevant increments (per 0.1-unit change) alongside the per-unit coefficient, to aid clinical interpretation. As ASCVD risk was estimated using two versions of the WHO risk chart depending on data availability (lipid-based vs. BMI-based), calculation method was included as a covariate in the multiple regression model to account for potential differences in risk calibration between the two approaches.

Results

Baseline characteristics

Of the 469 samples, only 191 met the inclusion criteria for this study. The baseline characteristics showed a median age of 62 years (IQR 57–62.5), with a predominance of female patients (58.64%). The relatively narrow interquartile range of the total population age (IQR: 57–62.5 years), despite an eligible age range of 40–74 years, may reflect the purposive sampling method employed in this study, which selected patients based on specific clinical criteria rather than random selection from the eligible population. A total of 132 patients had body mass index (BMI) data, with a median of 23.83 kg/m² (IQR 22.47–26.67), and 113 patients had total cholesterol data, with a median of 194 mg/dL (IQR 170–231). Regarding smoking status, most patients were nonsmokers (89.53%), and 75.92% had type 2 diabetes mellitus (Table 1).

Blood pressure control and treatment intensification

The grouping of patients by blood pressure outcomes showed that 39 patients (20.4%) had blood pressure below target, 41 patients (21.5%) had controlled blood pressure, and 111 patients (58.1%) had hypertension. The median therapy intensification (TI) score was -0.55

Table 2. Comparison of mean blood pressure between appropriate and inappropriate treatment intensification

		Mann-Whitney U Test			Simple Linear Regression			
Variables	**Appropriate Intensification (n = 35)**	**Inappropriate Intensification (n = 156)**	***P*-value**	**95% CI**	**R**	**R Square**	**B (Coefficient)**	**Regression *P*-value**
Systolic blood pressure (mmHg)	122.77 ± 9.49	143.28 ± 18.05	**<0.001**	−24.79 to −16.23	0.622	0.387	-31.629	**<0.001**
Diastolic blood pressure (mmHg)	72.94 ± 9.79	76.38 ± 15.39	0.208	−8.80 to 1.93	0.240	0.058	-9.576	**0.001**

Values are presented as mean and standard deviation. Bolds indicate significance at the α = 0.05 level. CI, confidence interval. The 95% CI for the mean difference is derived from the independent-samples comparison and is reported alongside the Mann-Whitney U test result for descriptive purposes.

Table 3. Distribution of types of antihypertensive therapy intensification among study participants

Type of therapy intensification	**Appropriate intensification (TI ≥ 0)**	**Inappropriate intensification (TI < 0)**	**Total**
Dose escalation only	3 (8.6)	15 (9.6)	18 (9.4)
Addition of new drug only	27 (77.1)	17 (10.9)	44 (23)
Both dose escalation and addition	5 (14.3)	9 (5.8)	14 (7.3)
No change in therapy (clinical inertia)	0 (0)	115 (73.7)	115 (60.2)
Total	35 (100)	156 (100)	191 (100)

Values are presented as numbers (%).

(IQR -0.83 to -0.21), with the lowest negative score in the below-target blood pressure group (-0.23) and the highest negative score in the hypertensive group (-0.63) (Table 1).

As shown in Table 2, patients who received appropriate antihypertensive therapy intensification had significantly lower final systolic blood pressure (SBP) than those who received inappropriate antihypertensive therapy intensification ($p < 0.001$; 95% CI: −24.79 to −16.23). The mean SBP in the appropriately intensified group was 122.77 mmHg, compared with 143.28 mmHg in the inappropriately intensified group, resulting in a mean difference of 20.51 mmHg. For diastolic blood pressure (DBP), the appropriately intensified group also showed a lower mean value by 3.44 mmHg; however, this difference was not statistically significant ($p = 0.208$; 95% CI: −8.80 to 1.93).

Table 3 shows the distribution of antihypertensive therapy intensification among study participants. Of the 191 patients included in this study, 35 experienced appropriate treatment intensification (TI ⩾ 0), whereas 156 showed inappropriate intensification or clinical inertia (TI < 0). Among patients who received appropriate intensification, the addition of a new antihypertensive drug was the most common adjustment (77.1%), followed by both dose escalation and addition (14.3%), and dose escalation only (8.6%). In contrast, within the inappropriate intensification group, most patients (73.7%) had no change in therapy, reflecting clinical inertia despite uncontrolled blood pressure. Although some patients in the inappropriate intensification group received dose escalation or an additional drug, their TI scores remained negative because the frequency of therapy modification was lower than recommended by guideline targets. A statistically significant relationship was found between the TI score and final blood pressure category ($\chi^2 = 55.721$, df = 2, $p < 0.001$). Among patients receiving appropriate intensification, 54.3% had below-target blood pressure and 42.9% achieved controlled blood pressure, while only 2.9% remained hypertensive. In contrast, among patients with inappropriate intensification, most patients (70.5%) remained hypertensive, 16.7% achieved controlled blood pressure, and 12.8% had

Table 4. Association between treatment intensification and blood pressure category

Final blood pressure category	Appropriate intensification	Inappropriate intensification	Total
Below-target blood pressure	19 (54.3%)	20 (12.8%)	39 (20.4%)
Controlled blood pressure	15 (42.9%)	26 (16.7%)	41 (21.5%)
Hypertension	1 (2.9%)	110 (70.5%)	111 (58.1%)
Total	35 (100%)	156 (100%)	191 (100%)

Chi-Square test (χ^2 = 55.721, df = 2, p < 0.001)

Table 5. Odds ratio (OR) for the association between blood pressure category and treatment intensification

Blood pressure comparison	OR	*P*-value	95% CI
Hypertension vs Controlled blood pressure	63.462	**<0.001**	8.017 to 502.354
Below-target blood pressure vs Controlled blood pressure	1.647	0.273	0.674 to 4.023

Bolds mean significant at α = 0.05 level. OR, odds ratio; CI, confidence interval.

below-target blood pressure. These findings suggest that appropriate therapy intensification is associated with a lower prevalence of hypertension and a higher proportion of patients achieving controlled blood pressure, although it may also increase the likelihood of below-target blood pressure (Table 4).

The odds ratio (OR) analysis showed that patients who received appropriate intensification of antihypertensive therapy were 63.462 times more likely to achieve controlled blood pressure than those who remained hypertensive (OR: 63.462; 95% CI: 8.017–502.354). Patients who received appropriate antihypertensive therapy intensification were also 1.647 times more likely to have blood pressure levels below the recommended therapeutic target; however, this difference was not statistically significant (95% CI: 0.674–4.023; p = 0.273) (Table 5). Because only one patient in the appropriate-intensification group remained hypertensive, this OR estimate is based on a small reference cell and should be interpreted with caution despite its statistical significance, as reflected in the wide 95% confidence interval.

Cardiovascular risk profile

ASCVD risk classification was calculated using two methods—total cholesterol data and BMI— due to the limited data availability. Among the 113 patients with available total cholesterol data, the majority were classified in the 10–20% risk category (n=62), followed by 5–10% (n=26), 20–30% (n=13), <5% (n=10), and ⩾30% (n=2). In this group, the median age increased with higher ASCVD risk categories, ranging from 48.5 years in the <5% risk group to 70 years in the 20–30% risk group. A total of 78 patients had their ASCVD risk calculated using BMI. The distribution was similar to that of the total cholesterol-based group, with the largest proportion in the 5–10% risk category (n=38). Across both ASCVD risk estimation methods, patients in higher risk categories tended to have higher systolic blood pressure, more negative TI scores, and a greater prevalence of type 2 diabetes mellitus (Table 6).

Regression analysis

Simple linear regression analysis showed a significant negative association between the TI score and both SBP and DBP. For SBP, the regression coefficient was -31.629 (p < 0.001) with an R^2 value of 0.387, indicating that antihypertensive therapy intensification accounted for 38.7% of the variance in SBP. Each one-unit increase in the TI score was associated with a 31.63 mmHg decrease in SBP, indicating a substantial clinical impact. For DBP, the regression coefficient was -9.576 (p = 0.001), with an R^2 value of 0.058, indicating that only 5.8% of the variance in DBP was explained by antihypertensive therapy intensification. Each one-unit increase in the TI score was associated with a significant decrease in diastolic blood pressure of 9.58 mmHg. Although this association was statistically significant, its explanatory power for changes in DBP remained limited (Table 2). Given the narrow observed range of TI scores in this cohort, these effects correspond to approximately a 3.16 mmHg decrease in SBP and a 0.96 mmHg decrease in DBP per 0.1-unit increase in the TI score, which better reflects the clinically observed range of therapy intensification.

Table 6. Baseline characteristics of the study patients with ASCVD risk

Variables	Total (N = 191)	ASCVD risk									
		Calculated using total cholesterol data (n=113)					Calculated using BMI data (n=78)				
		<5%	5% to 10%	10% to 20%	20% to 30%	≥30%	<5%	5% to 10%	10% to 20%	20% to 30%	≥30%
Age (yr)	62(57 — 62.5); n=191	48.5(43.25 — 51.25); n=10	58(53.5 — 63); n=26	64.5(60.25 — 68.75); n=62	70(63 — 72); n=13	63(63 — 63); n=2	48(42 — 53); n=9	58(51.5 — 63.5); n=38	65(61 — 68); n=28	60(58 — 65); n=3	-
Sex											
- Male	79(41.36)	2(20)	8(30.77)	34(54.84)	6(46.15)	2(100)	0(0)	8(21.05)	16(57.14)	3(100)	-
- Female	112(58.64)	8(80)	18(69.23)	28(45.16)	7(53.85)	0(0)	9(100)	30(78.95)	12(42.86)	0(0)	-
BMI (kg/m2)	23.83(22.47 — 26.67); n=132	-	24.61(23.28 — 28.91); n=8	24.31(22.84 — 28.05); n=35	25.91(22.66 — 26.57); n=9	23.22(23 — 23.44); n=2	23.53(20.89 — 24.97); n=9	24.05(22.27 — 26.06); n=38	24.91(23.44 — 26.89); n=28	24.22(22.15 — 28.64); n=3	-
Total cholesterol (mg/dL)	194(170 — 231); n=113	175.5(161.75 — 233.75); n=10	187(152.75 — 212.25); n=26	194(168 — 230); n=62	231.5(212.25 — 249.5); n=13	197.5(196.75 — 198.25); n=2	-	-	-	-	-
Smoking											
- No	171(89.53)	10(100)	26(100)	62(100)	13(100)	0(0)	9(100)	32(84.22)	19(67.86)	0(0)	-
- Yes	20(10.47)	0(0)	0(0)	0(0)	0(0)	2(100)	0(0)	6(15.79)	9(32.14)	3(100)	-
T2DM											
- No	46(24.08)	10(100)	16(61.54)	18(29.03)	0(0)	0(0)	1(11.11)	1(2.63)	0(0)	0(0)	
- Yes	145(75.92)	0(0)	10(38.46)	44(70.97)	13(100)	2(100)	8(88.89)	37(97.37)	28(100)	3(100)	
SBP (mmHg)	139(128 — 150.5); n=191	127.5(116.25 — 146.25); n=10	139(128.5 — 154.5); n=26	134(120 — 143); n=62	150.5(135.5 — 163.25); n=13	169.5(165.25 — 173.75); n=2	130(124 — 140); n=9	137.5(129.25 — 152.75); n=38	144(132 — 155.5); n=28	160(158.5 — 171); n=3	-
DBP (mmHg)	76(69 — 80); n=191	80(70 — 88); n=10	76.5(69.75 — 82.25); n=26	67.5(59.25 — 78.75); n=62	66(61 — 70.5); n=13	93.5(88.25 — 98.75); n=2	80(74 — 112); n=9	76.5(70.5 — 84); n=38	78(71.5 — 83.5); n=28	80(77.5 — 95); n=3	-
TI score	[-0.55] ([-0.83] — [-0.21]); n=191	[-0.36] ([-0.66] — [-0.08]); n=10	[-0.57] ([-0.79] — [-0.21]); n=26	[-0.5] ([-0.76] — [-0.31]); n=62	[-0.52] ([-0.70] — [-0.39]); n=13	[-0.94] ([-0.97] — [-0.91]); n=2	[-0.55] ([-0.75] — [-0.29]); n=9	[-0.6] ([-0.82] — [-0.3]); n=38	[-0.36] ([-0.6] — [-0.2]); n=28	[-0.82] ([-0.91] — [-0.7]); n=3	-

Values are presented as median (interquartile range) or numbers (%). ASCVD risk was classified according to the WHO CVD Risk Chart for Southeast Asia [30]. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; TI, treatment intensification

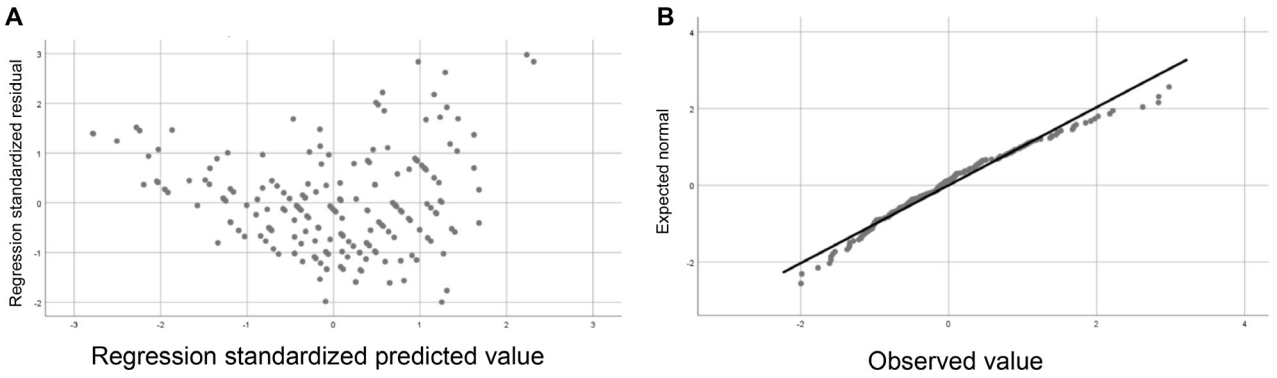

Figure 2. Regression diagnostic plots for the multiple linear regression model of estimated ASCVD risk. (A) Scatterplot of standardized residuals versus standardized predicted values, showing a random scatter without systematic trend, consistent with the assumptions of linearity and homoscedasticity. (B) Normal Q-Q plot of standardized residuals, showing close alignment with the reference diagonal, consistent with approximately normal residuals. Together, these diagnostics support the validity of the regression model used in this study.

Table 7. Results of linear regression analysis on ASCVD risk

Variables	Coefficient (B)	*P*-value	95% CI	Partial Eta Squared	Tolerance	VIF
Treatment intensification score	–3.481	**<0.001**	–4.694 to –2.267	0.148	0.928	1.078
Calculation method (Total cholesterol or BMI)	+5.540	**<0.001**	+4.483 to +6.598	0.367	0.673	1.487
Age	+0.484	**<0.001**	+0.424 to +0.543	0.582	0.851	1.176
Smoking status	+6.420	**<0.001**	+4.705 to +8.135	0.229	0.659	1.519
Type 2 diabetes mellitus status	+4.602	**<0.001**	+3.467 to +5.737	0.258	0.771	1.297
Sex	+1.067	**0.038**	+0.061 to +2.074	0.023	0.739	1.353

Model R^2 = 0.761; Adjusted R^2 = 0.753; F = 97.424; $p < 0.001$. Bolds mean significant at $\alpha = 0.05$ level. CI, confidence interval.

The relationship between antihypertensive therapy intensification and ASCVD risk was further analyzed using multiple linear regression, accounting for age, smoking status, type 2 diabetes mellitus status, sex, and calculation method (total cholesterol vs. BMI). The results showed that antihypertensive therapy intensification was significantly associated with a reduction in ASCVD risk. The model demonstrated a strong explanatory capacity, with an R^2 value of 0.761, indicating that 76.1% of the variance in ASCVD risk was explained by the included variables. The regression coefficient for antihypertensive therapy intensification was –3.481 ($p < 0.001$), indicating that each one-unit increase in the TI score was associated with a 3.48% reduction in ASCVD risk. The partial eta-square value of 0.148 indicated that antihypertensive therapy intensification independently accounted for approximately 14.8% of the variance in ASCVD risk, making it a relevant, though not exclusive, determinant in the regression model. All assumptions for multiple linear regression were examined and met, including linearity, normality of residuals, homoscedasticity, and absence of multicollinearity (Tolerance > 0.1 and VIF < 5 for all predictors), confirming the validity of the regression model (Table 7; Figure 2). Expressed per clinically observed increments, this corresponds to an approximately 0.35% reduction in estimated ASCVD risk per 0.1-unit increase in the TI score.

Discussion

This retrospective cohort study of 191 hypertensive patients in Bali showed that appropriate antihypertensive therapy intensification, achieved by only 35 patients (18.3%), was strongly associated with better blood pressure control and lower estimated ASCVD risk. Patients with appropriate intensification had a substantially lower mean systolic blood pressure than those with inappropriate intensification (122.77 vs. 143.28 mmHg; $p < 0.001$) and were far more likely to achieve controlled blood pressure (OR = 63.462; 95% CI: 8.017–502.354). Antihypertensive therapy intensification was also significantly associated with lower estimated 10-year ASCVD risk in multiple linear regression (B = –3.481; $p < 0.001$; $R^2 = 0.761$), while the non-significant increase in below-target blood pressure among appropriately intensified patients supports the clinical safety of this approach when applied judiciously.

The total study population had a median age of 62 years (IQR: 57–62.5). When stratified by blood pressure outcome, the median age was 64 years (IQR: 56–69) in the below-target group, 60 years (IQR: 53–66) in the controlled group, and 59.5 years (IQR: 51.25–66.75) in the hypertensive group. Vascular aging is characterized by reduced arterial elasticity and increased stiffness, both of which contribute to increased blood pressure [31,32]. At the physiological level, arterial wall thickening and endothelial dysfunction associated with aging and hypertension accelerate the inflammatory process, oxidative stress, and vascular remodeling, thereby increasing the risk of cardiovascular complications [32,33]. More than two-thirds of individuals aged over 65 years have hypertension, most commonly in the form of isolated systolic hypertension, which is strongly associated with reduced arterial compliance in the elderly population [33]. Furthermore, hypertension in the elderly substantially increases the risk of heart failure, stroke, myocardial infarction, dementia, physical disability, and mortality [34]. Therefore, effective management of hypertension in the elderly is essential to reduce the risk of future cardiovascular events.

Consistent with the findings of Żurański et al. (2024), the proportion of individuals classified as having a very high risk of ASCVD increases significantly with age, with nearly all participants aged ⩾75 years categorized in the very high-risk group [35]. Age and hypertension are major contributors to this increased risk, which may be further exacerbated by modifying factors such as malnutrition, polypharmacy, and multimorbidity, which are common in the elderly population [35]. These factors underscore the importance of implementing targeted secondary prevention strategies through rigorous blood pressure management and comprehensive cardiovascular risk management, particularly among the elderly.

From a metabolic perspective, more than two-thirds of patients in this study (75.92%) had type 2 diabetes mellitus, which is a significant determinant of ASCVD. The synergistic coexistence of hypertension and diabetes can accelerate vascular damage, worsen atherosclerosis, and significantly increase the incidence of major adverse cardiovascular events (MACE) [10]. An integrated therapeutic strategy is needed to prevent ASCVD in patients with both hypertension and diabetes, as previous evidence suggests that the combination of hypertension and diabetes can increase the risk of cardiovascular disease compared to either disease alone (hypertension or diabetes alone) [36].

Based on BMI calculations, this study reported a median of 23.83 (IQR: 22.47–26.67), which falls within the normal-to-overweight range [37]. The prevalence of patients with a history of smoking was relatively low (10.47%). However, smoking remains a strong risk factor for ASCVD because it increases the risk of cardiovascular morbidity and mortality, especially in patients with hypertension and diabetes [38]. In diabetic patients, smoking increases the risk of mortality by 1.5 times and the risk of cardiovascular events by 1.4–2.15 times compared to nonsmokers [38].

The high prevalence of hypertension observed in this study may be influenced by factors such as clinical inertia and poor adherence to antihypertensive therapy. Although these factors were not directly assessed in our analysis, previous studies have shown that they contribute significantly to inadequate blood pressure control among hypertensive patients. Durand et al. study showed that non-adherence to medication is a significant factor in the development of resistant hypertension [39]. Similarly, Backer et al. (2021), in the SIMPLIFY study, confirmed that clinical inertia remains a significant issue. Nearly half of patients with uncontrolled hypertension were still receiving monotherapy after eight years of treatment [40]. The addition of new medications or increased dosages of therapy can contribute to increased patient non-adherence, making physicians reluctant to add additional therapy. One solution to reduce clinical

inertia is a single-pill combination (SPC), which can simplify the treatment regimen [40].

These findings confirm that SBP is more responsive to intensification of antihypertensive therapy than DBP, consistent with previous studies. A recent analysis by Montano et al. showed that antihypertensive drugs can reduce SBP by an average of 16.24 mmHg, which is greater than the average reduction in DBP of 3.08 mmHg [41]. A meta-analysis conducted by Park et al. concluded that controlling SBP < 140 mmHg can significantly reduce the risk of cardiovascular death; if more intensive control is achieved (< 130 mmHg), it can further reduce the risk of primary cardiovascular events such as heart failure and stroke [42]. The study by Kim et al. (2025) provides additional information, emphasizing that achieving SBP targets alone is not enough; maintaining low blood pressure variability (BPV) is equally important, as patients with high BPV are at significantly greater risk of cardiovascular events, even when SBP levels reach the target [43]. An increase in systolic blood pressure (SBP) above 140 mmHg has been associated with an 18% higher risk of cardiovascular events for every one standard deviation (z-score) increase in SBP. In comparison, an increase in diastolic blood pressure (DBP) ⩾90 mmHg shows a weaker association, with a 6% higher risk per 1 standard deviation (z-score) increase, according to a study by Flint et al. [44]. These findings suggest that appropriate intensification of antihypertensive therapy plays an important role in achieving optimal systolic blood pressure control, which is an essential component in reducing long-term cardiovascular risk, especially among the elderly.

Regression analysis provided additional evidence regarding the impact of antihypertensive therapy intensification, demonstrating a strong negative association with SBP. The TI score demonstrated substantially greater predictive capacity for SBP reduction (B = -31.629 mmHg; R^2 = 0.387) compared to DBP reduction (B = -9.576 mmHg; R^2 = 0.058). Although the association between the TI score and DBP reduction reached statistical significance (p = 0.001), the low R^2 value suggests that the clinical meaningfulness of this association is limited. This observation is consistent with previous findings, which show that therapeutic intensity scores correlate closely with systolic blood pressure reduction, whereas diastolic blood pressure responses tend to be more moderate [45]. This differential responsiveness reflects age-related vascular changes, in which arterial stiffness disproportionately increases systolic blood pressure, making it a more important therapeutic target in the elderly [31]. Although intensification of antihypertensive therapy was also associated with a statistically significant reduction in diastolic blood pressure, its predictive value was weak. This finding aligns with the results of Canoy et al. (2022), who demonstrated that intensive antihypertensive therapy consistently reduced both systolic and diastolic blood pressure; however, the magnitude of the reduction in systolic blood pressure varied across age groups and clinical subpopulations [46].

Intensification of antihypertensive therapy was strongly associated with the final blood pressure category. This finding aligns with a review by Hameed and Dasgupta (2019), which showed that intensification of antihypertensive therapy significantly improved blood pressure control in patients with resistant hypertension over 1 year [47]. Importantly, intensification was not significantly associated with below-target blood pressure (OR = 1.647, p = 0.273), supporting its clinical safety when applied judiciously. This aligns with previous meta-analytic evidence indicating that antihypertensive therapy carries only a small risk of mild adverse events such as hypotension [48]. Other studies have even shown a protective effect against orthostatic hypotension in the elderly, suggesting that antihypertensive therapy does not necessarily increase the risk of orthostatic symptoms when appropriately managed [49]. Collectively, these observations support the notion that aggressive, yet selective intensification can be clinically effective and safe, particularly in high-risk populations.

In addition to its association with blood pressure outcomes, this study also demonstrated that intensification of antihypertensive therapy was statistically significantly associated with a reduced risk of ASCVD.Consistent with our results, a study by Coca et al., which simulated more than 1.1 million hypertensive patients, showed that combination therapy with two antihypertensive agents significantly reduced the risk of cardiovascular events over 10 years. In patients with complete adherence to a regimen such as irbesartan plus amlodipine, the absolute risk reduction (ARR) for the primary outcome (non-fatal myocardial infarction, non-fatal stroke, heart failure hospitalization, and cardiovascular death) was 8.7% compared with untreated patients. Particularly in those with established ASCVD, the ARR reached 15.9%, underscoring the substantial clinical benefit of this intensification strategy [50].

Our findings suggest that appropriate intensification of antihypertensive therapy is associated with better blood pressure control and lower estimated ASCVD risk, particularly among elderly patients and those with type 2 diabetes mellitus, with a non-significant trend toward below-target blood pressure that supports its clinical safety when applied cautiously. These findings support the need to optimize evidence-based intensification strategies and overcome clinical inertia to improve long-term cardiovascular outcomes. Several limitations should be noted. The retrospective design based on medical records may be subject to information bias and incomplete data, particularly for BMI and total cholesterol, and single-region data collection in Bali—together with the inclusion criterion of at least three outpatient visits, which likely enriched the sample with multimorbid patients—limits generalizability to primary care or other regional settings. Medication adherence was not assessed and may have influenced blood pressure outcomes. In addition, because the TI score reflects how closely therapy adjustments matched guideline recommendations relative to a patient's blood pressure, some residual confounding by indication cannot be fully excluded, and effect estimates are best interpreted within the narrow range of TI scores actually observed in this cohort (see Results). Prospective, multi-center studies with larger samples are needed to confirm these findings and establish causality.

Conclusion

Appropriate intensification of antihypertensive therapy was associated with better blood pressure control and lower estimated ASCVD risk among elderly patients and those with type 2 diabetes mellitus, with systolic blood pressure more responsive to intensification than diastolic blood pressure. A non-significant increase in the proportion of patients with below-target blood pressure was observed among those receiving appropriate intensification. These associative findings strengthen the clinical rationale for optimizing antihypertensive therapy intensification as part of secondary cardiovascular prevention, pending confirmation in prospective studies that can establish causality.

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Conflict of Interest

The authors confirm that the entire research process is free from conflicts of interest.

Author contributions

Conceptualization: IPDNP, DMV, PH. Methodology: IPDNP, PH. Formal Analysis: IPDNP, DMV. Data Curation: IPDNP. Writing – Original Draft: IPDNP. Writing – Review & Editing: IPDNP, DMV, PH. Supervision: DMV, PH.

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