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Research Article

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Association of systolic blood pressure target and variability with long-term clinical outcomes in patients undergoing percutaneous coronary intervention

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Abbreviations
AMI, acute myocardial infarction; ARV, average real variability; BARC, Bleeding Academic Research Consortium; BMI, body mass index; BP, blood pressure; BPV, blood pressure variability; CAD, coronary artery disease; CI, confidence interval; DAPT, dual antiplatelet

ABSTRACT

Background: The combined impact of achieving target systolic blood pressure (SBP) and blood pressure variability (BPV) on long-term clinical outcomes in patients with coronary artery disease following percutaneous coronary intervention (PCI) remains unclear. This study aimed to investigate the combined effect of SBP target achievement and BPV on the risk of cardiovascular events in patients undergoing PCI.
Methods: Consecutive patients who underwent PCI between 2012 and 2016 were included. Patients were classified into four groups based on average follow-up SBP (< 130 or ≥ 130 mmHg) and BPV (categorized as low or high, using the median of the standard deviation of SBP during follow-up). The primary outcome was net adverse clinical events (NACE; defined as all-cause death, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or major bleeding) for up to 5 years.
Results: Among 2,845 patients, 787 (27.7%) experienced NACE during a median follow-up of 5.43 years. Patients with high BPV had a significantly increased risk of long-term clinical outcomes, regardless of whether the target SBP was achieved. Additionally, patients with SBP ≥ 130 mmHg and high BPV had a significantly higher risk of 5-year major adverse cardiac and cerebrovascular events (adjusted hazard ratio [HR], 1.342; 95% confidence interval [CI], 1.067–1.688; $P = 0.012$) and NACE (adjusted HR, 1.262; 95% CI, 1.036–1.537; $P = 0.021$) than those with SBP < 130 mmHg and low BPV.
Conclusions: The combined impact of SBP target achievement and BPV was significantly associated with the risk of long-term adverse outcomes in patients who underwent PCI. These findings underscore the importance of achieving target SBP while recognizing that patients with high BPV represent a high-risk group requiring focused monitoring and management to mitigate cardiovascular events.

Trial Registration: ClinicalTrials.gov Identifier: NCT05935397

Keywords: Blood pressure; Blood pressure variability; Coronary artery disease; Percutaneous coronary intervention

therapy; DBP, diastolic blood pressure; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NACE, net adverse clinical events; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Trial Registration
ClinicalTrials.gov Identifier: NCT05935397

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Competing interest
The authors declare that they have no competing interests.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Hanyang University Seoul Hospital (approval number: 2022-06-064) and Hanyang University Guri Hospital (approval number: 2022-06-010). The requirement for written informed consent was waived by the Institutional Review Board.

Consent for publication
Not applicable.

Authors' contributions
Conceptualization: Shin JH; Data curation: Kim BS; Formal analysis: Kim BS; Investigation: Kim BS; Methodology: Shin JH; Writing - original draft: Kim BS, Shin JH; Writing - review & editing: Lim YH, Shin J.

BACKGROUND

Coronary artery disease (CAD) is the most common type of heart disease and a leading cause of morbidity and mortality worldwide [1]. In patients with CAD, hypertension is a significant risk factor for disease development and progression and is closely linked to adverse prognosis [2]. Therefore, optimal blood pressure (BP) management is crucial for this population.

Observational studies have reported a J- or U-shaped relationship between BP and adverse outcomes in patients with CAD, suggesting that an excessively low BP (particularly below 120/70 mmHg) may increase risk [3,4]. However, substantial evidence supports strict BP control to reduce cardiovascular events [5,6]. Consequently, adhering to the current clinical guidelines that recommend targeting systolic blood pressure (SBP) below 130 mmHg and diastolic blood pressure (DBP) below 80 mmHg in patients with CAD is important [7,8].

Achieving the target BP is the primary focus of treating hypertension. Numerous studies have investigated this, and clinical guidelines recommend appropriate target BP levels based on comorbidities and overall cardiovascular risk [2,7,8]. However, evaluating BP control at a single time point fails to account for the dynamic nature of BP fluctuations. Blood pressure variability (BPV), reflecting these fluctuations, has been independently associated with cardiovascular events, independent of mean BP levels [9].

Despite extensive research on BP levels and BPV individually, few studies have explored their combined impact on the clinical outcomes of patients with CAD [10,11]. Understanding the interplay between achieving target BP level and minimizing BPV could provide valuable insights for optimizing BP management strategies in this high-risk population. This study investigated the association between achieving a target SBP of 130 mmHg, visit-to-visit BPV, and long-term clinical outcomes in patients undergoing percutaneous coronary intervention (PCI).

METHODS

Study participants

Data were obtained from the 'HanYang University Medical Center (HYUMC) Registry' (NCT05935397), a comprehensive observational database encompassing consecutive patients with CAD who underwent PCI between January 2012 and December 2016 at Seoul and Guri Hospitals in Korea. Patients treated with one or more drug-eluting stents (DES) at either hospital were eligible for inclusion, regardless of their characteristics or lesion complexity [12].

Initially, 3,525 patient records were reviewed. Following the application of exclusion criteria, 680 patients were excluded for the following reasons: 288 had repeated admissions, 110 died during the index hospitalization, seven received treatment with first-generation DES, 244 were lost to follow-up within six months, and 31 had insufficient medical records. Consequently, the final study population consisted of 2,845 patients.

Based on their average SBP and SBP variability during the follow-up period after PCI, the patients were subsequently classified into 4 groups (**Fig. 1**): SBP < 130 mmHg and low BPV (n = 1,073), SBP < 130 mmHg and high BPV (n = 818), SBP ≥ 130 mmHg and low BPV (n = 349), and SBP ≥ 130 mmHg and high BPV (n = 605). The average SBP was categorized as < 130 or ≥ 130 mmHg. BPV was assessed using the standard deviation (SD) of SBP measurements

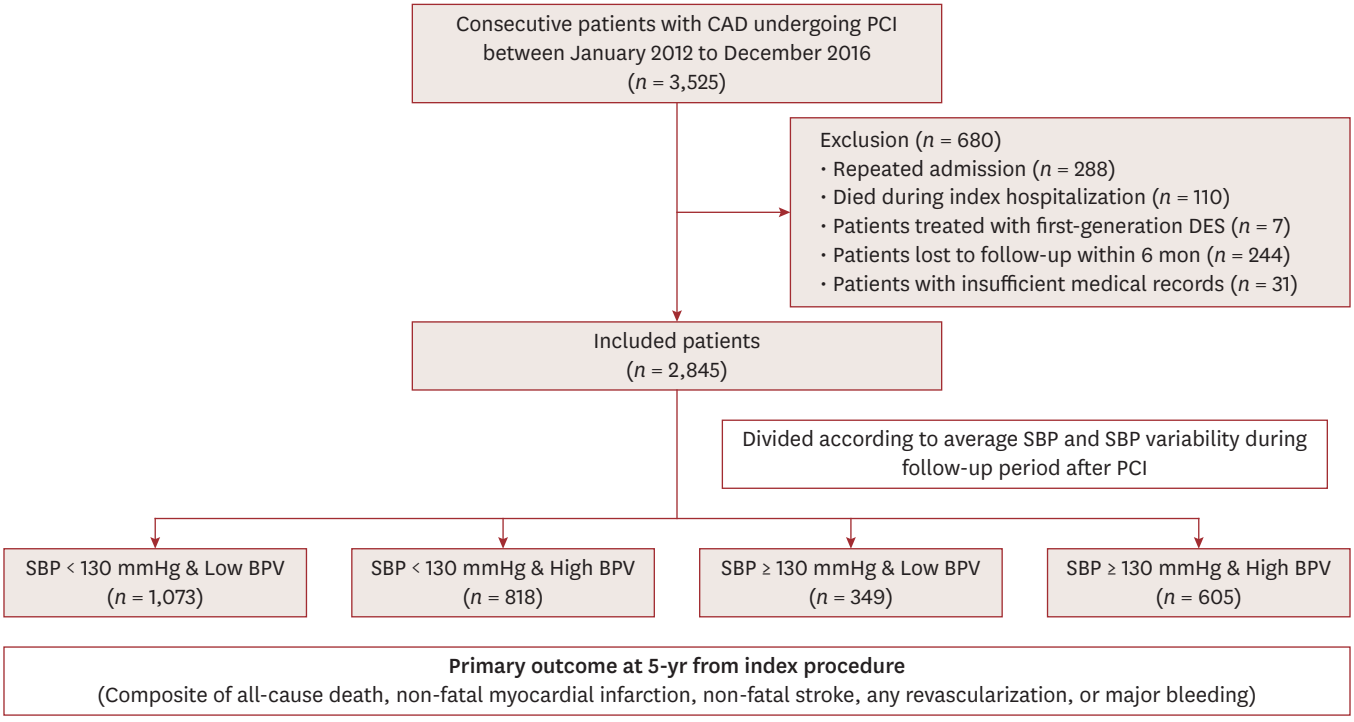

Fig. 1. Flow diagram depicting the study design.
CAD, coronary artery disease; PCI, percutaneous coronary intervention; DES, drug-eluting stent; SBP, systolic blood pressure; BPV, blood pressure variability.

obtained from visit-to-visit and categorized as either low or high based on a median SD value of 12.1 mmHg.

Data collection and patient management

Trained investigators collected data from electronic health database under the close supervision of the Principal Investigator. The detailed methodology and patient characteristics have been described previously [12]. Briefly, demographic and clinical characteristics of all included patients, such as sex, age, body mass index (BMI), and vital signs at the time of hospital admission were extracted. Data on traditional cardiovascular risk factors including the presence of hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, smoking status, history of CAD, and prior ischemic or hemorrhagic stroke, were also collected. Additionally, detailed medication records at discharge following the index PCI, laboratory data at admission and discharge, angiographic and procedural data, and left ventricular ejection fraction (LVEF) assessed using transthoracic echocardiography during the index hospitalization were recorded.

Patients were managed according to prevailing standard practices at each hospital, following contemporary clinical practice guidelines [13-16]. The interventional cardiologist determined the specific treatment approach, including stent implantation, based on the clinical and angiographic findings. At discharge, all patients were prescribed a dual antiplatelet therapy (DAPT) containing aspirin and either clopidogrel, ticagrelor, or prasugrel. DAPT was prescribed for at least 6 months in patients with stable ischemic heart disease and for 12 months in those presenting with acute coronary syndrome. Patients were scheduled for routine clinical follow-up at 1 month, and subsequently at 3-month intervals, with more frequent visits scheduled as clinically indicated.

BP measurement and variability

During each follow-up visit, BP was measured using an automated device (OMRON HEM-907XL, Omron Healthcare Co. Ltd., Kyoto, Japan), a validated machine for clinical use. To ensure accuracy, measurements were taken after the patient had rested in a seated position for at least 5 minutes in a quiet environment, following standardized BP measurement guidelines [2,7].

For each patient, the average SBP and DBP were calculated as the mean of the available BP measurements. BPV was primarily assessed using the SD of the SBP from visit-to-visit BP measurements. For sensitivity analysis, the average real variability (ARV), calculated as the average absolute difference between consecutive BP measurements, was also used as an alternative measure of BPV to ensure robustness [17].

Outcome definitions

The primary outcome of this study was net adverse clinical events (NACE), defined as a composite of major adverse cardiac and cerebrovascular events (MACCE) and major bleeding, for up to 5 years. The secondary outcome was MACCE, a composite of all-cause death, nonfatal myocardial infarction (MI), nonfatal stroke, or any revascularization. Additional secondary outcomes included major bleeding and individual components of MACCE, specifically all-cause death, nonfatal MI, nonfatal stroke, and any revascularization.

Clinical outcomes were defined according to the Academic Research Consortium guidelines [18]. MI was defined as the presence of clinical symptoms accompanied by electrocardiographic changes or imaging evidence indicating a new loss of viable myocardium or new regional wall motion abnormalities along with elevated cardiac biomarkers above the 99th percentile upper reference limit. Peri-procedural MI was excluded from the analysis. Stroke was defined as a neurological deficit resulting from acute focal damage to the central nervous system due to a vascular cause, and confirmed by a neurologist through imaging and the requirement of hospitalization. Any revascularization included PCI or coronary artery bypass grafting performed on either the target or non-target vessels. Major bleeding was classified according to the Bleeding Academic Research Consortium (BARC) criteria; major bleeding being defined as BARC type 3 or 5 bleeding [19].

Statistical analysis

Categorical variables are presented as numerical values and percentages. Continuous variables are expressed as means with SDs or as medians with interquartile ranges (IQR), depending on whether they followed a normal distribution. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test and by visually inspecting Q-Q plots. For categorical variables, comparisons among groups were performed using the chi-square test. For continuous variables, one-way analysis of variance was applied if the data were normally distributed; if not, the Kruskal–Wallis test was employed.

To estimate cumulative event rates, survival analysis was conducted using the Kaplan–Meier method, and differences between the groups were evaluated using the log-rank test. Further, based on the average SBP and BPV categories, Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical outcomes. Multivariate Cox regression analyses were adjusted for potential confounding factors, including age, sex, BMI, presentation with MI, current smoking status, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous PCI, prior stroke, LVEF, troponin-I levels, estimated glomerular filtration rate (eGFR), presence of multivessel

disease, and use of medications such as anticoagulants, statins, angiotensin receptor blockers, and beta-blockers. A backward elimination method using Akaike's information criterion was applied to refine the model. The proportional hazard assumption was tested using scaled Schoenfeld residual.

All statistical analyses were performed using the R software (version 4.4.0; www.R-project.org) and RStudio (version 2023.12.1; www.rstudio.com). The following R packages were utilized: 'rms' for regression modeling strategies, 'descr' for descriptive statistics, 'survival' for survival analysis, 'tableone' for creating summary tables, 'survminer' for visualizing survival curves, and 'ggplot2' for data visualization. All tests were 2-sided, and a *P*-value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics of the study participants stratified by average SBP and SBP variability are presented in **Table 1**. Patients with SBP ≥ 130 mmHg and high BPV were generally older and had a higher prevalence of comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, previous PCI, and previous stroke (all $P < 0.05$). This group also had a lower eGFR. Conversely, patients with SBP < 130 mmHg and low BPV were more likely to be men, current smokers, and to present with acute MI ($P < 0.05$). These patients had higher eGFR and were more frequently prescribed potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) at discharge. In contrast, those with higher SBP and BPV were more commonly prescribed clopidogrel and calcium channel blockers.

There were no significant differences between the groups in terms of multivessel disease or most angiographic characteristics. However, the use of medications, such as statins, angiotensin receptor blockers, and diuretics, varied significantly between the groups ($P < 0.05$).

Clinical outcomes according to average SBP and SBP variability categories

The median follow-up duration was 5.43 years (IQR, 2.05–8.42 years), during which NACE occurred in 787 patients (27.7%). The association between average SBP (< 130 or ≥ 130 mmHg) and SBP variability (low or high BPV) with clinical outcomes is presented in **Supplementary Table 1**. Patients with SBP ≥ 130 mmHg demonstrated significantly higher risks for MACCE (adjusted HR, 1.227; 95% CI, 1.029–1.464; $P = 0.023$) and all-cause death (adjusted HR, 1.471; 95% CI, 1.081–2.001; $P = 0.014$) compared to those with SBP < 130 mmHg. Similarly, high BPV was significantly associated with an increased risk for NACE (adjusted HR, 1.179; 95% CI, 1.016–1.367; $P = 0.030$), major bleeding (adjusted HR, 1.329; 95% CI, 1.069–1.651; $P = 0.010$), and any revascularization (adjusted HR, 1.272; 95% CI, 1.025–1.579; $P = 0.029$) compared to low BPV. For other outcomes, trends of increased risk with higher SBP or BPV were observed; however, these associations did not reach statistical significance.

The Kaplan–Meier curves for the cumulative incidence rates of NACE, MACCE, and major bleeding, stratified by average SBP and SBP variability, are presented in **Fig. 2**. The incidence rates of NACE, MACCE, and major bleeding were highest in patients with SBP ≥ 130 mmHg and high BPV (35.7% for NACE, 26.1% for MACCE, and 19.7% for major bleeding), followed by those with SBP < 130 mmHg and high BPV. Except nonfatal stroke, a similar trend was observed for the other secondary outcomes (**Fig. 2**, **Table 2**).

Table 1. Baseline characteristics according to average SBP and SBP variability

Characteristics	SBP < 130 & Low BPV (< 12.1) (*n* = 1,073)	SBP < 130 & High BPV (≥ 12.1) (*n* = 818)	SBP ≥ 130 & Low BPV (< 12.1) (*n* = 349)	SBP ≥ 130 & High BPV (≥ 12.1) (*n* = 605)	*P*-value
Age (yr)	61.4 ± 11.6	66.7 ± 11.1[a]	65.3 ± 12.5[a]	67.8 ± 12.1[ac]	< 0.001
Men	835 (77.8)	535 (65.4)	238 (68.2)	341 (56.4)	< 0.001
BMI (kg/m^2)	24.9 ± 3.2	24.5 ± 3.4[a]	25.4 ± 3.4[b]	25.1 ± 3.6[b]	< 0.001
Index presentation					< 0.001
Stable angina	432 (40.3)	328 (40.1)	160 (45.8)	272 (45.0)	
Unstable angina	176 (16.4)	137 (16.7)	48 (13.8)	117 (19.3)	
NSTEMI	224 (20.9)	211 (25.8)	87 (24.9)	143 (23.6)	
STEMI	241 (22.5)	142 (17.4)	54 (15.5)	73 (12.1)	
Index presentation with AMI	465 (43.3)	353 (43.2)	141 (40.4)	216 (35.7)	0.012
Risk factors					
Current smoking	361 (33.6)	237 (29.0)	86 (24.6)	132 (21.8)	< 0.001
Hypertension	466 (43.4)	484 (59.2)	256 (73.4)	487 (80.5)	< 0.001
Diabetes mellitus	308 (28.7)	283 (34.6)	118 (33.8)	277 (45.9)	< 0.001
Dyslipidemia	436 (40.6)	328 (40.1)	139 (39.8)	232 (38.4)	0.846
Chronic kidney disease	31 (2.9)	46 (5.6)	17 (4.9)	69 (11.4)	< 0.001
Previous PCI	117 (10.9)	99 (12.1)	50 (14.3)	93 (15.4)	0.043
Previous stroke	74 (6.9)	85 (10.4)	41 (11.7)	76 (12.6)	0.001
Laboratory findings					
LVEF (%)	56.7 ± 10.8	55.7 ± 12.1	58.6 ± 10.3[ab]	56.5 ± 11.4[c]	0.001
Troponin-I (ng/L)	20 (10–210)	30 (10–250)[a]	20 (10–160)[b]	30 (10–180)[ac]	0.019[d]
eGFR (mL/min/1.73 m^2)	86.6 ± 19.7	79.6 ± 23.1[a]	78.6 ± 25.8[a]	71.2 ± 28.1[abc]	< 0.001
Total cholesterol (mg/dL)	173 (146–204)	163 (136–194)[a]	168 (141–199)	167 (141–199)	< 0.001[d]
LDL cholesterol (mg/dL)	101 (79–129)	96 (73–121)[a]	98 (77–121)	100 (78–126)	0.001[d]
HDL cholesterol (mg/dL)	41 (35–49)	40 (34–48)	41 (34–47)	41 (35–48)	0.469[d]
Triglyceride (mg/dL)	124 (87–184)	119 (86–174)	120 (87–186)	122 (87–173)	0.508[d]
HbA1c (%)	5.8 (5.5–6.5)	5.8 (5.5–6.7)	5.9 (5.5–6.4)	6.0 (5.6–7.0)[abc]	< 0.001[d]
Procedural characteristics					
Multivessel disease	368 (34.3)	319 (39.0)	121 (34.7)	240 (39.7)	0.060
Target lesion					
Left main coronary artery	25 (2.3)	20 (2.4)	9 (2.6)	17 (2.8)	0.943
Left anterior descending artery	743 (69.2)	538 (65.8)	223 (63.9)	418 (69.1)	0.147
Left circumflex artery	337 (31.4)	301 (36.8)	119 (34.1)	224 (37.0)	0.042
Right coronary artery	419 (39.0)	347 (42.4)	146 (41.8)	255 (42.1)	0.424
Chronic total occlusion	70 (6.5)	65 (8.0)	21 (6.0)	43 (7.1)	0.562
In-stent restenosis	37 (3.4)	35 (4.3)	16 (4.6)	32 (5.3)	0.332
Discharge medication					
Aspirin	1,056 (98.4)	800 (97.8)	342 (98.0)	597 (98.7)	0.593
Type of $P2Y_{12}$ inhibitor					
Clopidogrel	650 (60.6)	571 (69.8)	232 (66.5)	457 (75.5)	< 0.001
Ticagrelor	272 (25.3)	181 (22.1)	79 (22.6)	106 (17.5)	0.003
Prasugrel	118 (11.0)	46 (5.6)	23 (6.6)	27 (4.5)	< 0.001
Cilostazol	138 (12.9)	105 (12.8)	37 (10.6)	85 (14.0)	0.502
Anti-coagulant	11 (1.0)	25 (3.1)	6 (1.7)	6 (1.0)	0.003
Statin	1,008 (93.9)	750 (91.7)	315 (90.3)	544 (89.9)	0.014
Nitrate	601 (56.0)	477 (58.3)	208 (59.6)	389 (64.3)	0.011
Angiotensin blockade	575 (53.6)	486 (59.4)	195 (55.9)	377 (62.3)	0.003
Beta-blocker	742 (69.2)	596 (72.9)	248 (71.1)	432 (71.4)	0.363
Calcium channel blocker	103 (9.6)	80 (9.8)	48 (13.8)	110 (18.2)	< 0.001
Diuretics	162 (15.1)	162 (19.8)	38 (10.9)	116 (19.2)	< 0.001
MRA	117 (10.9)	128 (15.6)	25 (7.2)	64 (10.6)	< 0.001
Average follow-up BP (mmHg)					
SBP	119.6 ± 7.1	121.4 ± 6.7[a]	137.2 ± 7.4[ab]	139.3 ± 8.8[abc]	< 0.001
DBP	71.5 ± 6.2	70.4 ± 6.7[a]	77.9 ± 7.2[ab]	76.5 ± 7.7[abc]	< 0.001
SBP variability					
SD of SBP	9.5 (8.2–10.9)	14.5 (13.2–17.1)[a]	9.8 (8.1–10.9)[ab]	16.1 (14.0–19.4)[abc]	< 0.001[d]
ARV of SBP	10.0 (8.4–11.8)	15.1 (13.0–18.1)[a]	10.0 (8.3–12.0)[ab]	16.5 (13.6–20.5)[abc]	< 0.001[d]

Data are presented as numbers (%), median (interquartile range), or mean ± standard deviation.

SBP, systolic blood pressure; BPV, blood pressure variability; BMI, body mass index; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; MRA, mineralocorticoid receptor antagonist; BP, blood pressure; DBP, diastolic blood pressure; SD, standard deviation; ARV, average real variability.

[a]Post hoc *P*: Statistically significant difference $P < 0.05$, compared with the SBP < 130 mmHg & Low BPV groups.

[b]Post hoc *P*: Statistically significant difference $P < 0.05$, compared to the SBP < 130 mmHg & High BPV groups.

[c]Post hoc *P*: Statistically significant difference $P < 0.05$ compared to the SBP ≥ 130 mmHg & High BPV group.

[d]As assessed using nonparametric tests.

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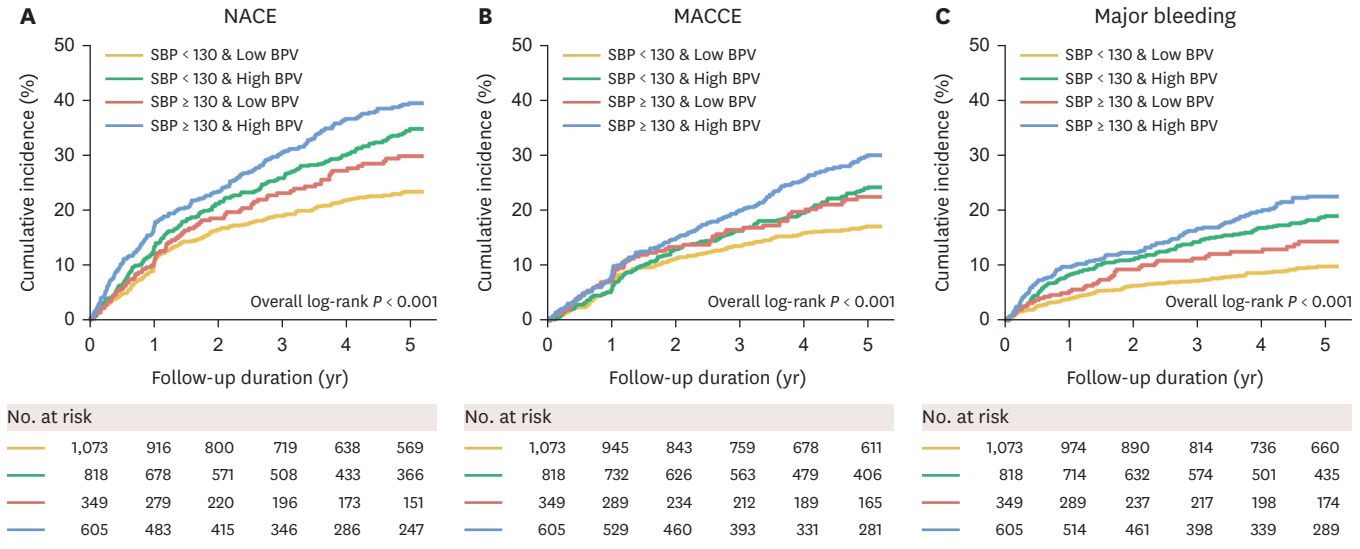

Fig. 2. Kaplan–Meier curves for the cumulative incidence of the clinical outcomes according to average SBP and SBP variability. (A) NACE, (B) MACCE, and (C) major bleeding.
SBP, systolic blood pressure; NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; BPV, blood pressure variability.

Table 2 summarizes the incidence rates and HRs for both primary and secondary outcomes according to the groups categorized by average SBP and SBP variability. In comparison to the reference group (lower SBP and low BPV), after adjusting for relevant covariates, patients with SBP ≥ 130 mmHg and high BPV showed a significantly elevated risk of 5-year NACE (adjusted HR, 1.262; 95% CI, 1.036–1.537; $P = 0.021$) and MACCE (adjusted HR, 1.342; 95% CI, 1.067–1.688; $P = 0.012$). Patients with SBP ≥ 130 mmHg and high BPV also demonstrated a higher risk of major bleeding (adjusted HR, 1.364; 95% CI, 1.022–1.819; $P = 0.035$), all-cause death (adjusted HR, 1.584; 95% CI, 1.032–2.431; $P = 0.035$), and any revascularization (adjusted HR, 1.341; 95% CI, 1.008–1.785; $P = 0.044$). The group with SBP < 130 mmHg and high BPV was associated with a significantly increased risk of major bleeding (adjusted HR, 1.401; 95% CI, 1.069–1.837; $P = 0.015$); however, no significant differences in other outcomes compared to the reference group were noted. Furthermore, patients with SBP ≥ 130 mmHg and low BPV exhibited a significantly increased risk of all-cause death (adjusted HR, 2.105; 95% CI, 1.265–3.503; $P = 0.004$) but did not show significant differences in other outcomes when compared to the reference group.

For the sensitivity analysis, BPV was assessed using ARV instead of SD to categorize the patients (**Supplementary Table 2**). These results are largely consistent with those of the primary analysis.

Association between SBP variability and clinical outcomes by SBP category

Table 3 presents the analysis of the association between SBP variability and clinical outcomes stratified by average SBP (< 130 or ≥ 130 mmHg). In both patients with lower SBP (< 130 mmHg) (adjusted HR, 1.221; 95% CI, 1.105–1.350; $P < 0.001$) and those with higher SBP (≥ 130 mmHg) (adjusted HR, 1.166; 95% CI, 1.057–1.287; $P = 0.002$), an increase in BPV (per 1-SD increase) was associated with a significantly elevated risk of the primary outcome, NACE. Additionally, increased BPV was significantly associated with a higher risk of major bleeding in both SBP categories (SBP < 130 mmHg: adjusted HR, 1.268; 95% CI, 1.107–1.454; $P = 0.001$ and SBP ≥ 130 mmHg: adjusted HR, 1.198; 95% CI, 1.052–1.364; $P = 0.006$, respectively). Moreover,

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Table 2. Incidence rates and HRs for clinical outcomes based on average SBP and SBP variability categories

Categories	Events (%)	Univariable analysis		Multivariable analysis[a]	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
NACE[b]					
SBP < 130 & Low BPV	229/1,073 (21.3)	Reference		Reference	
SBP < 130 & High BPV	255/818 (31.2)	1.532 (1.282–1.832)	< 0.001	1.196 (0.995–1.438)	0.056
SBP ≥ 130 & Low BPV	87/349 (24.9)	1.292 (1.010–1.654)	0.042	1.136 (0.882–1.462)	0.324
SBP ≥ 130 & High BPV	216/605 (35.7)	1.832 (1.521–2.206)	< 0.001	1.262 (1.036–1.537)	0.021
MACCE[c]					
SBP < 130 & Low BPV	165/1,073 (15.4)	Reference		Reference	
SBP < 130 & High BPV	171/818 (20.9)	1.387 (1.120–1.718)	0.003	1.134 (0.911–1.412)	0.260
SBP ≥ 130 & Low BPV	65/349 (18.6)	1.345 (1.009–1.792)	0.043	1.235 (0.922–1.655)	0.157
SBP ≥ 130 & High BPV	158/605 (26.1)	1.784 (1.434–2.219)	< 0.001	1.342 (1.067–1.688)	0.012
Major bleeding[d]					
SBP < 130 & Low BPV	94/1,073 (8.8)	Reference		Reference	
SBP < 130 & High BPV	138/818 (16.9)	2.025 (1.558–2.632)	< 0.001	1.401 (1.069–1.837)	0.015
SBP ≥ 130 & Low BPV	41/349 (11.7)	1.499 (1.039–2.164)	0.031	1.146 (0.785–1.671)	0.480
SBP ≥ 130 & High BPV	119/605 (19.7)	2.450 (1.869–3.211)	< 0.001	1.364 (1.022–1.819)	0.035
All-cause death					
SBP < 130 & Low BPV	37/1,073 (3.4)	Reference		Reference	
SBP < 130 & High BPV	57/818 (7.0)	2.071 (1.369–3.132)	0.001	1.304 (0.855–1.989)	0.217
SBP ≥ 130 & Low BPV	29/349 (8.3)	2.744 (1.688–4.462)	< 0.001	2.105 (1.265–3.503)	0.004
SBP ≥ 130 & High BPV	62/605 (10.2)	3.124 (2.079–4.694)	< 0.001	1.584 (1.032–2.431)	0.035
Non-fatal MI					
SBP < 130 & Low BPV	31/1,073 (2.9)	Reference		Reference	
SBP < 130 & High BPV	25/818 (3.1)	1.079 (0.637–1.827)	0.778	0.960 (0.562–1.641)	0.882
SBP ≥ 130 & Low BPV	10/349 (2.9)	1.122 (0.550–2.289)	0.751	1.059 (0.518–2.165)	0.875
SBP ≥ 130 & High BPV	28/605 (4.6)	1.680 (1.008–2.801)	0.047	1.456 (0.859–2.467)	0.163
Non-fatal stroke					
SBP < 130 & Low BPV	20/1,073 (1.9)	Reference		Reference	
SBP < 130 & High BPV	18/818 (2.2)	1.203 (0.637–2.275)	0.569	0.761 (0.397–1.460)	0.412
SBP ≥ 130 & Low BPV	11/349 (3.2)	1.887 (0.904–3.938)	0.091	1.610 (0.757–3.423)	0.216
SBP ≥ 130 & High BPV	19/605 (3.1)	1.761 (0.940–3.300)	0.077	1.083 (0.560–2.097)	0.812
Any revascularization					
SBP < 130 & Low BPV	116/1,073 (10.8)	Reference		Reference	
SBP < 130 & High BPV	111/818 (13.6)	1.280 (0.987–1.661)	0.063	1.244 (0.955–1.619)	0.105
SBP ≥ 130 & Low BPV	36/349 (10.3)	1.064 (0.732–1.546)	0.746	1.038 (0.713–1.510)	0.846
SBP ≥ 130 & High BPV	93/605 (15.4)	1.485 (1.130–1.951)	0.005	1.341 (1.008–1.785)	0.044

HR, hazard ratio; SBP, systolic blood pressure; CI, confidence interval; NACE, net adverse clinical events; BPV, blood pressure variability; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.
[a]Adjusted for age, sex, body mass index, presentation with MI, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous percutaneous coronary intervention, previous stroke, left ventricular ejection fraction, troponin-I, estimated glomerular filtration rate, multivessel disease, and use of anticoagulants, statins, angiotensin blockades, and beta-blockers.
[b]NACE was defined as a composite of all-cause death, non-fatal MI, non-fatal stroke, revascularization, or major bleeding.
[c]MACCE were defined as a composite of all-cause death, nonfatal MI, nonfatal stroke, or revascularization.
[d]Major bleeding was defined as Bleeding Academic Research Consortium 3 or 5 bleeding.

increased BPV was associated with an elevated risk of MACCE, all-cause death, and any revascularization in patients with lower SBP (< 130 mmHg), while a significant association was seen with an increased risk of non-fatal MI in those with higher SBP (≥ 130 mmHg).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the combined impact of achieving target SBP levels and BPV on long-term clinical outcomes, including ischemic and bleeding events, in patients with CAD undergoing PCI. The key findings of our study were: 1) Regardless of achieving the target SBP, BPV significantly influences the risk of long-term clinical outcomes; 2) patients with high SBP (≥ 130 mmHg) and high BPV demonstrate

Table 3. Association between SBP variability and clinical outcomes by SBP category

Categories	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Average SBP < 130 mmHg				
NACE[b]	1.394 (1.270–1.531)	< 0.001	1.221 (1.105–1.35)	< 0.001
BPV (per 1-SD increase)				
MACCE[c]	1.275 (1.133–1.434)	< 0.001	1.159 (1.024–1.312)	0.019
BPV (per 1-SD increase)				
Major bleeding[d]	1.556 (1.377–1.758)	< 0.001	1.268 (1.107–1.454)	0.001
BPV (per 1-SD increase)				
All-cause death	1.624 (1.345–1.96)	< 0.001	1.289 (1.041–1.594)	0.020
BPV (per 1-SD increase)				
Non-fatal MI	1.099 (0.805–1.501)	0.552	1.118 (0.807–1.548)	0.504
BPV (per 1-SD increase)				
Non-fatal stroke	1.137 (0.785–1.646)	0.496	1.017 (0.713–1.451)	0.927
BPV (per 1-SD increase)				
Any revascularization	1.255 (1.087–1.449)	0.002	1.233 (1.065–1.427)	0.005
BPV (per 1-SD increase)				
Average SBP ≥ 130 mmHg				
NACE[b]	1.276 (1.164–1.400)	< 0.001	1.166 (1.057–1.287)	0.002
BPV (per 1-SD increase)				
MACCE[c]	1.249 (1.120–1.392)	< 0.001	1.120 (0.999–1.256)	0.051
BPV (per 1-SD increase)				
Major bleeding[d]	1.351 (1.197–1.526)	< 0.001	1.198 (1.052–1.364)	0.006
BPV (per 1-SD increase)				
All-cause death	1.365 (1.165–1.600)	< 0.001	1.134 (0.964–1.333)	0.128
BPV (per 1-SD increase)				
Non-fatal MI	1.522 (1.197–1.937)	0.001	1.487 (1.152–1.921)	0.002
BPV (per 1-SD increase)				
Non-fatal stroke	0.925 (0.654–1.307)	0.657	0.791 (0.573–1.092)	0.154
BPV (per 1-SD increase)				
Any revascularization	1.186 (1.022–1.376)	0.024	1.161 (0.991–1.361)	0.064
BPV (per 1-SD increase)				

SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval; NACE, net adverse clinical events; BPV, blood pressure variability; SD, standard deviation; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

[a]Adjusted for age, sex, body mass index, presentation with MI, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous percutaneous coronary intervention, previous stroke, left ventricular ejection fraction, troponin-I, estimated glomerular filtration rate, multivessel disease, and use of anticoagulants, statins, angiotensin blockades, and beta-blockers.

[b]NACE was defined as a composite of all-cause death, non-fatal MI, non-fatal stroke, revascularization, or major bleeding.

[c]MACCE were defined as a composite of all-cause death, nonfatal MI, nonfatal stroke, or any revascularization.

[d]Major bleeding was defined as Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding.

the highest risk of adverse events, including ischemic and bleeding events; and 3) the associations persist even after adjusting for confounding variables (as these were consistent in the sensitivity analysis using different BPV indices). Given that BPV plays a critical role in influencing clinical outcomes, these findings underscore the importance of monitoring and addressing BPV, in addition to achieving the target SBP, as part of the comprehensive secondary prevention strategies for patients undergoing PCI.

As recommended by clinical guidelines, achieving and maintaining target BP levels are essential for optimizing clinical outcomes, both in preventing cardiovascular disease and managing patients with established cardiovascular disease [7]. However, achieving the target BP at a specific time point does not reflect the dynamic nature of BP over time. BPV is one of the most representative indicators of BP fluctuation documented as a cardiovascular risk factor [17]. Previous studies evaluating the association between BPV and clinical outcomes in patients with CAD focused on whether BPV has an independent association, that was

separate from SBP [11,20-22]. Given that lower BP levels are generally linked to reduced BPV, it is clinically significant to determine whether BPV remains associated with adverse outcomes even in patients who have achieved target BP levels [23]. Our study adds to this body of evidence by demonstrating that patients who failed to achieve target SBP and exhibited a high BPV had the highest incidence of adverse events. Importantly, patients with high BPV, even if they achieved the target SBP, remained at an elevated risk for adverse clinical outcomes. Furthermore, we identified an association between BPV and bleeding events, a link not addressed in previous studies.

The mechanisms underlying the impact of elevated BPV on adverse outcomes in patients with CAD, even when the target SBP is achieved, are not fully understood. Nevertheless, several hypotheses have been proposed. First, elevated BPV may cause repeated surges in arterial wall stress, leading to endothelial dysfunction and increased arterial stiffness, which eventually contributing to adverse cardiovascular outcomes [24,25]. Second, BP fluctuations may negatively affect the myocardial structure as well as systolic and diastolic functions [26]. Third, there are concerns about the J-curve association between BP and cardiovascular outcomes, particularly in patients with CAD [27]. The overall BP of patients achieving the target SBP, is relatively lower compared to those who did not. In these patients, an elevated BPV may suggest transient episodes of excessively low BP, which could lead to harmful effects and potentially increase the risk of adverse cardiovascular events. Additionally, previous studies have suggested that visit-to-visit BPV may partly result from antihypertensive medication non-adherence, which contributes to higher BP fluctuations and poorer cardiovascular outcomes [28]. All these factors ultimately contribute to long-term adverse clinical events in patients with CAD.

The findings of the present study have important clinical implications. In addition to targeting SBP, clinicians should stratify patients with high BPV as a high-risk group and focus on close monitoring and investigating the potential causes of increased BPV to improve long-term outcomes in patients with CAD undergoing PCI. Treatment strategies are also evolving with ongoing efforts to improve cardiovascular prognosis. Particularly, the benefits of intensive BP control have been emphasized recently, which has led to stricter BP targets, especially in high-risk patients [6,7]. In our study, patients who achieved the target SBP and maintained a low BPV had fewer ischemic and bleeding events. Particularly, high SBP and BPV were strongly associated with fatal bleeding events [29]. Our findings emphasize the importance of achieving the target SBP and minimizing BPV to mitigate bleeding risk in high-risk patients, who necessarily require intensive antiplatelet therapy and are therefore predisposed to bleeding complications. Therefore, our findings provide a rationale for developing strategies not only to achieve sufficient BP control but also to effectively reduce BPV in patients who have reached target SBP levels.

This study had several limitations. First, due to its observational design, the study was vulnerable to residual confounding despite thorough adjustments for known variables. Despite inclusion of consecutive patients, a selection bias may have influenced the results. Second, data were collected from two hospitals within a single university medical system, limiting the generalizability of our findings to other populations. Third, data on out-of-hospital blood pressure measurements were not available, which prevented the identification of patients with white-coat or masked hypertension. Finally, we did not account for factors such as medication adherence, lifestyle modifications after PCI, or adverse events related to BP-lowering treatments, all of which may have affected the study outcomes. Further

randomized controlled trials are necessary to establish causal relationships and validate our findings across a broader population.

CONCLUSIONS

This study underscores the significant combined influence of suboptimal SBP target achievement and high BPV on long-term adverse cardiovascular outcomes, encompassing both ischemic and bleeding events, in patients undergoing PCI. Patients with these combined risk factors demonstrated significantly worse outcomes, underscoring the need for close monitoring and targeted management in this high-risk population. These findings emphasize the need for early and continuous interventions to reduce BP fluctuations and optimize cardiovascular risk management in high-risk populations.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Association between average SBP or SBP variability categories and clinical outcomes

Supplementary Table 2

Sensitivity analysis of clinical outcomes based on average SBP and SBP variability categories using ARV instead of SD

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