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Association of office blood pressure with ischemic and bleeding events in patients undergoing percutaneous coronary intervention

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Optimal blood pressure (BP) for patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) remains unclear. This study aims to identify the optimal BP by investigating the association between average office BP and future clinical events in patients undergoing PCI. Consecutive patients undergoing PCI from 2012 to 2016 were included. They were divided into five groups according to the average follow-up BP after discharge. The co-primary outcomes were net adverse clinical events (NACE) and major adverse cardiac and cerebrovascular events (MACCE) up to 5 years. NACE was defined as a composite of MACCE (all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, or any revascularization) or major bleeding. A total of 2845 patients were included, and among them, 787 (27.7%) experienced the NACE during the follow-up period. Patients in the highest SBP group (adjusted hazard ratio [HR] 1.495, confidence interval [CI] 1.189–1.880) and lowest SBP group (adjusted HR 1.625, CI 1.214–2.176) had a significantly higher risk of 5-year NACE. Similar associations were observed between SBP and the risk of MACCE, and similar results based on DBP categories were also observed. There was a J-curve relationship between SBP and DBP with respect to 5-year NACE and MACCE. The nadir point of risk for NACE and MACCE was found at 121.4/74.8 and 120.4/73.7 mmHg. In patients underwent PCI, there is a significant correlation between office BP level and clinical events, indicates the importance of efforts for optimal BP control to reduce ischemic and bleeding events.

Trial registration: HanYang University Medical Center (HYUMC) Registry, NCT05935397.

Keywords Blood pressure, Coronary artery disease, Hypertension, Percutaneous coronary intervention

Coronary artery disease (CAD) is the main cause of death globally, and accounting for > 9 million deaths in 2017[1]. Percutaneous coronary interventions (PCI) have increasingly been performed for revascularization in patients with CAD and have become the standard treatment in acute coronary syndrome[2]. Revascularization had advanced in not only procedural aspect, but also aspect of medical treatment[3,4]. However, the incidence of death or cardiovascular events after revascularization is still high with a 24 to 30% event rate at 10 years[5,6]. To mitigate these risks of adverse events following revascularization, effective secondary prevention strategies are essential, including lifestyle management, antiplatelet therapy, and treatments for hypertension, dyslipidemia, and diabetes.

There are strong epidemiological relationships between high blood pressure (BP) and CAD[7]. Despite hypertension being a major modifiable risk factor for CAD[8], the optimal BP target for patients with CAD remains unclear. Clinical guidelines for the hypertension recommending a BP target of below 130 mmHg for the systolic blood pressure (SBP) and below 80 mmHg for the diastolic blood pressure (DBP) levels[9–11]. However, the basis

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for these recommendations relies on studies conducted primarily on hypertensive patients, including some who also have CAD. Particularly, there is a notable lack of evidence regarding patients who have undergone PCI[12]. In addition, there have also been reports of a J- or U-curve association between BP and risk of adverse cardiovascular events, suggesting that excessive low BP (particularly < 110/70 or 120/70 mmHg) may be dangerous in patients with CAD[13,14]. Therefore, this study aimed to identify the optimal BP target by investigating the association between average follow-up office BP and future adverse clinical events after PCI in patients with CAD.

Methods

Study participants

We used data from the HanYang University Medical Center (HYUMC) registry (NCT05935397), an observational, two-center database including consecutive patients with CAD who underwent PCI between 2012 and 2016 at the Division of Cardiology of Hanyang University Seoul Hospital and Hanyang University Guri Hospital in Korea. Consecutive patients treated with one or more drug-eluting stents (DES) at each hospital were eligible for inclusion, irrespective of patient characteristics or lesion complexity.

We reviewed the medical records of 3525 patients and applied the following exclusion criteria: duplicate patients, patients who died during the index hospitalization, patients who were treated with first-generation DES, patients lost to follow-up within 6 months, and patients with insufficient medical records. Finally, the study included 2845 patients who received PCI. Patients were classified according to average office SBP and DBP measured at the outpatient department during the follow-up period after PCI (Fig. 1).

Data collection

All data were collected from electronic medical records by experienced investigators under the supervision of the principal investigator. Demographic and clinical characteristics, traditional cardiovascular risk factors and comorbidity were obtained. Medication records were collected at the time of discharge, including antiplatelet drugs, anticoagulants, statins, nitrates, angiotensin blockades, β-blockers, calcium channel blockers, diuretics, and mineralocorticoid receptor antagonists.

The following laboratory data were collected: creatinine, fasting glucose, hemoglobin A1c, lipid profiles, and cardiac troponin-I levels. Moreover, the angiographic data were obtained. The left ventricular ejection fraction (LVEF) measured through transthoracic echocardiography performed during the index hospitalization was also acquired.

Patient management and clinical follow-up

Patients were treated in accordance with the standard practices at the respective hospitals. Based on the guidelines, the operator decided on the treatment strategy, including stent implantation and medication selection[3]. Patients were followed up clinically for 1 month after the procedure and every 3 subsequent months. During outpatient

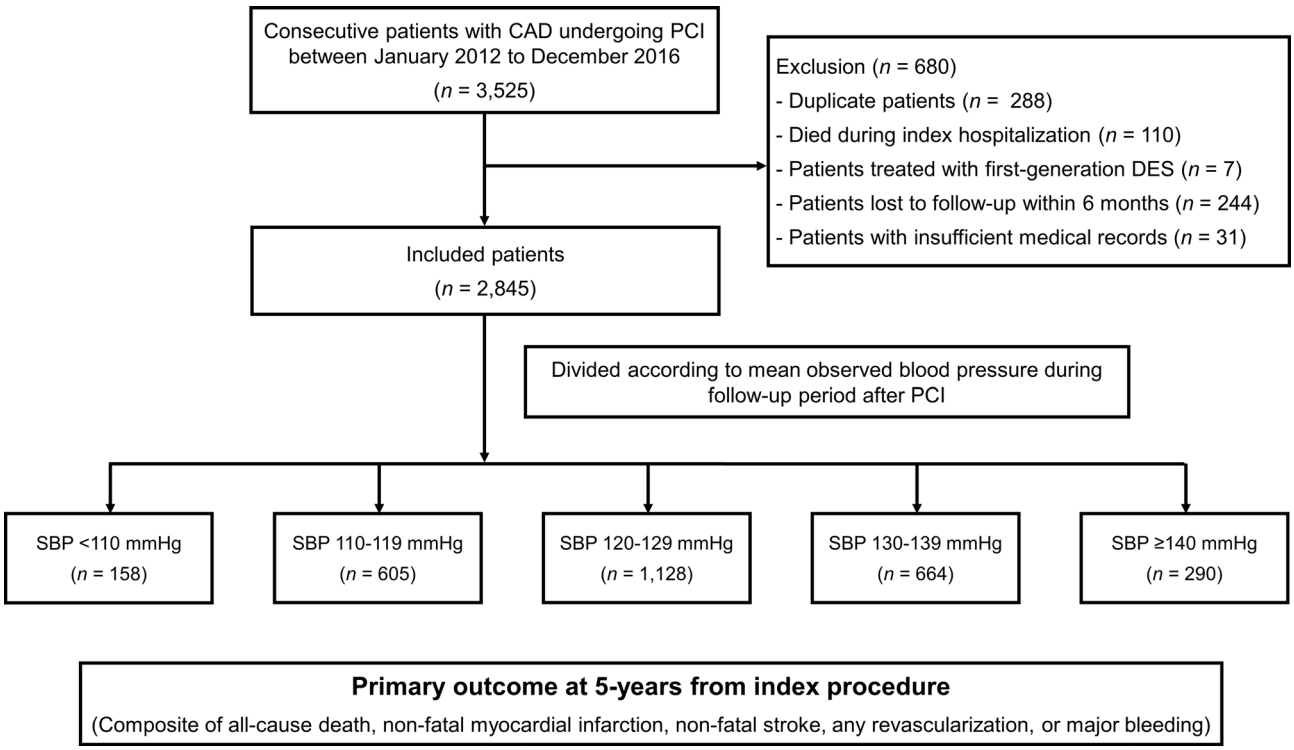

Fig. 1. Flow diagram of the study. CAD, coronary artery disease; PCI, percutaneous coronary intervention; DES, drug-eluting stent; SBP, systolic blood pressure.

visits, BP measurements were taken using an automated BP machine, OMRON HEM-907XL (OMRON, Kyoto, Japan), after 5 min of quiet rest on seated position. All available office BP readings from the outpatient records were compiled, spanning up to 5 years or including the initial 20 readings following discharge. Average SBP and DBP values were calculated from the obtained SBP and DBP data for subsequent analysis.

Outcome definitions

The co-primary outcomes in this study were net adverse clinical events (NACE) and major adverse cardiac and cerebrovascular events (MACCE) up to 5 years. NACE was defined as a composite of MACCE or major bleeding and MACCE as a composite of all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, or any revascularization. The secondary outcomes included each component of the primary outcomes.

Clinical outcomes were defined based on the Academic Research Consortium recommendations[15]. MI was defined as the presence of clinical symptoms accompanied by electrocardiographic changes or imaging evidence indicating new loss of viable myocardium or new regional wall motion abnormalities, including elevated levels of cardiac biomarkers above the 99th percentile upper reference limit. Peri-procedural MI was excluded. Stroke was defined as a neurological deficit resulting from acute focal damage to the central nervous system due to a vascular cause, requiring hospitalization and confirmed by a neurologist through imaging findings. Any revascularization included PCI or coronary artery bypass surgery on either target or non-target vessels. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding[16].

Statistical analysis

Categorical variables are reported as frequencies and percentages, while continuous variables are presented as means with standard deviations or medians with interquartile ranges (IQR), depending on their distribution. The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test and Q-Q plots for visual inspection. Differences between groups were assessed using the chi-square test for categorical variables and one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables.

Cumulative event rates were estimated with the Kaplan–Meier curve and compared using the log-rank test. Using a Cox proportional hazard regression model, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) for the clinical outcomes according to the BP categories. Multivariable Cox proportional hazard models were conducted adjusting for clinically relevant variables such as age, sex, body mass index, MI presentation, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous PCI, previous stroke, LVEF, troponin-I, estimated glomerular filtration rate (eGFR), multivessel disease, and use of anticoagulants, statins, angiotensin blockades, and β-blockers. Subsequently, reduced models were constructed through a backward elimination procedure using the best Akaike's information criterion. The associations between BP as a continuous variable and the risks of clinical outcomes were assessed by fitting them with a restricted cubic spline curve featuring five knots. Additionally, a sensitivity analysis was performed by excluding the 735 patients who were lost to follow-up and analyzing the hazard ratios of clinical outcomes according to SBP groups for the remaining 2110 patients.

All statistical analyses were conducted using the open-source statistical software R (version 4.3.1, www.R-project.org) and R-studio (version 2023.06.2, www.rstudio.com) and statistical packages, including rms, descr, survival, tableone, survminer, ggplot2, forestploter, and plotRCS. All tests were 2-sided, and P-value of < 0.05 was considered statistically significant.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board of Hanyang University Seoul Hospital (No. 2022-06-064) and Hanyang University Guri Hospital (No. 2022-06-010). Patient consent is not applicable to this article as it involves a retrospective cohort analysis of deidentified data. The Institutional Review Board waived the need for written informed consent.

Results

Baseline characteristics

Baseline characteristics according to systolic and diastolic BP categories are demonstrated in Table 1 and Supplementary Table 1, respectively. Patients in the higher SBP groups tended to be older, have higher body mass index values, and exhibited a higher prevalence of comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, previous PCI, and previous stroke. Conversely, patients in the lower SBP groups were more likely to be male, had a higher rate of current smoking, and more frequently presented with MI (Table 1).

Contrastingly, patients in the lower DBP groups were more likely to be older, female, leaner and had a higher prevalence of diabetes mellitus, while those in the higher DBP groups had a higher rate of current smoking and a greater prevalence of hypertension and dyslipidemia (Supplementary Table 1). However, the angiographic characteristics were similar across all groups.

Clinical outcomes

The median duration of follow-up was 5.43 (IQR: 2.05–8.42) years, and the median number of BP readings was 20 (IQR: 10–20). During the follow-up period, NACE and MACCE occurred in 787 (27.7%) and 559 (19.6%) patients, respectively. Kaplan–Meier curves for the incidence rates of the primary and secondary outcomes according to SBP and DBP categories are presented in Figs. 2 and 3. The incidence rates of NACE and MACCE were highest in patients with the highest SBP (≥ 140 mmHg), followed by patients with the lowest SBP

		Systolic blood pressure (mmHg)					
	All patients (n = 2845)	< 110 (n = 158)	110–119 (n = 605)	120–129 (n = 1128)	130–139 (n = 664)	≥ 140 (n = 290)	*P*-value
Age, years	64.79 ± 11.99	64.45 ± 11.24	63.43 ± 11.69	63.75 ± 11.81	66.54 ± 11.95	67.79 ± 12.89	< 0.001
Men, n (%)	1949 (68.5)	127 (80.4)	425 (70.2)	818 (72.5)	412 (62.0)	167 (57.6)	< 0.001
Body mass index, kg/m^2	24.88 ± 3.39	23.70 ± 3.05	24.46 ± 3.18	25.00 ± 3.37	25.36 ± 3.25	24.87 ± 4.06	< 0.001
Average follow-up BP, mmHg							
Systolic BP	126.45 ± 11.37	104.98 ± 4.63	115.66 ± 2.72	125.05 ± 2.77	134.17 ± 2.84	148.48 ± 8.29	< 0.001
Diastolic BP	73.01 ± 7.39	63.16 ± 5.54	68.91 ± 5.20	73.22 ± 5.88	75.61 ± 6.67	80.16 ± 8.51	< 0.001
Index presentation with AMI, n (%)	1175 (41.3)	91 (57.6)	260 (43.0)	467 (41.4)	246 (37.0)	111 (38.3)	0.001
Risk factors, n (%)							
Current smoking	816 (28.7)	54 (34.2)	202 (33.4)	342 (30.3)	148 (22.3)	70 (24.1)	< 0.001
Hypertension	1693 (59.5)	50 (31.6)	248 (41.0)	652 (57.8)	498 (75.0)	245 (84.5)	< 0.001
Diabetes mellitus	986 (34.7)	43 (27.2)	197 (32.6)	351 (31.1)	247 (37.2)	148 (51.2)	< 0.001
Dyslipidemia	1135 (39.9)	63 (39.9)	235 (38.8)	466 (41.3)	273 (41.1)	98 (33.9)	0.203
Chronic kidney disease	163 (5.7)	7 (4.4)	27 (4.5)	43 (3.8)	36 (5.4)	50 (17.2)	< 0.001
Previous PCI	359 (12.6)	18 (11.4)	72 (11.9)	126 (11.2)	105 (15.8)	38 (13.1)	0.066
Previous stroke	276(9.7)	8 (5.1)	55 (9.1)	96 (8.5)	67 (10.1)	50 (17.2)	< 0.001
Laboratory findings							
LVEF, %	56.61 ± 11.29	51.56 ± 12.37	56.18 ± 11.16	57.01 ± 11.24	57.94 ± 10.75	55.65 ± 11.56	< 0.001
Troponin-I	20 (10, 210)	40 (10, 1100)	20 (10, 230)	20 (10, 180)	20 (10, 150)	40 (10, 250)	0.001[a]
eGFR, mL/min/1.73 m2	80.34 ± 24.12	81.93 ± 21.89	83.32 ± 21.46	83.96 ± 21.52	77.64 ± 24.55	65.35 ± 31.66	< 0.001
Total cholesterol, mg/dL	168 (141, 200)	167 (140, 203)	165 (136, 196)	170 (144, 201)	169 (144, 201)	164 (135, 198)	0.057[a]
LDL cholesterol, mg/dL	99 (77, 125)	103 (77, 131)	98 (74, 123)	101 (77, 125)	100 (79, 123)	98 (74, 127)	0.490[a]
HDL cholesterol, mg/dL	41 (35, 48)	41 (34, 49)	41 (35, 48)	41 (34, 48)	41 (35, 48)	41 (34, 48)	0.975[a]
Triglyceride, mg/dL	122 (87, 178)	121 (85, 154)	121 (84, 174)	123 (89, 183)	125 (89, 182)	115 (81, 171)	0.056[a]
HbA1c, %	5.9 (5.5, 6.6)	5.8 (5.5, 6.2)	5.8 (5.5, 6.6)	5.8 (5.5, 6.5)	5.9 (5.6, 6.6)	6.0 (5.5, 7.1)	0.006[a]
Procedural characteristics							
Multivessel disease, n (%)	1048 (36.8)	49 (31.0)	202 (33.4)	436 (38.7)	243 (36.6)	118 (40.7)	0.065
Target lesion, n (%)							
Left main coronary artery	71 (2.5)	4 (2.5)	20 (3.3)	21 (1.9)	16 (2.4)	10 (3.4)	0.331
Left anterior descending artery	1922 (67.6)	104 (65.8)	405 (66.9)	772 (68.4)	433 (65.2)	208 (71.7)	0.321
Left circumflex artery	981 (34.5)	52 (32.9)	191 (31.6)	395 (35.0)	242 (36.4)	101 (34.8)	0.443
Right coronary artery	1167 (41.0)	56 (35.4)	240 (39.7)	470 (41.7)	280 (42.2)	121 (41.7)	0.541
Chronic total occlusion, n (%)	199 (7.0)	11 (7.0)	34 (5.6)	90 (8.0)	42 (6.3)	22 (7.6)	0.399
In-stent restenosis, n (%)	120 (4.2)	5 (3.2)	22 (3.6)	45 (4.0)	39 (5.9)	9 (3.1)	0.167
Discharge medication, n (%)							
Aspirin	2795 (98.2)	157 (99.4)	592 (97.9)	1107 (98.1)	653 (98.3)	286 (98.6)	0.728
Type of $P2Y_{12}$ inhibitor							
Clopidogrel	1910 (67.1)	88 (55.7)	365 (60.3)	768 (68.1)	475 (71.5)	214 (73.8)	< 0.001
Ticagrelor	638 (22.4)	52 (32.9)	156 (25.8)	245 (21.7)	128 (19.3)	57 (19.7)	0.001
Prasugrel	214 (7.5)	17 (10.8)	67 (11.1)	80 (7.1)	42 (6.3)	8 (2.8)	< 0.001
Cilostazol	365 (12.8)	23 (14.6)	68 (11.2)	152 (13.5)	78 (11.7)	44 (15.2)	0.363
Anti-coagulant	48 (1.7)	1 (0.6)	10 (1.7)	25 (2.2)	6 (0.9)	6 (2.1)	0.224
Statin	2617 (92.0)	146 (92.4)	567 (93.7)	1045 (92.6)	606 (91.3)	253 (87.2)	0.014
Nitrate	1675 (58.9)	70 (44.3)	323 (53.4)	685 (60.7)	416 (62.7)	181 (62.4)	< 0.001
Angiotensin blockade	1633 (57.4)	92 (58.2)	354 (58.5)	615 (54.5)	387 (58.3)	185 (63.8)	0.056
Beta-blocker	2018 (70.9)	120 (75.9)	427 (70.6)	791 (70.1)	467 (70.3)	213 (73.4)	0.504

Continued

	All patients (n = 2845)	Systolic blood pressure (mmHg)					*P*-value
		< 110 (n = 158)	110–119 (n = 605)	120–129 (n = 1128)	130–139 (n = 664)	≥ 140 (n = 290)	
Calcium channel blocker	341 (12.0)	8 (5.1)	61 (10.1)	114 (10.1)	92 (13.9)	66 (22.8)	< 0.001
Diuretics	478 (16.8)	49 (31.0)	107 (17.7)	168 (14.9)	94 (14.2)	60 (20.7)	< 0.001
MRA	334 (11.7)	39 (24.7)	81 (13.4)	125 (11.1)	62 (9.3)	27 (9.3)	< 0.001

Table 1. Baseline characteristics according to systolic blood pressure categories. Data are presented as n (%) or median (interquartile range). BP, blood pressure; 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; MRA, mineralocorticoid receptor antagonist. [a]As assessed using nonparametric tests.

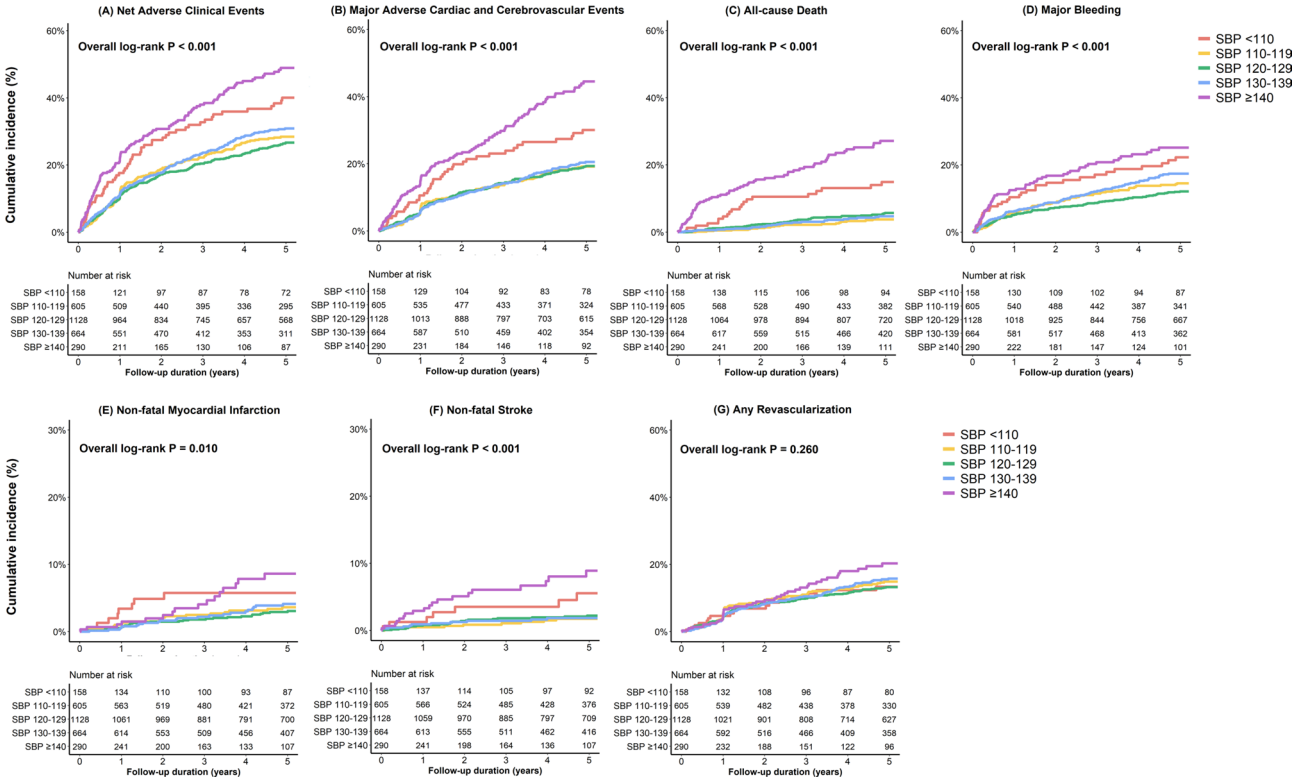

Fig. 2. Kaplan–Meier curves for the cumulative incidence of the clinical outcomes according to SBP categories. (**A**) NACE, (**B**) MACCE, (**C**) all-cause death, (**D**) major bleeding, (E) non-fatal myocardial infarction, (**F**) non-fatal stroke, and (**G**) any revascularization. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; SBP, systolic blood pressure.

(< 110 mmHg), while the remaining patients exhibited similar incidence rates. A similar trend was observed for the other secondary outcomes, excluding any revascularization (Fig. 2 and Table 2).

Regarding the incidence rates of the primary and secondary outcomes according to DBP categories, the highest rates of MACCE, all-cause death, non-fatal MI, and any revascularization were observed in the highest DBP group (≥ 90 mmHg), followed by the lowest DBP group (< 60 mmHg). The incidence rate of NACE and non-fatal stroke was highest in the lowest DBP group, followed by the highest DBP group. Additionally, the incidence rate of major bleeding was highest in the lowest DBP group, and there was a decreasing trend in the incidence rate as the DBP increased (Fig. 3 and Table 3).

Tables 2 and 3 present the incidence rates of the primary and secondary outcomes and the corresponding HR for these outcomes, using the reference intervals of 120–129 mmHg for SBP and 70–79 mmHg for DBP. After adjusting for the clinically relevant covariates, the highest SBP (adjusted HR 1.495, CI 1.189–1.880 for NACE and adjusted HR 2.053, CI 1.598–2.637 for MACCE) and lowest SBP groups (adjusted HR 1.625, CI 1.214–2.176 for NACE and adjusted HR 1.642, CI 1.166–2.311 for MACCE) demonstrated a significantly higher risk of 5-year NACE, MACCE, all-cause death, and non-fatal stroke. The highest SBP group also had a higher risk of 5-year non-fatal MI, while the lowest SBP group had a higher risk of 5-year major bleeding (Table 2 and Supplementary Fig. 1).

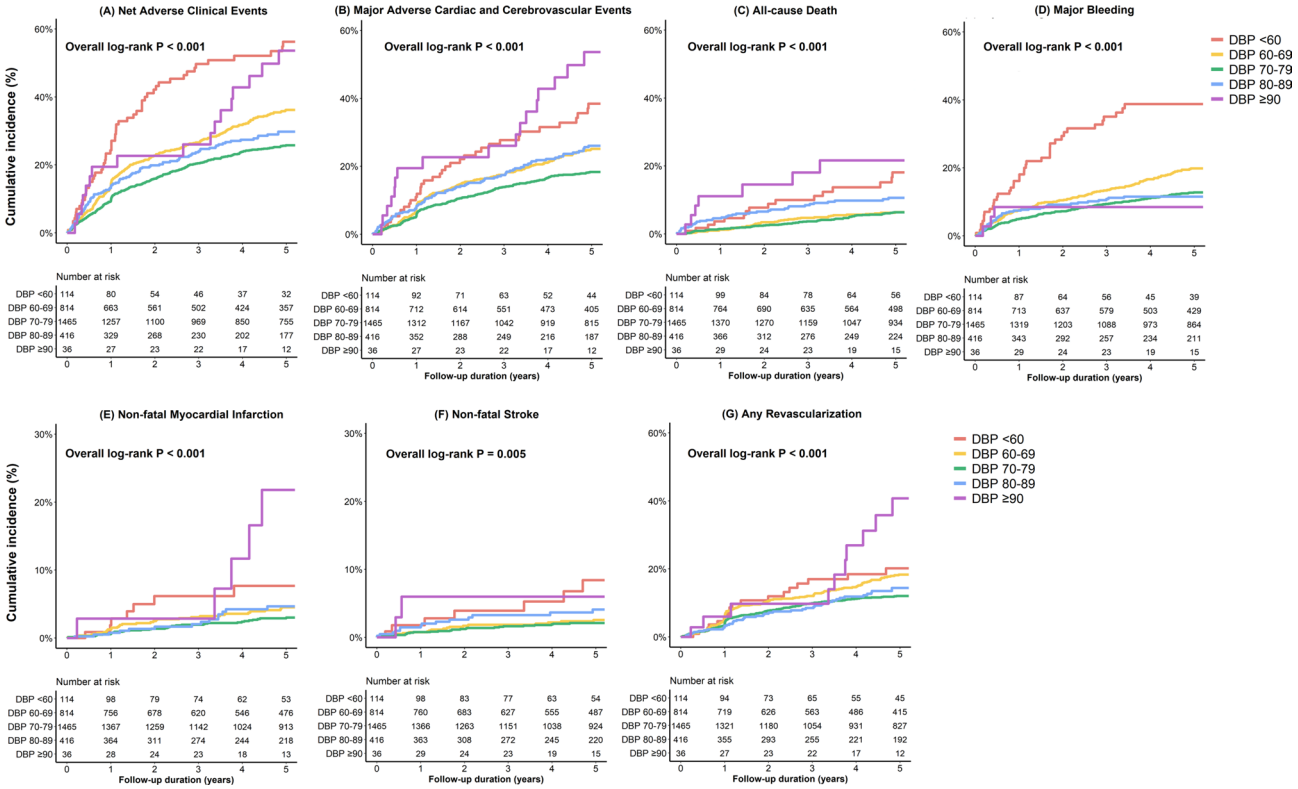

Fig. 3. Kaplan–Meier curves for the cumulative incidence of the clinical outcomes according to DBP categories. (**A**) NACE, (**B**) MACCE, (**C**) all-cause death, (**D**) major bleeding, (**E**) non-fatal myocardial infarction, (**F**) non-fatal stroke, and (**G**) any revascularization. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; DBP, diastolic blood pressure.

The risk of NACE and MACCE according to DBP showed higher HRs in the highest DBP group, lowest DBP group, DBP 80–89 mmHg group, and DBP 60–69 mmHg group compared to the reference group (DBP 70–79 mmHg), and all of these differences were statistically significant. For major bleeding, a significantly higher risk was observed only in the lowest DBP group (Table 3 and Supplementary Fig. 2).

The restrictive cubic spline curves illustrate the continuous relationship between BP and the risk of primary and secondary outcomes (Figs. 4 and 5). The results revealed that SBP exhibited a J- or U-shaped curve in relation to the risk of primary and secondary outcomes. The analysis identified a nadir of 121.4 and 120.4 mmHg for SBP, indicating the point at which the risk of NACE and MACCE was the lowest (Fig. 4). Similarly, DBP followed a J- or U-shaped curve in relation to the risk of primary and secondary outcomes, although it was less pronounced than SBP. The nadir for DBP was found to be 74.8 and 73.7 mmHg, indicating the point at which the risk of NACE and MACCE was the lowest (Fig. 5).

We performed a subgroup analysis stratified by age (< 60, 60–74, or ≥ 75 years), sex, LVEF (≤ 40, 41–49, or ≥ 50%), and eGFR (< 30, 30–59, or ≥ 60 mL/min/1.73 m^2). The results showed a J- or U-shaped association in most subgroups, with the lowest risk point of primary and secondary outcomes observed between SBP 120–135 mmHg and DBP 70–80 mmHg. In patients under 60 years, a J- or U-shaped association was observed between DBP and the primary outcome but not for SBP (Supplementary Fig. 3–6). Additionally, a comparison of the baseline characteristics according to dropout status revealed that the groups were largely similar, with the exception of differences in the prevalence of diabetes mellitus and dyslipidemia (Supplementary Table 2). A sensitivity analysis was conducted, excluding the 735 patients who were lost to follow-up. The results were found to be consistent with those of the primary analysis (Supplementary Table 3).

Discussion

This is the first study to demonstrate the long-term association between follow-up BP and adverse clinical events, including ischemic and bleeding events, in patients with CAD who underwent PCI. The key findings of this study were as follows: (1) A strong correlation was found between office BP and 5-year MACCE and NACE. (2) The lowest risk of primary outcomes was associated with a nadir BP point of 121.4/74.8 mmHg for NACE and 120.4/73.7 mmHg for MACCE. (3) A J-shaped relationship was observed, indicating that BP below 110/70 mmHg were associated with an elevated risk of NACE and MACCE. This suggests that excessively low BP may indicate an unfavorable prognosis in patients who underwent PCI.

The optimal BP targets for hypertensive patients with CAD are still a subject of debate, given the limited number of randomized clinical trials specifically addressing this question. A post-hoc analysis of the INternational VErapamil SR Trandolapril STudy (INVEST) suggested that reducing SBP below 140 mmHg may benefit

		Univariable analysis		Multivariable analysis[a]	
	Cumulative incidence (%)	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
NACE[a]					
SBP < 110	57/158 (36.1)	1.695 (1.274–2.255)	< 0.001	1.625 (1.214–2.176)	0.001
SBP 110–119	156/605 (25.8)	1.091 (0.896–1.328)	0.387	1.131 (0.927–1.380)	0.226
SBP 120–129	271/1128 (24.0)	Reference		Reference	
SBP 130–139	181/664 (27.3)	1.178 (0.976–1.422)	0.088	1.077 (0.888–1.306)	0.453
SBP ≥ 140	122/290 (42.1)	2.177 (1.758–2.696)	< 0.001	1.495 (1.189–1.880)	0.001
MACCE[c]					
SBP < 110	41/158 (25.9)	1.710 (1.221–2.396)	0.002	1.642 (1.166–2.311)	0.005
SBP 110–119	102/605 (16.9)	0.991 (0.780–1.260)	0.944	0.993 (0.780–1.266)	0.957
SBP 120–129	193/1128 (17.1)	Reference		Reference	
SBP 130–139	117/664 (17.6)	1.047 (0.833–1.318)	0.692	0.983 (0.779–1.242)	0.888
SBP ≥ 140	106/290 (36.6)	2.639 (2.082–3.346)	< 0.001	2.053 (1.598–2.637)	< 0.001
All-cause death					
SBP < 110	20/158 (12.7)	2.895 (1.735–4.830)	< 0.001	2.941 (1.744–4.961)	< 0.001
SBP 110–119	19/605 (3.1)	0.642 (0.381–1.082)	0.096	0.619 (0.363–1.056)	0.078
SBP 120–129	55/1128 (4.9)	Reference		Reference	
SBP 130–139	26/664 (3.9)	0.817 (0.512–1.302)	0.395	0.647 (0.400–1.046)	0.076
SBP ≥ 140	65/290 (22.4)	5.780 (4.034–8.282)	< 0.001	3.540 (2.399–5.221)	< 0.001
Major bleeding[d]					
SBP < 110	31/158 (19.6)	1.992 (1.343–2.955)	0.001	1.854 (1.237–2.780)	0.003
SBP 110–119	79/605 (13.1)	1.225 (0.923–1.626)	0.159	1.294 (0.971–1.724)	0.079
SBP 120–129	122/1128 (10.8)	Reference		Reference	
SBP 130–139	100/664 (15.1)	1.444 (1.108–1.881)	0.006	1.207 (0.919–1.586)	0.175
SBP ≥ 140	60/290 (20.7)	2.371 (1.740–3.230)	< 0.001	1.313 (0.942–1.829)	0.108
Non-fatal MI					
SBP < 110	8/158 (5.1)	2.255 (1.031–4.934)	0.042	1.891 (0.859–4.159)	0.113
SBP 110–119	19/605 (3.1)	1.226 (0.687–2.186)	0.491	1.143 (0.634–2.059)	0.656
SBP 120–129	29/1128 (2.6)	Reference		Reference	
SBP 130–139	22/664 (3.3)	1.310 (0.753–2.281)	0.339	1.267 (0.727–2.207)	0.404
SBP ≥ 140	16/290 (5.5)	2.711 (1.471–4.994)	0.001	2.147 (1.134–4.065)	0.019
Non-fatal stroke					
SBP < 110	7/158 (4.4)	2.517 (1.076–5.887)	0.033	2.636 (1.048–6.632)	0.040
SBP 110–119	9/605 (1.5)	0.762 (0.351–1.655)	0.492	0.821 (0.376–1.793)	0.621
SBP 120–129	22/1128 (2.0)	Reference		Reference	
SBP 130–139	11/664 (1.7)	0.864 (0.419–1.782)	0.692	0.821 (0.393–1.715)	0.599
SBP ≥ 140	19/290 (6.6)	4.084 (2.208–7.553)	< 0.001	3.216 (1.665–6.212)	0.001
Any revascularization					
SBP < 110	17/158 (10.8)	1.024 (0.618–1.697)	0.928	1.032 (0.621–1.716)	0.268
SBP 110–119	79/605 (13.1)	1.133 (0.857–1.498)	0.381	1.131 (0.853–1.499)	0.393
SBP 120–129	131/1128 (11.6)	Reference		Reference	
SBP 130–139	88/664 (13.3)	1.161 (0.886–1.521)	0.280	1.118 (0.852–1.466)	0.423
SBP ≥ 140	41/290 (14.1)	1.486 (1.046–2.110)	0.027	1.206 (0.829–1.753)	0.327

Table 2. Incidences and hazard ratios for the primary and secondary outcomes according to systolic blood pressure. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; SBP, systolic blood pressure; MI, myocardial infarction; CI, confidence interval. [a]Adjustment for age, sex, body mass index, presentation with MI, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous PCI, previous stroke, left ventricular ejection fraction, troponin-I, estimated glomerular filtration rate, multivessel disease, and use of anticoagulants, statins, angiotensin blockades, and β-blockers. [b]NACE was defined as a composite of all-cause death, non-fatal MI, non-fatal stroke, any revascularization, or major bleeding. [c]MACCE was defined as a composite of all-cause death, non-fatal MI, non-fatal stroke, or any revascularization. [d]Major bleeding was defined as Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding.

	Cumulative incidence	Univariable analysis		Multivariable analysis[a]	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
NACE[b]					
DBP < 60	57/114 (50.0)	2.816 (2.127–3.728)	< 0.001	2.038 (1.525–2.724)	< 0.001
DBP 60–69	265/814 (32.6)	1.477 (1.258–1.734)	< 0.001	1.268 (1.074–1.496)	0.005
DBP 70–79	341/1465 (23.3)	Reference		Reference	
DBP 80–89	107/416 (41.6)	1.224 (0.985–1.521)	0.069	1.369 (1.097–1.708)	0.005
DBP ≥ 90	17/36 (47.2)	2.310 (1.419–3.759)	0.001	2.794 (1.685–4.633)	< 0.001
MACCE[c]					
DBP < 60	36/114 (31.6)	2.285 (1.609–3.245)	< 0.001	1.827 (1.277–2.613)	0.001
DBP 60–69	179/814 (22.0)	1.404 (1.156–1.705)	0.001	1.241 (1.017–1.515)	0.033
DBP 70–79	238/1465 (16.2)	Reference		Reference	
DBP 80–89	89/416 (21.4)	1.462 (1.146–1.866)	0.002	1.629 (1.270–2.090)	< 0.001
DBP ≥ 90	17/36 (47.2)	3.573 (2.193–5.823)	< 0.001	4.403 (2.638–7.348)	< 0.001
All-cause death					
DBP < 60	16/114 (14.0)	2.940 (1.717–5.032)	< 0.001	1.494 (0.859–2.598)	0.155
DBP 60–69	45/814 (5.5)	1.037 (0.719–1.495)	0.847	0.728 (0.497–1.066)	0.102
DBP 70–79	79/1465 (5.4)	Reference		Reference	
DBP 80–89	38/416 (9.1)	1.897 (1.288–2.794)	0.001	2.557 (1.708–3.828)	< 0.001
DBP ≥ 90	7/36 (19.4)	4.394 (2.030–9.511)	< 0.001	7.817 (3.526–17.326)	< 0.001
Major bleeding[d]					
DBP < 60	39/114 (34.2)	3.788 (2.671–5.371)	< 0.001	2.140 (1.484–3.084)	< 0.001
DBP 60–69	141/814(17.3)	1.580 (1.262–1.977)	< 0.001	1.245 (0.987–1.571)	0.064
DBP 70–79	166/1465 (11.3)	Reference		Reference	
DBP 80–89	43/416 (10.3)	1.008 (0.720–1.409)	0.964	1.184 (0.841–1.666)	0.334
DBP ≥ 90	3/36 (8.3)	0.829 (0.265–2.598)	0.748	1.155 (0.367–3.638)	0.805
Non-fatal MI					
DBP < 60	7/114 (6.1)	2.812 (1.253–6.308)	0.012	2.678 (1.191–6.023)	0.017
DBP 60–69	31/814 (3.8)	1.535 (0.953–2.474)	0.078	1.411 (0.869–2.290)	0.164
DBP 70–79	37/1465 (2.5)	Reference		Reference	
DBP 80–89	14/416 (3.4)	1.493 (0.807–2.762)	0.201	1.359 (0.722–2.558)	0.342
DBP ≥ 90	5/36 (13.9)	6.844 (2.690–17.411)	< 0.001	6.840 (2.679–17.467)	< 0.001
Non-fatal stroke					
DBP < 60	7/114 (6.1)	3.714 (1.617–8.531)	0.002	2.116 (0.885–5.059)	0.092
DBP 60–69	18/814 (2.2)	1.215 (0.669–2.205)	0.523	0.972 (0.528–1.789)	0.928
DBP 70–79	27/1465 (1.8)	Reference		Reference	
DBP 80–89	14/416 (3.4)	2.021 (1.059–3.854)	0.033	2.498 (1.293–4.826)	0.006
DBP ≥ 90	2/36 (5.6)	3.590 (0.853–15.099)	0.081	5.385 (1.249–23.218)	0.024
Any revascularization					
DBP < 60	18/114 (15.8)	1.710 (1.050–2.786)	0.031	1.815 (1.107–2.974)	0.018
DBP 60–69	127/814 (15.6)	1.509 (1.194–1.907)	.001	1.527 (1.203–1.937)	< .001
DBP 70–79	156/1465 (10.6)	Reference		Reference	
DBP 80–89	45/416 (10.8)	1.119 (0.803–1.560)	0.506	1.100 (0.786–1.540)	0.578
DBP ≥ 90	10/36 (27.8)	3.203 (1.695–6.053)	< 0.001	3.001 (1.528–5.893)	0.001

Table 3. Incidences and hazard ratios for the primary and secondary outcomes according to diastolic blood pressure. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; SBP, systolic blood pressure; MI, myocardial infarction; CI, confidence interval. [a]Adjustment for age, sex, body mass index, presentation with MI, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous PCI, previous stroke, left ventricular ejection fraction, troponin-I, estimated glomerular filtration rate, multivessel disease, anticoagulant, statin, angiotensin blockade, and β-blockers. [b]NACE was defined as a composite of all-cause death, non-fatal MI, non-fatal stroke, any revascularization, or major bleeding. [c]MACCE was defined as a composite of all-cause death, non-fatal MI, non-fatal stroke, or any revascularization. [d]Major bleeding was defined as Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding.

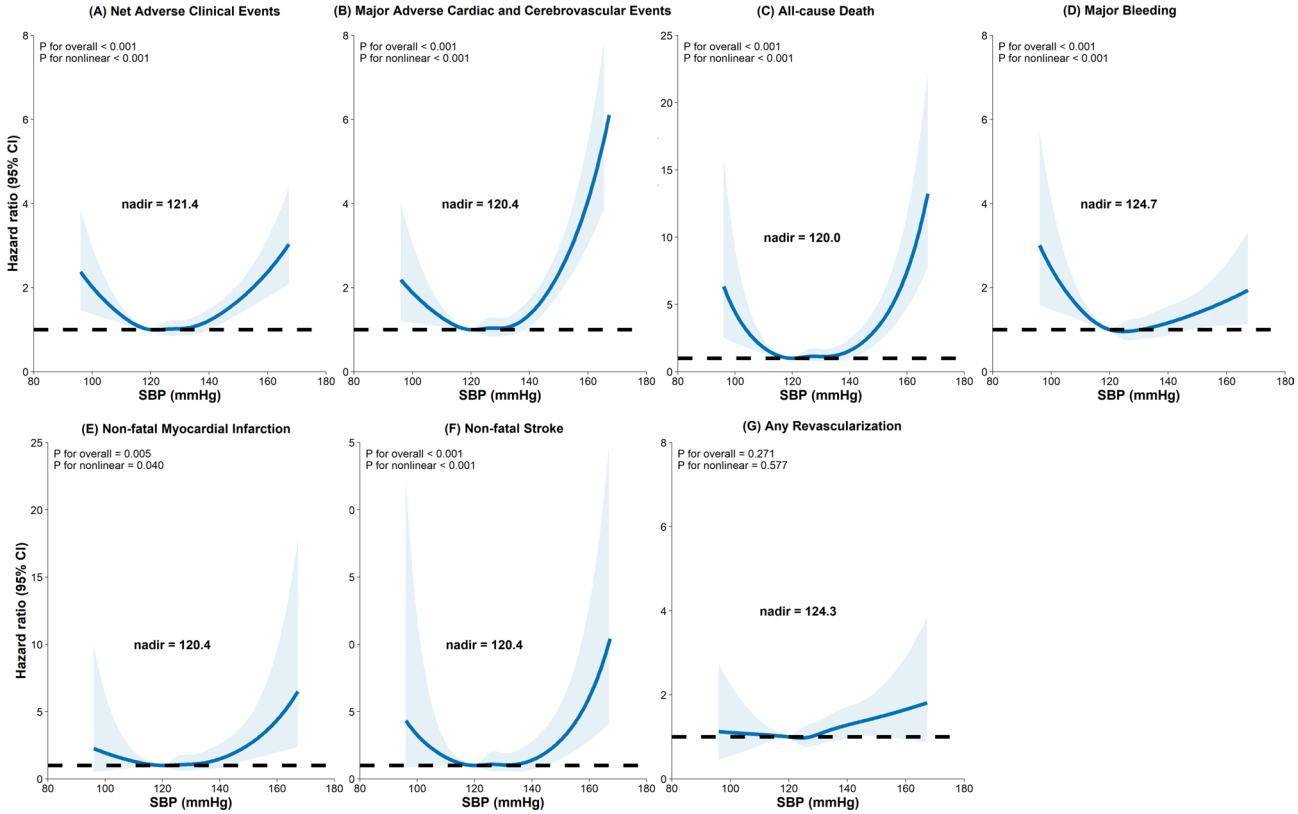

Fig. 4. Continuous association between SBP and the risk of clinical outcomes. (**A**) NACE, (**B**) MACCE, (**C**) all-cause death, (**D**) major bleeding, (**E**) non-fatal myocardial infarction, (**F**) non-fatal stroke, and (**G**) any revascularization. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; SBP, systolic blood pressure; CI, confidence interval.

elderly hypertensive patients with CAD[17]. Similarly, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) trial observed that the lowest event rates were associated with an SBP range of 130–140 mmHg in patients with acute coronary syndrome[14]. Additionally, the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study demonstrated that amlodipine treatment reduced cardiovascular events in normotensive CAD patients[18]. Furthermore, in a recent post hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), positive cardiovascular benefits from intensive BP control were found to be attenuated in patients with CAD compared with those without CAD; however, intensive BP control in CAD patients showed beneficial effects in reducing all-cause mortality. Considering these findings, incorporating CAD patients as high-risk individuals in conjunction with meta-analyses[19–22], clinical practice guidelines for hypertension management recommend a BP target of < 130/80 mmHg for hypertensive patients with CAD[9–11], even though there have been no specific studies on optimal BP levels for CAD patients.

The evidence supporting the applicability of the same BP target in CAD patients who underwent PCI is even more limited. A previous single-center registry study demonstrated that lower SBP values below 120 mmHg were associated with future cardiovascular benefits[23]. A recent study utilizing the Korean National Health Insurance System (NHIS) database identified that a nadir BP of 119/74 mmHg was associated with the lowest all-cause mortality in CAD patients who underwent PCI[12]. Although the study only investigated all-cause mortality and utilized a single measurement of BP, the observed BP nadir in that study closely aligned with the BP nadir observed in our study. In contrast, our study collected follow-up BP measurements in the outpatient department after PCI, allowing us to demonstrate results more reflective of real-world clinical situations.

While the benefits of intensive BP control have been emphasized recently, concerns remain regarding the presence of J-shaped relationships, particularly in CAD patients. Moreover, higher mortality rates and cardiovascular adverse events are associated with high and low SBP and DBP values[12–14,24–26]. Taking this into consideration, the guidelines recommend not lowering BP below 110 ~ 120/70 mmHg for patients with CAD[9,11].

The J-curve phenomenon was more pronounced in DBP, aligning with the rationale that coronary perfusion occurs during diastole[27]. However, these J-shaped relationships can vary depending on the patient's revascularization status. A post hoc analysis of the INVEST study revealed that the relationship between DBP and cardiovascular outcomes was J-shaped in PCI patients but not in CABG patients, where it was linear and positive[28]. In our study, we similarly observed a J-curve phenomenon for SBP and DBP, but it was more pronounced in the SBP curve than in the DBP curve, which may be attributed to the effects of revascularization. Additionally, the relationship between BP and clinical outcomes remained consistent across most subgroups. Notably, although no

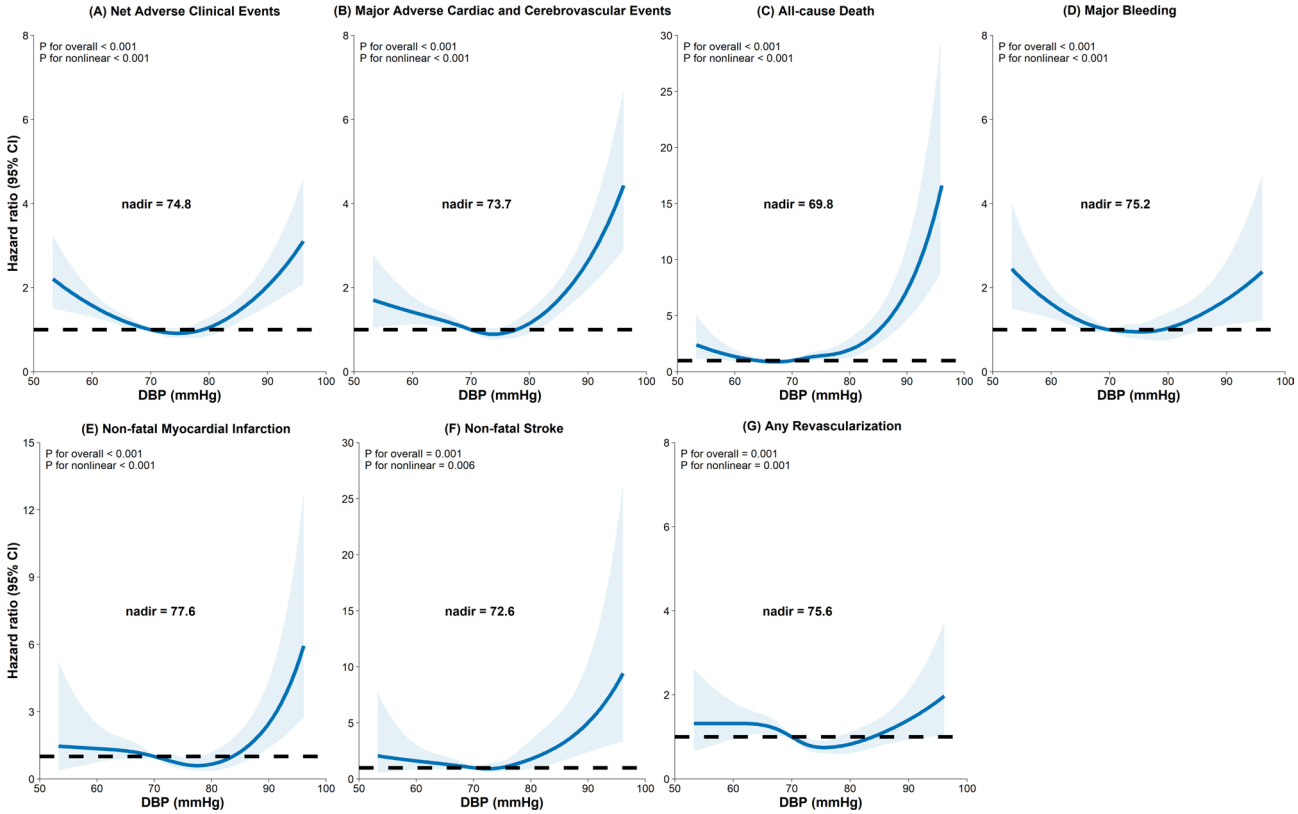

Fig. 5. Continuous association between DBP and the risk of clinical outcomes. (**A**) NACE, (**B**) MACCE, (**C**) all-cause death, (**D**) major bleeding, (**E**) non-fatal myocardial infarction, (**F**) non-fatal stroke, and (**G**) any revascularization. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; DBP, diastolic blood pressure; CI, confidence interval.

significant interaction was found, among patients under 60 years of age, SBP did not display a J-curve phenomenon concerning NACE and MACCE. This suggests that situations where SBP is lowered due to medications for other compelling indications might be relatively safe. These novel findings in younger patients warrant further prospective evidence.

Strong evidence supports the use of dual antiplatelet therapy in patients with CAD undergoing PCI[4]. However, these benefits come with an increased risk of bleeding. Given the significant association between bleeding events and mortality[29], efforts have been made identify high-risk groups for bleeding events and to tailor antiplatelet therapy to reduce bleeding events after PCI[30,31]. The risk of recurrent ischemia and bleeding after PCI varies over time; therefore, optimizing the balance between ischemic and bleeding risk remains a challenge for physicians managing patients undergoing PCI[32]. BP represents a crucial factor that can be associated with both ischemic and bleeding risks[12,33]. However, there have been no studies on the association between BP and bleeding events after PCI. In our study, we observed a J-curve relationship between BP and bleeding events in both SBP and DBP. While there are no previous studies with a similar clinical setting, a J-curve association between BP levels and bleeding risk was also observed in patient on long-term anticoagulation treatment[34]. These findings suggest that patients with low BP may potentially be frailer and, consequently, have a higher risk of experiencing bleeding events. Moreover, low BP might be linked to vascular vulnerability[35]. Further prospective studies investigating the association between BP and the risk of bleeding are necessary to validate these findings.

Overall, this study holds clinical significance as it provides insights into the importance of intensive BP management and offers clues regarding target BP levels in CAD patients who underwent PCI. It utilizes a large dataset from follow-up BP data from consecutive PCI patients treated with second-generation DES, reflecting real-world clinical scenarios. In addition, this study analyzed the associations between these patients and bleeding events, which has not been thoroughly explored previously. Concerning BP relationship, rather than a trade-off, bleeding events are similarly associated with ischemic events, thus suggesting that appropriately managing BP may be even more critical than expected for patients who underwent PCI, a high-risk group for bleeding and ischemic events simultaneously.

This study had several limitations. First, it was observational in nature, as a consequence, was subject to the inherent limitations associated with such a design. Notwithstanding the rigorous adjustments for the known risk factors, the possibility of unmeasured confounding factors remains. Additionally, the inherent selection bias of observational studies, including patient characteristics and treatment decisions, may have influenced the outcomes. Second, important variables, such as compliance with antiplatelet and antihypertensive agents, familial history of premature atherosclerotic cardiovascular events, socioeconomic status, job stress, mental

health, smoking cessation, and other lifestyle factors (e.g., diet, exercise) after PCI, were unavailable for analysis. Furthermore, the impact of alterations in treatment regimens over the course of the follow-up period was not taken into account. These factors are indeed significant and have the potential to influence both BP levels and cardiovascular outcomes, which may in turn affect the results of the study. Moreover, adverse events associated with BP-lowering treatment, such as hypotension, syncope, bradycardia, electrolyte imbalance, and acute kidney injury, were not considered. This is a crucial omission, as it precludes a comprehensive understanding of the full spectrum of risks associated with different BP targets. Third, the data were collected from two PCI centers within the same university medical system in Korea, which may limit the generalizability of our findings to other settings and populations. Therefore, further studies are needed to validate our findings in diverse populations. Fourth, the longitudinal analysis may be influenced by dropouts during the follow-up, introducing potential unknown biases. Finally, although we utilized average follow-up BP measurements, we cannot completely exclude the reverse causality risk. To address these limitations, future randomized controlled trials are necessary to confirm our findings and establish definitive causal relationships.

This study provides valuable insights into the association between follow-up office BP and clinical outcomes in CAD patients who underwent PCI, leveraging a large dataset reflecting real-world clinical scenarios. Although a J-curve relationship was observed between BP and clinical outcomes, the lowest BP nadir associated with the lowest risk of future cardiovascular events in CAD patients who underwent PCI was identified as 121.4/74.8 mmHg for NACE and 120.4/73.7 mmHg for MACCE, indicating the potential benefits of strict BP control strategies. However, further research, including randomized controlled trials, is needed to establish definitive BP targets and optimize cardiovascular outcomes in this specific group of patients.

Data availability

The datasets generated the current study are available from the corresponding author on reasonable request.

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Author contributions

B.S.K. contributed to the acquisition and interpretation of data, and was a major contributor in writing the manuscript. J.-H.S. contributed to the interpretation of data and also was a major contributor in writing the manuscript. W.K. and H.K. contributed to the acquisition and analysis of data. Y.L., J.-K.P., and J.S. provided critical revisions to the manuscript. Y.-H.L. was responsible for study design, data interpretation, and manuscript preparation. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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