Received: 17 June 2022 | Revised: 9 August 2022 | Accepted: 10 August 2022

DOI: 10.1111/jch.14565

ORIGINAL ARTICLE

WILEY

Association between visit-to-visit blood pressure variability and adverse events in coronary artery disease patients after coronary intervention

Tsung-Ying Tsai MD[1,2] | Hsin-Bang Leu MD[1,3,4,5] | Pai-Feng Hsu MD, PhD[1,3,4,5] | Ya-Ling Yang MD[1,5] | Su-Chan Chen MD[1,5] | Shao-Sung Huang MD[1,3,4] | Wan Leong Chan MD[1,4] | Shing-Jong Lin MD[1,4,5] | Jaw-Wen Chen MD[1,3,4,5] | Ju-Pin Pan MD[1,4] | Min-Ji Charng MD[1,4] | Ying-Hwa Chen MD[1,4] | Tao-Cheng Wu MD[1,4] | Tse-Min Lu MD[1,3,4] | Po-Hsun Huang MD[1,4] | Hao-Min Cheng MD[1,4,5] | Chin-Chou Huang MD[1,4] | Shih-Hsien Sung MD[1,4] | Yenn-Jiang Lin MD[1,4] | Cheng-Hsueh Wu MD[1,4]

[1]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

[2]Division of Cardiology, Department of Cardiovascular Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

[3]Healthcare and Management Center, Taipei Veterans General Hospital, Taipei, Taiwan

[4]Faculty of Medicine, National Yang-Ming Chiao Tung University, Taipei, Taiwan

[5]Institute of Clinical Medicine and Cardiovascular Research Center, National Yang-Ming Chiao Tung University, Taipei, Taiwan

Correspondence
Cheng-Hsueh Wu, MD, Department of Critical Care Medicine, Taipei Veterans General Hospital, Taiwan, 112, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan.
Email: chwu32@gmail.com

Funding information
Research Foundation of Cardiovascular Medicine, Grant/Award Number: 107-02-006

Abstract

Blood pressure variability (BPV) is independently associated with higher cardiovascular risks. However, whether BPV is associated with poor outcomes for coronary artery disease (CAD) patients after percutaneous coronary intervention (PCI) remained undetermined. We aimed to investigate the relationship between BPV and the outcomes of CAD patients undergoing PCI. Two thousand seven hundred and sixty-two CAD patients (1938 males, mean age 69.6 ± 12.9) who received PCI at Taipei Veterans General Hospital from 2006 to 2015 with multiple blood pressure measurements before and after the index PCI were enrolled. We calculated the standard deviation of systolic blood pressure, diastolic blood pressure, and pulse pressure as parameters of BPV. The primary endpoint was the composite of major adverse cardiovascular events [MACE comprising of cardiovascular death, nonfatal myocardial infarction (MI), and non-fatal stroke] and heart failure hospitalization (HHF). The key secondary endpoint was MACE. Both pre-PCI and post-PCI BPV were associated with CV events even after adjusting for co-morbidities and mean blood pressure. In Cox analysis, for every 1 mmHg increase in systolic BPV, the hazard ratio for the MACE + HHF, MACE, HHF, and cardiovascular death was 1.04 (95%CI: 1.03–1.05), 1.04 (95%CI: 1.02–1.05), 1.05 (95%CI: 1.04–1.06), and 1.06 (95%CI: 1.03–1.09), respectively. The association between BPV and cardiovascular risk is independent of blood pressure control status. The prognostic value of BPV was superior to mean blood pressure in both pre-PCI and post-PCI period. BPV is independently associated with cardiovascular events after PCI

and has a better prognostic value than mean blood pressure suggesting the importance of maintaining stable blood pressure for CAD patients.

KEYWORDS
blood pressure variability, coronary artery disease, outcome, percutaneous coronary intervention

1 | BACKGROUND

Blood pressure is the pressure in the artery generated from the force of heart contractions. Variations in blood pressure from different recordings represent the physiologic response to environmental challenges or stimuli to maintain cardiovascular "homeostasis". However, increased blood pressure variability (BPV) is a result of exaggerated differences in blood pressure recordings. It may reflect maladaptive alterations in the cardiovascular regulatory system. Prolonged exposure to hemodynamic fluctuation can even to contribute to the pathophysiology of atherosclerosis.[1]

Recently, BPV has been recognized as an important risk factor for the development and progression of cardiovascular disease.[2,3] Importantly, increased BPV was significantly associated with increased future cardiovascular risk regardless of whether in hypertensive status. Among the various components of BPV, long-term (visit-to-visit) BPV has been subjected to the most rigorous studies.[4] Visit-to-visit BPV has been found to be independently associated with the development of coronary artery disease (CAD),[5] heart failure, cardiovascular death,[6] stroke, chronic kidney disease (CKD), and cognitive function decline.[7] Higher visit-to-visit BPV was found to be associated with coronary atheroma progression in serial intravascular ultrasound evaluation.[8] However, whether visit-to-visit BPV is associated with poor outcomes for patients with coronary artery disease (CAD) after percutaneous coronary interventions (PCIs) remained unclear. In addition, most studies of visit-to-visit BPV focus on the baseline visit-to-visit BPV before PCI while the prognostic value of post-PCI visit-to-visit BPV remained unknown. Here, we aimed to analyze the prognostic value of pre-PCI visit-to-visit BPV, post-PCI visit-to-visit BPV, and the achieved mean blood pressure post-PCI to provide a comprehensive picture of the prognostic value of visit-to-visit BPV in PCI patients.

2 | METHODS

2.1 | Study design

We retrospectively reviewed patients who have received PCI for coronary artery disease (CAD) at the Taipei Veterans General hospital between 2006 and 2015. We enroll patients who fit the inclusion criteria: (1) age over 20 years old, (2) Under regular follow-up at the Taipei Veterans General hospital with multiple outpatient blood pressure readings before and after the index PCI, (3) Had received a successful PCI procedure. We excluded patients who (1) Do not have a complete PCI record, (2) Have lost follow-up outpatient visits for over 6 months. The demographic characteristics, biochemical data, procedural details, and clinical outcomes of these patients were extracted from the electronic medical record review. This study followed the Declaration of Helsinki and was approved by the Internal Research Board of Taipei Veterans General Hospital (IRB No. 2016-03-014CC).

2.2 | Procedure details

PCI procedures were performed in conformity with the 2010 ESC/EACTS guidelines on myocardial revascularization.[1] In brief, coronary angiography was performed with standard procedures. Unfractionated heparin was administered to achieve an activated clotting time of >300 s. After successful wire-crossing, lesion modification was usually performed by balloon dilatations. Following dilatation and/or lesion modification, a stent was deployed for most lesions. Successful PCI was defined as residual stenosis <30% with thrombolysis in myocardial infraction grade 3 flow at the end of the procedure. All patients received aspirin (100 mg/d) indefinitely and a P2Y12 inhibitor for at least one month if a bare metal stent was deployed or at least six months if a drug-eluting stent was deployed after PCI. Patients were all observed for a minimum of 8 h and then discharged under stable conditions.

2.3 | Demographic and biochemical analysis

Baseline information such as age, gender, body mass index (BMI), and smoking status were collected. We obtained a detailed medical history for comorbid conditions the day before the index PCI procedure, including hypertension, diabetes, dyslipidemia, stroke, chronic kidney disease (CKD), and heart failure transcribed from the diagnosis and medication list of the electronic medical records. Hypertension was defined as the usage of blood pressure lowering medication for more than two outpatient visits or a diagnosis on electronic medical records. Diabetes was defined as the usage of anti-diabetic medications or a diagnosis on electronic medical records. CKD and heart failure were defined by the diagnosis on electronic medical records. Heart failure with preserved ejection fraction and heart failure of reduced ejection fractions were both counted as heart failure. Procedure details of the PCI including indications for the procedure [acute coronary syndrome or elective], number of diseased vessels,

and the type of deployed stents were collected from the procedure notes. Baseline biochemical parameters including serum creatinine, uric acid, hemoglobin, low-density lipoprotein-cholesterol (LDL), and high-density lipoprotein-cholesterol (HDL) were measured in a central lab using a TBA-c16000 automatic analyzer (Toshiba Medical Systems, Tochigi, Japan) following an overnight fast before the index procedure. The left ventricle ejection fraction from the left ventriculography and echocardiographic study were also evaluated when available.

2.4 | Blood pressure measurement and visit-to-visit BPV

Blood pressure was measured at each clinical visit via automatic oscillometers (BPBIO320, Inbody Co., Ltd., Chungcheongnam-do, Korea) after at least 5 min of rest in a sitting position. The visit-to-visit BPV of the pre-PCI outpatient follow-up period, and the post-PCI outpatient follow-up at 1 month, 3 months, and 1 year follow-up period were accessed respectively. To avoid the interference of acute illness, or pain, blood pressure measurement during hospitalizations were not counting into BPV calculation. Visit-to-visit BPV was defined as the standard deviation of systolic blood pressure (SBPsd) and the standard deviation of diastolic blood pressure (DBPsd).

2.5 | Clinical outcome

After the index PCI procedure, all patients received regular cardiology clinic follow-up at the Taipei Veterans General hospital and its allied hospitals. The patients were contacted by the study staff via telephone to trace all cardiovascular events. Causes of death was derived from the national death registration system. The primary endpoint was the composite of major adverse cardiovascular events (MACE) including cardiovascular deaths, nonfatal MIs, and nonfatal strokes plus heart failure hospitalization (HHF) (MACE + HHF). The key secondary outcomes were major MACE. Other secondary outcomes included the individual components of MACE, HHF, and repeat revascularization. Cardiovascular death was defined as deaths that result from an MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cerebral hemorrhage, and death due to other cardiovascular causes. MI was defined by the in-charge cardiologist according to the third definition of MI. Stroke was defined as the combination of ischemic and hemorrhagic stroke. HHF was defined as any hospitalization with a primary diagnosis of heart failure or with one of the first two secondary diagnoses being heart failure. Similar definitions of clinical outcome have been reported in our previous studies.[9–11]

2.6 | Statistical analysis

The data was expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. The study population was categorized into four groups by their pre-PCI SBPsd and DBPsd quartile value. Demographic characteristics and biochemical variables were compared between quartiles of visit-to-visit BPV. We used Student's *t*-test and the Mann–Whitney *U* test to compare continuous variables when appropriate; a chi-squared test was used for categorical variables. Survival to the primary and secondary endpoints of the quartiles was compared with stepwise Cox proportional hazards models while backward selection was used to calculate hazard ratios (HRs) and 95% CI for visit-to-visit BPV categories. To adjust for confounding variables, a second Cox hazard ratio was performed with adjustment for age, gender, BMI, hypertension, diabetes, CKD, stroke, heart failure, hemoglobin, creatinine, LDL, ACEI/ARB use, beta-blocker use, CCB use and the corresponding mean blood pressure. Subgroup and sensitivity analyses were also performed. Prespecified subgroups in these analyses were defined according to blood pressure control status (controlled, uncontrolled), age (<65 years of age, or >65 years of age or older), gender, diabetes, hypertension, smoking, BMI (<22 kg/m^2, or 22 kg/m^2 or more), LDL (<70 mg/dl, 70 mg/dl or more), HDL (<40 mg/dl, 40 mg/dl or more), the presence of acute coronary syndrome, left ventricular ejection fraction (<50%, 50% or more), DES use, and hypertension control status. Statistical significance was set as $P < 0.05$. To evaluate the prognostic role of achieved mean blood pressure and visit-to-visit BPV after the index PCI, we conducted a similar COX regression analysis to investigate the prognostic value of post-PCI mean blood pressure and post-PCI visit-to-visit BPV at 1 month, 3 months, and 1 year interval after the index procedure. To evaluate the different prognostic power of pre-PCI and post-PCI BPV, we performed receiver operating characteristic curve analysis for both pre-PCI and post-PCI BPV and compared the area under curve to determine which has a better prognostic value. To evaluate the association between other parameters of BPV and clinical outcomes. We performed an additional analysis for the coefficient variation (ratio of the standard deviation to the mean) of pre-PCI and post-PCI SBP and DBP in a similar manner. All statistical analyses were carried out with SPSS 26.0 software (IBM, Inc. Chicago, IL, USA).

3 | RESULTS

3.1 | Patient demographics

A total of 2762 CAD patients (1938(70.2%) male, aged 68.6 ± 12.9) with multiple pre-PCI and post-PCI blood pressure recordings were enrolled. The mean SBP/DBP pre-PCI and post-PCI were 132.0 ± 14.6/73.8 ± 9.2 mmHg and 127.3 ± 12.5/70.1 ± 7.8 mmHg respectively. During a median follow-up of 50.3 ± 24.5 months, 463(16.8%) patients met the primary endpoint of MACE + HHF while 248(9.0%) patients met the key secondary endpoint of MACE. For the other secondary endpoints, there were 55 cardiovascular deaths, 63 nonfatal strokes, 153 nonfatal MIs, 272 HHF, and 585 repeated revascularization procedures in the follow-up period. The patients received a median of 12 blood pressure measurements

before PCI and a median of 58 blood pressure measurements after PCI.

The demographic characteristics of the participants according to the pre-PCI quartiles of SBPsd are shown in Table 1 while those according to pre-PCI DBPsd are shown in Supplemental Table 1. As compared with patients with a lower pre-PCI SBPsd, those with higher pre-PCI SBPsd were more likely to be older and female with a lower BMI, hemoglobin, and DBP; and they were more likely to have higher creatinine, uric acid, SBP, and pulse pressure. They also had a higher prevalence of diabetes, hypertension, heart failure, CKD, stroke, and acute coronary syndrome as demonstrated in Table 1. Patient with higher pre-PCI SBPsd were more likely to be prescribed with angiotensin converting enzyme inhibitor/ angiotensin receptor blockers (ACEI/ARB), beta-blockers, calcium channel blockers (CCB) and thiazide diuretics. Regarding pre-PCI DBPsd, the trend was similar to that of pre-PCI SBPsd. Those with the higher pre-PCI DBPsd were more likely to be older, female, higher hemoglobin, LDL-C, creatinine, SBP, and pulse pressure.

3.2 | Relationship between pre-PCI visit-to-visit BPV and future events

Figure 1 shows the Kaplan–Meier survival analysis of MACE + HHF according to pre-PCI SBPsd, and pre-PCI DBPsd quartiles. Higher pre-PCI visit-to-visit BPV were significantly associated with higher risk of future adverse cardiovascular events (log-rank $P < 0.0001$). After adjusted with age, gender, BMI, hypertension, diabetes, CKD, stroke, heart failure, hemoglobin, creatinine, LDL, ACEI/ARB use, beta-blocker use, CCB use and the corresponding mean blood pressure, the risk of MACE+HHF was significantly increased with increasing pre-PCI SBPsd [HR: 1.02(1.01–1.04), $P < 0.001$]. After adjusted with age, gender, BMI, diabetes, CKD, stroke, heart failure, hemoglobin, creatinine, LDL and the corresponding mean blood pressure, the risk of MACE + HHF was significantly increased with increasing pre-PCI DBPsd [HR: 1.06(1.03–1.08), $P < 0.001$] (Table 2, Supplemental Table 2). Figure 2 shows a stepwise increased in risk for MACE+HHF from pre-PCI visit-to-visit BPV quartile 1 to 4 suggesting a linear association between visit-to-visit BPV and future risk in patients who underwent PCI. In addition, the association between pre-PCI visit-to-visit BPV and other important secondary endpoints such as MACE, myocardial infarction, stroke, and HHF were also observed (Table 2, Supplemental Table 2). No association between visit-to-visit pre-PCI BPV and future revascularization was seen. Figure 3 shows that mean blood pressure has a much weaker association with cardiovascular endpoints when compared with pre-PCI SBPsd. Table 3 presents the prespecified subgroup analysis. Significant associations between pre-PCI visit-to-visit BPV and future cardiovascular risk were found in all subgroups. Importantly, the association between pre-PCI visit-to-visit BPV and cardiovascular risk remained robust regardless of the blood pressure control status and the standard of blood pressure control used (120/80 mmHg or 140/90 mmHg).

3.3 | The importance of blood pressure control after PCI procedure

Because most previous studies report the association of visit-to-visit BPV and cardiovascular risk focus on the baseline blood pressure recordings, we further analyzed the prognostic value of the mean achieved blood pressure and visit-to-visit BPV after PCI procedures during follow-up. Table 4 showed a significant association between post-PCI visit-to-visit BPV in the short-term (30 days), mid-term (90 days), and long-term (1 year) follow-up period after PCI. However, the mean post-PCI blood pressure was not associated with MACE+HHF after PCI in any follow-up periods. This relationship suggests that post-PCI visit-to-visit BPV has a stronger prognostic value than the post-PCI mean blood pressure for patients with CAD after PCI. The receiver operating characteristic curve analysis showed that the area-under-curve of pre-PCI and post-PCI PBV were not significantly different as demonstrated by Supplemental Figures 1 and 2. This suggest pre-PCI and post-PCI BPV have similar prognostic values.

3.4 | The association between other BPV parameters and future events

Besides standard deviation, other statistical analysis such as coefficient variation which is a more standardized way to represent the dispersion of values. The coefficient variation of pre-PCI SBP and DBP were 10.94 ± 5.00% and 12.08 ± 5.46%, respectively. The coefficient variation of post-PCI SBP and DBP were 12.71 ± 3.58% and 14.60 ± 4.09%, respectively. The results of COX analysis regression showed that the pre-PCI and post-PCI SBP and DBP coefficient variation are significantly associated with MACE+HHF risk and that the association remained robust after adjusting for age, gender, BMI, hypertension, diabetes, CKD, stroke, heart failure, hemoglobin, creatinine, LDL, ACEI/ARB use, beta-blocker use, CCB use and the corresponding mean blood pressure (Supplemental Table 3).

4 | DISCUSSION

4.1 | Main findings

In this cohort study of 2762 Asian patients with CAD undergoing PCI, we demonstrated that (1) both pre-PCI and post-PCI visit-to-visit BPV are significantly associated with adverse clinical outcomes after PCI procedures. This association remain robust after adjusting for co-morbidities and mean blood pressure. (2) The association between visit-to-visit BPV and cardiovascular risk are independent of blood pressure control status. These findings suggest that visit-to-visit BPV has association with cardiovascular risk even among those with well-controlled blood pressure. (3) Our results also show the stronger association to outcomes between visit-to-visit BPV (in both the pre-PCI and post-PCI periods) versus mean blood pressure. To the best of

TABLE 1 Baseline clinical characteristics among patients with different quartiles of pre-PCI standard deviation of SBP (SBPsd)

Participant characteristics	Overall ($n = 2762$)	1st quartile (<10.1 mmHg) ($n = 690$)	2nd quartile (10.1~14.0 mmHg) ($n = 691$)	3rd quartile (14.0~18.2 mmHg) ($n = 691$)	4th quartile (>18.2 mmHg) ($n = 690$)	*p* value
SBPsd	14.5 ± 6.9	6.4 ± 2.8	12.1 ± 1.1	16.0 ± 1.2	23.4 ± 5.5	<0.001
Male gender (*n*, %)	1938(70.2%)	546(79.1%)	516(74.7%)	458(66.3%)	418(60.6%)	<0.001
Age(y/o)	69.6 ± 12.9	65.6 ± 13.0	69.1 ± 12.7	71.7 ± 12.8	72.0 ± 12.2	<0.001
BMI	25.8 ± 4.6	26.2 ± 4.2	25.9 ± 5.7	25.6 ± 4.0	25.4 ± 4.3	0.020
Smoking (*n*, %)	878(31.8%)	212(30.7%)	212(30.7%)	220(31.8%)	234(33.9%)	0.860
Dyslipidemia (*n*, %)	1381(50.0%)	357(51.7%)	374(54.1%)	329(47.6%)	321(46.5%)	0.270
Diabetes (*n*, %)	1231(44.6%)	250(36.2%)	296(42.8%)	327(47.3%)	358(51.9%)	<0.001
Hypertension (*n*, %)	2615(94.7%)	643(93.2%)	649(93.9%)	655(94.8%)	668(96.8%)	0.001
Heart failure (*n*, %)	410(14.8%)	68(9.9%)	93(13.5%)	125(18.1%)	124(18.0%)	<0.001
Stroke (*n*, %)	167(6.0%)	29(4.2%)	41(5.9%)	38(5.5%)	59(8.6%)	<0.001
CKD (*n*, %)	185(6.7%)	25(3.6%)	28(4.1%)	50(7.2%)	82(11.9%)	<0.001
Acute coronary syndrome (*n*, %)	935(33.9%)	165(23.9%)	212(30.7%)	272(39.4%)	286(41.4%)	<0.001
Diseased vessels	2.12 ± 0.83	2.01 ± 0.03	2.09 ± 0.03	2.19 ± 0.03	2.18 ± 0.03	0.001
Creatinine	1.6 ± 1.9	1.3 ± 1.2	1.4 ± 1.4	1.6 ± 1.8	2.4 ± 2.6	<0.001
Hemoglobin	12.6 ± 2.0	13.4 ± 1.8	12.9 ± 1.8	12.4 ± 1.9	11.8 ± 2.1	<0.001
Uric acid	6.4 ± 1.8	6.3 ± 1.6	6.4 ± 1.8	6.4 ± 1.8	6.5 ± 2.0	0.203
HDL	42.7 ± 11.9	43.2 ± 11.9	42.9 ± 11.1	42.1 ± 12.0	42.9 ± 12.8	0.589
LDL	105.0 ± 33.9	106.7 ± 35.3	107.4 ± 33.8	103.1 ± 32.8	103.0 ± 33.6	0.012
Pre-PCI mean SBP	132.0 ± 14.6	128.2 ± 14.4	129.3 ± 13.4	131.7 ± 13.3	139.0 ± 14.7	<0.001
Pre-PCI mean DBP	73.8 ± 9.2	74.5 ± 9.8	73.9 ± 9.0	72.6 ± 8.6	74.2 ± 9.2	<0.001
Post-PCI mean SBP	127.3 ± 12.5	124.3 ± 11.6	125.7 ± 11.8	127.7 ± 12.2	131.6 ± 12.9	<0.001
Post-PCI mean DBP	70.1 ± 7.8	71.4 ± 7.8	70.3 ± 7.7	69.5 ± 7.6	69.1 ± 8.0	<0.001
DBPsd	8.8 ± 3.8	5.7 ± 3.5	8.0 ± 2.7	9.7 ± 2.7	11.7 ± 3.4	<0.001
ACEI/ARB	1560(56.5%)	369(53.5%)	378(54.7%)	393(56.9%)	420(60.9%)	0.031
Beta-blockers	1397(50.6%)	344(49.9%)	330(47.8%)	343(49.6%)	380(55.1%)	0.043
CCB	1100(39.8%)	261(37.8%)	252(36.5%)	266(38.5%)	321(46.5%)	0.001
Thiazide diuretics	270(9.8%)	47(6.8%)	70(10.1%)	71(10.3%)	82(11.9%)	0.014
Statins	1685(61.0%)	433(62.8%)	417(60.3%)	418(60.5%)	417(60.4%)	0.757

Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; CKD, chronic kidney disease; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol.

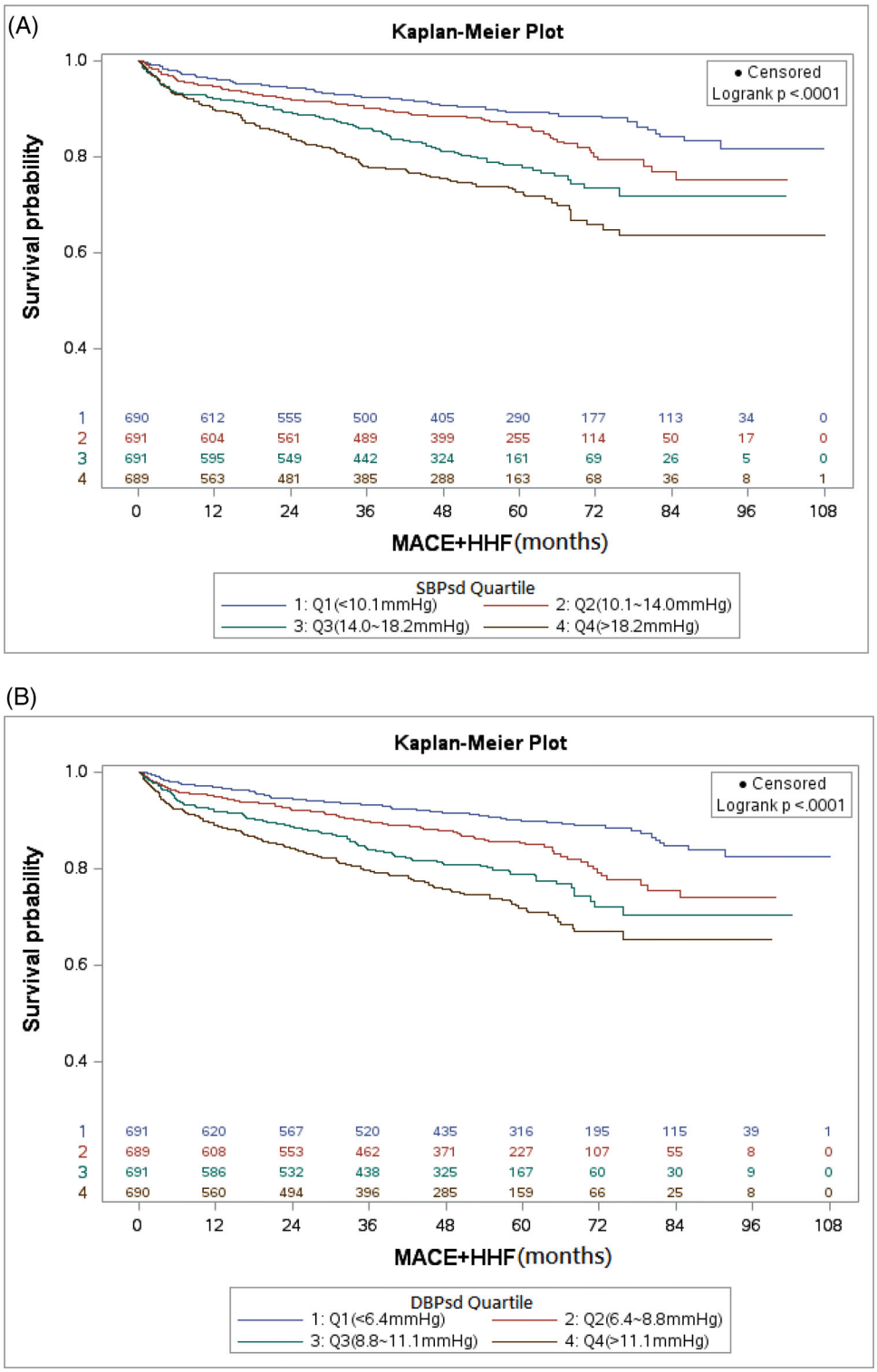


FIGURE 1 (A) The Kaplan-Meier curve for survival to MACE+HHF divided by quartiles of pre-PCI SBPsd. P values are for the overall comparison among the groups using the log rank test. SBPsd = standard deviation of SBP. MACE = major adverse cardiovascular events, HHF = heart failure hospitalization. (B) The Kaplan-Meier curve for survival to MACE+HHF divided by quartiles of pre-PCI DBPsd. P values are for the overall comparison among the groups using the log rank test. DBPsd = standard deviation of DBP

TABLE 2 Association between pre-PCI SBPsd in quartiles and the hazard ratio clinical outcomes

		Unadjusted (model 1)		Adjusted* (model 2)	
	Events, *n* (%)	HR (95% CI)	*p* value	HR (95% CI)	*p* value
MACE + HHF					
Q1(<10.1 mmHg)	72(11.6%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	96(16.1%)	1.42(1.05–1.93)	0.024	1.05(0.76–1.45)	0.761
Q3(14.0~18.2 mmHg)	129(23.0%)	2.13(1.60–2.85)	<0.001	1.26(0.93–1.72)	0.143
Q4(>18.2 mmHg)	166(31.7%)	2.90(2.20–3.83)	<0.001	1.57(1.15–2.14)	0.004
Cont. (per 1 mmHg)	463(16.8%)	1.04 (1.03–1.05)	<0.001	1.02(1.01–1.04)	0.003
MACE					
Q1(<10.1 mmHg)	40(6.2%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	54(8.4%)	1.43(0.95–2.15)	0.089	1.19(0.78–1.82)	0.422
Q3(14.0~18.2 mmHg)	68(10.9%)	1.97(1.33–2.91)	0.001	1.31(0.86–1.91)	0.215
Q4(>18.2 mmHg)	86(14.2%)	2.59(1.78–3.77)	<0.001	1.48(0.96–2.26)	0.073
Cont. (per 1 mmHg)	248(9.0%)	1.04 (1.02–1.05)	<0.001	1.01(0.99–1.03)	0.178
MI					
Q1(<10.1 mmHg)	28(4.2%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	33(5.0%)	1.25(0.75–2.06)	0.392	1.05(0.62–1.78)	0.849
Q3(14.0~18.2 mmHg)	40(6.1%)	1.65(1.02–2.68)	0.043	1.14(0.68–1.93)	0.618
Q4(>18.2 mmHg)	52(8.2%)	2.24(1.41–3.55)	0.001	1.30(0.77–2.21)	0.331
Cont. (per 1 mmHg)	153(5.5 %)	1.03 (1.01–1.05)	0.003	1.00(0.98–1.03)	0.761
Stroke					
Q1(<10.1 mmHg)	10(1.5%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	14(2.1%)	1.46(0.65–3.28)	0.364	1.26(0.53–2.95)	0.602
Q3(14.0~18.2 mmHg)	21(3.1%)	2.43(1.14–5.18)	0.021	1.66(0.73–3.80)	0.227
Q4(>18.2 mmHg)	18(2.7%)	2.16(0.99–4.68)	0.052	1.51(0.64–3.56)	0.349
Cont. (per 1 mmHg)	63(2.3%)	1.04 (1.01–1.07)	0.0141	1.02(0.99–1.06)	0.236
CV death					
Q1(<10.1 mmHg)	4(0.6%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	11(1.6%)	2.85(0.91–8.96)	0.073	2.82(0.78–10.18)	0.113
Q3(14.0~18.2 mmHg)	15(2.2%)	4.21(1.39–12.70)	0.011	2.77(0.78–9.82)	0.114
Q4(>18.2 mmHg)	25(3.8%)	7.23(2.51–20.82)	<0.001	3.72(1.07–12.96)	0.039
Cont. (per 1 mmHg)	55(2.0%)	1.06 (1.03–1.09)	<0.001	1.03(0.99–1.07)	0.153
HHF					
Q1(<10.1 mmHg)	36(5.5%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	54(8.5%)	1.59(1.04–2.42)	0.032	1.06(0.69–1.64)	0.785
Q3(14.0~18.2 mmHg)	77(12.5%)	2.53(1.70–3.77)	<0.001	1.28(085–1.95)	0.243
Q4(>18.2 mmHg)	105(17.9%)	3.63(2.48–5.32)	<0.001	1.82(1.20–2.76)	0.005
Cont. (per 1 mmHg)	272(9.8%)	1.05 (1.04–1.06)	<0.001	1.03(1.01–1.05)	0.001
Revascularization					
Q1(<10.1 mmHg)	167(31.9%)	Reference	–	Reference	–
Q2(10.1~14.0 mmHg)	147(27.0%)	0.91(0.73–1.14)	0.429	0.94(0.74–1.18)	0.571
Q3(14.0~18.2 mmHg)	136(24.5%)	0.90(0.71–1.12)	0.344	0.94(0.74–1.21)	0.649
Q4(>18.2 mmHg)	135(24.3%)	0.91(0.72–1.14)	0.396	0.88(0.67–1.14)	0.325
Cont. (per 1 mmHg)	585(21.2%)	0.99 (0.98–1.00)	0.117	0.99(0.98–1.01)	0.079

Abbreviations: MI, myocardial infraction; HHF, hospitalization for decompensated heart failure; MACE, major adverse cardiovascular events including cardiovascular deaths, non-fatal stroke and non-fatal MI.

Adjusted*(Model 2) was age, gender, BMI, hypertension, diabetes, CKD, stroke, heart failure, hemoglobin, creatinine, LDL, ACEI/ARB use, beta-blocker use, CCB use and the corresponding mean blood pressure.

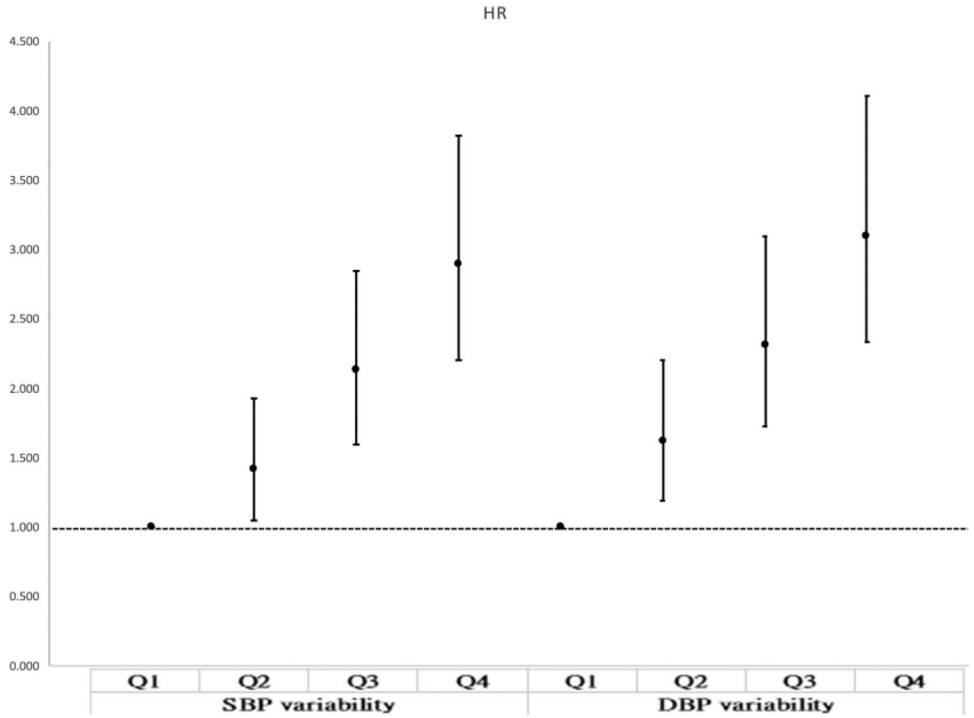


FIGURE 2 The comparative risk of MACE+HHF between quartile 1–4 of pre-PCI SBPsd and pre-PCI DBPsd using the quartile 1 as reference. The results suggest a linear association between pre-PCI BPV and future risk in patient underwent PCI. PCI = percutaneous coronary intervention

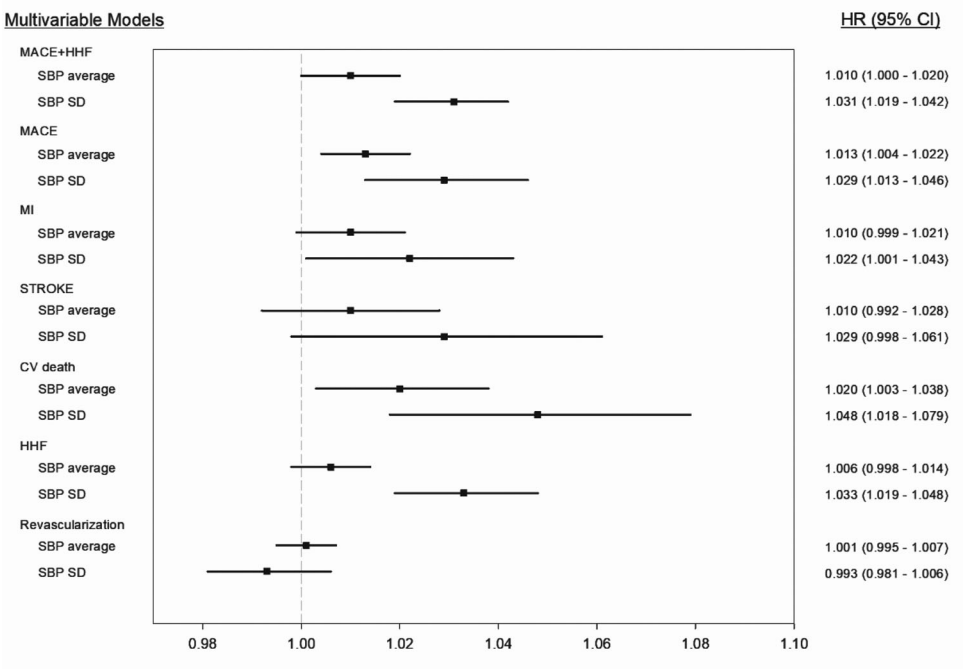
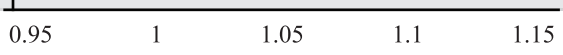


FIGURE 3 The relationship between CV endpoints and pre-PCI SBPsd or pre-PCI mean SBP. In the adjusted model, pre-PCI SBPsd was significantly associated with the risk of MACE+HHF, MACE, MI, CV death, and HHF. On the other hand, average pre-PCI SBP was only weakly associated with increased MACE + HHF, CV death and MACE and not associated with MI, and HHF

TABLE 3 Subgroup analysis showing the hazard ratio of MACE+HHF for 1 mmHg increase in pre-PCI SBPsd across different prespecified subgroups

Subgroup	Hazzard ratio (95% CI)	*p* value	*p* for interaction	
Overall		1.04 (1.03–1.05)	<0.001	
Age				
<65 years		1.07 (1.04–1.09)	<0.001	0.031
≧65 years		1.03 (1.02–1.04)	<0.001	
Sex				
Female		1.04 (1.01–1.06)	0.001	0.654
Male		1.04 (1.03–1.06)	<0.001	
Diabetes				
No		1.03 (1.01–1.05)	<0.001	0.306
Yes		1.04 (1.03–1.06)	<0.001	
Hypertension				
No		1.06 (0.99–1.13)	0.088	0.618
Yes		1.04 (1.03–1.05)	<0.001	
Smoking				
No		1.04 (1.03–1.06)	<0.001	0.773
Yes		1.04 (1.02–1.06)	<0.001	
BMI				
<25 kg/m^2		1.04 (1.03–1.05)	<0.001	0.798
≧25 kg/m^2		1.04 (1.03–1.06)	<0.001	
LDL				
<70 mg/dl		1.05 (1.02–1.07)	0.001	0.802
≧70 mg/dl		1.04 (1.03–1.05)	<0.001	
HDL				
<40 mg/dl		1.04 (1.03–1.06)	<0.001	0.644
≧40 mg/dl		1.04 (1.02–1.06)	<0.001	
ACS				
No		1.04 (1.03–1.06)	<0.001	0.379
Yes		1.04 (1.02–1.05)	<0.001	
EF				
<50%		1.04 (1.02–1.06)	<0.001	0.241
≧50%		1.06 (1.04–1.08)	<0.001	
DES				
No		1.03 (1.02–1.05)	<0.001	0.065
YES		1.05 (1.04–1.07)	<0.001	
SBP control status				
<140 mmHg		1.05 (1.04–1.07)	<0.001	0.019
>140 mmHg		1.03 (1.01–1.04)	0.001	
SBP control status				
<120 mmHg		1.05 (1.02-1.08)	0.003	0.650
>120 mmHg		1.04 (1.03–1.05)	<0.001	



Abbreviations: BMI, body mass index; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; MI, myocardial infraction; eGFR, estimated Glomerular filtration rate; EF, left ventricular ejection fraction; DES, drug eluting stent.

TABLE 4 Association between post PCI BP, BPV and MACE+HHF

	Unadjusted (model 1)		Adjusted* (model 2)	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
MACE+HHF				
Mean SBP (30days)	1.00(0.99–1.01)	0.442	1.00(0.99–1.01)	0.871
Mean DBP (30days)	0.98(0.97–1.00)	0.021	0.99(0.98–1.01)	0.356
SBPsd (30days)	1.02(1.01–1.04)	0.004	1.01(1.00–1.03)	0.117
DBPsd(30days)	1.05(1.02–1.08)	<0.001	1.04(1.01–1.07)	0.007
MACE+HHF				
Mean SBP (90days)	1.01(1.00–1.01)	0.050	1.00(1.00–1.01)	0.446
Mean DBP (90days)	0.98(0.97–0.99)	<0.001	1.00(0.99–1.01)	0.574
SBPsd (90days)	1.05 (1.04–1.06)	<0.001	1.03(1.02–1.04)	<0.001
DBPsd (90days)	1.08(1.06-1.10)	<0.001	1.06(1.04–1.09)	<0.001
MACE+HHF				
Mean SBP (365days)	1.01(1.00–1.01)	0.036	1.00(1.00–1.01)	0.644
Mean DBP (365days)	0.97 (0.96–0.98)	<0.001	0.99(0.98–1.00)	0.201
SBPsd (365days)	1.06(1.05–1.07)	<0.001	1.04(1.03–1.06)	<0.001
DBPsd (365days)	1.11(1.09–1.13)	<0.001	1.09(1.07–1.11)	<0.001

Adjusted*(Model 2) was age, gender, BMI, hypertension, diabetes, CKD, stroke, heart failure, hemoglobin, creatinine, LDL, ACEI/ARB use, beta-blocker use, CCB use and the corresponding mean blood pressure.

our knowledge, this is the first study to report in detail the prognostic significance of visit-to-visit BPV in CAD patients undergoing PCI procedures. Our study adds to the growing evidence suggesting that visit-to-visit BPV is an important and potentially modifiable risk factor for cardiovascular events.

4.2 | Visit-to-visit BPV and atherosclerosis

Although there is mounting evidence for the deleterious effect of high visit-to-visit BPV, the underlying mechanisms of this phenomenon remain unclear. Visit-to-visit BPV was believed to be attributed by poor medication adherence.[12] However, evidence from well-conducted trials have shown that high visit-to-visit BPV is common even among patients with good adherence.[6,13] On the other hand, elevated visit-to-visit BPV can be considered as a marker for homeostatic imbalance. A post-hoc analysis from the large Multi-Ethnic Study of Atherosclerosis (MESA) study performed by Shimbo et al. demonstrated that SBPsd values were independently associated with worse aortic distensibility.[14] A subsequent study from the MESA cohort showed that patients with a higher BPV have a higher decline in distensibility coefficient in long-term follow up.[3] Further studies have shown the association between visit-to-visit BPV and endothelial dysfunction, vasomotor dysfunction, and sympathetic activation.[15–17] Studies have also found an independent association between visit-to-visit BPV and atheroma volume and poor cognitive function.[18] Other studies have linked visit-to-visit BPV with the progression of atheroma volume.[8] Another proposed mechanism is the direct hemodynamic effect of highly fluctuating blood pressure thus inducing increased oscillatory shear stress and microcirculatory dysfunction.[19] The sum of all these effects may explain the pro-atherosclerotic effect of visit-to-visit BPV. However, more studies are needed to establish a causal link between visit-to-visit BPV and cardiovascular risk.

4.3 | BPV and CV events

Our study confirmed the association of increased visit-to-visit BPV and future risk in CAD patients after PCI. High blood pressure is the most important risk factor for premature death in the world, accounting for more than 10.4 million deaths each year.[20] However, patients with hypertension remained at elevated risk even at controlled blood pressure levels.[21,22] Fluctuation in blood pressure may be responsible for some of these excessive risks. In the past two decades, visit-to-visit BPV has been repeatedly demonstrated to be an independent risk factor for all-cause mortality, cardiovascular mortality, CAD incidence, and stroke incidence in the general population.[23,24] visit-to-visit BPV is associated with events in patients with pre-existing CAD, stroke, and heart failure suggesting that visit-to-visit BPV may have important roles in the secondary prevention of cardiovascular events as well.[25–27]

Clark et al. reported a post-hoc analysis of seven randomized control trial enrolling a total of 3912 patients with serial intravascular ultrasound studies.[8] The study showed that SBPsd is significantly associated with coronary atheroma progression and MACE. Importantly, the association between atheroma progression and visit-to-visit BPV was significant even among those with well-controlled blood pressure of less than 140/90 mm Hg. The finding of Clark et al. echoes our results that both pre-PCI and post-PCI visit-to-visit BPV parameters including

SBP and DBP are associated with cardiovascular risks and that the association remained robust regardless of blood pressure control status. Another post-hoc analysis of two randomized control trial by Park et al. showed that visit-to-visit BPV, but not mean blood pressure, was associated with cardiovascular events in patients with angiographically established CAD. BPV was also associated with cardiovascular outcomes in patients with well-controlled blood pressure.[25] These findings agreed with our analysis, suggesting that elevated visit-to-visit BPV may portend risk regardless of blood pressure control status.

In our study, we found that post-PCI visit-to-visit BPV was associated with increased risks of adverse cardiovascular event while mean post-PCI blood pressure were not associated with increased cardiovascular risk. We believe mean post-PCI blood pressure were not associated with cardiovascular risk for several reasons. First, the post-PCI mean SBP/DBP was 127.3 ± 12.5/70.1 ± 7.8 mmHg, meaning that most patients in our study have achieved well controlled blood pressure. The SBP levels were within the range of 120–140 mmHg and DBP levels were within the range of 65–80 mmHg. Therefore, the benefit of lower blood pressure was not obvious. Second, the blood pressure target for the PCI population is quite different from other diseases and lower blood pressure may not always associate with lower risk. There are many pieces of evidence showing that over-zealous blood pressure lowering may in fact be harmful to patients after PCI.[28] Importantly, given that coronary perfusion occurs mainly during diastole, lower mean DBP is consistently associated with poor cardiovascular outcomes.[29] Our previous CAD cohort also demonstrated that SBP at the range of 120–140 mmHg and DBP at 65–80 mmHg are associated with the lowest cardiovascular event rate.[30,31] Therefore, less visit-to-visit BPV rather than lower blood pressure values were found to be associated with lower future risks.

4.4 | Study limitations

There are some potential limitations associated with this study. First, the study is retrospective; therefore, causality cannot be determined. Second, the study excluded patients who have less than two blood pressure monitoring before and after PCI. Thus, some patients with poor compliance or had been referred to other healthcare system for follow up were excluded. This may introduce some potential selection bias. Third, although outcomes were collected and ascertained by following a standardized protocol, some events may go unrecorded given the size of our population and the length of follow-up. Fifth, we could not obtain detailed medication regimen and adherence of our patients, which may substantially affect their visit-to-visit BPV.

5 | CONCLUSION

High BPV before and after PCI procedures are significantly associated with poor outcomes in CAD patients receiving PCI. The association between visit-to-visit BPV and clinical outcome is independent of underlying comorbidities and mean blood pressure. In addition, the association between BPV and cardiovascular risk remained robust regardless of blood pressure control status. Furthermore, post-PCI visit-to-visit BPV remained a significant risk factor for adverse outcome. Our results indicate that visit-to-visit BPV merits consideration as an important risk factor for future cardiovascular outcomes after PCI.

AUTHOR CONTRIBUTIONS

Conceptualization, Tsung-Ying Tsai, Cheng-Hsueh Wu, Pai-Feng Hsu, and Hsin-Bang Leu; methodology, Tsung-Ying Tsai, Ya-Ling Yang, Su-Chan Chen, and Hsin-Bang Leu;validation, Cheng-Hsueh Wu; formal analysis, Tsung-Ying Tsai; investigation, Tsung-Ying Tsai;resources, Cheng-Hsueh Wu, Ju-Pin Pan; Min-Ji Charng, Shao-Sung Huang, Ying-Hwa Chen, Tao-Cheng Wu, Tse-Min Lu, Po-Hsun Huang, Hao-Min Cheng, Chin-Chou Huang, Shih-Hsien Sung, Pai-Feng Hsu, and Hsin-Bang Leu; data curation, Ya-Ling Yang, Su-Chan Chen;writing—original draft preparation, Tsung-Ying Tsai; writing—review and editing, Cheng-Hsueh Wu, and Hsin-Bang Leu;supervision Wan Leong Chan, Shing-Jong Lin, and Jaw-Wen Chen; funding acquisition, Cheng-Hsueh Wu, and Hsin-Bang Leu. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGEMENTS

The current study was funded by the research foundation of cardiovascular medicine, Taiwan. No. 107-02-006.

CONFLICT OF INTEREST

The authors have nothing to disclose.

ORCID

Hsin-Bang Leu MD https://orcid.org/0000-0001-6832-3234
Hao-Min Cheng MD https://orcid.org/0000-0002-3885-6600
Chin-Chou Huang MD https://orcid.org/0000-0002-4217-8734

REFERENCES

1. Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens Res*. 2020;43(7):609-620.
2. Diaz KM, Tanner RM, Falzon L, et al. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality. *Hypertension*. 2014;64(5):965-982.
3. Tedla YG, Yano Y, Carnethon M, Greenland P. Association between long-term blood pressure variability and 10-year progression in arterial stiffness. *Hypertension*. 2017;69(1):118-127.
4. Parati G, Stergiou GS, Dolan E, Bilo G. Blood pressure variability: clinical relevance and application. *J Clin Hypertens*. 2018;20(7):1133-1137.
5. Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality. *Ann Intern Med*. 2015;163(5):329-338.
6. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375(9718):895-905.
7. Yano Y, Fujimoto S, Kramer H, et al. Long-term blood pressure variability, new-onset diabetes mellitus, and new-onset chronic kidney disease in the Japanese general population. *Hypertension*. 2015;66(1):30-36.

8. Clark D 3rd, Nicholls SJ, St John J, et al. Visit-to-visit blood pressure variability, coronary atheroma progression, and clinical outcomes. *JAMA Cardiol*. 2019;4(5):437-443.
9. Lim SS, Yang YL, Chen SC, et al. Association of variability in uric acid and future clinical outcomes of patient with coronary artery disease undergoing percutaneous coronary intervention. *Atherosclerosis*. 2020;297:40-46.
10. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. *Eur J Clin Invest*. 2020;50(5):e13230.
11. Chen SC, Yang YL, Wu CH, et al. Association between preoperative nutritional status and clinical outcomes of patients with coronary artery disease undergoing percutaneous coronary intervention. *Nutrients*. 2020;12(5):1295.
12. Krakoff LR. Fluctuation. *Circulation*. 2012;126(5):525-527.
13. Muntner P, Levitan EB, Joyce C, et al. Association between antihypertensive medication adherence and visit-to-visit variability of blood pressure. *J Clin Hypertens (Greenwich)*. 2013;15(2):112-117.
14. Shimbo D, Shea S, McClelland RL, et al. Associations of aortic distensibility and arterial elasticity with long-term visit-to-visit blood pressure variability: the multi-ethnic study of atherosclerosis (MESA). *Am J Hypertens*. 2013;26(7):896-902.
15. Palatini P, Julius S. The role of cardiac autonomic function in hypertension and cardiovascular disease. *Curr Hypertens Rep*. 2009;11(3):199-205.
16. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: new independent determinants for carotid artery measures in the elderly at high risk of cardiovascular disease. *J Am Soc Hypertens*. 2011;5(3):184-192.
17. Diaz KM, Veerabhadrappa P, Kashem MA, et al. Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function in African Americans. *Hypertens Res*. 2012;35(1):55-61.
18. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the european lacidipine study on atherosclerosis. *Circulation*. 2012;126(5):569-578.
19. Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? *Eur Heart J Supplements*. 2020;22:E1-E6. Supplement_E.
20. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923-1994.
21. Andersson OK, Almgren T, Persson B, Samuelsson O, Hedner T, Wilhelmsen L. Survival in treated hypertension: follow up study after two decades. *BMJ*. 1998;317(7152):167-171.
22. Lawlor DA, Kim L, Morris R, Amuzu A, Whincup P, Ebrahim S. Survival with treated and well-controlled blood pressure: findings from a prospective cohort study. *PloS one*. 2011;6(4):e17792.
23. Wang J, Shi X, Ma C, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens*. 2017;35(1):10-17.
24. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2016;354:i4098.
25. Park S, Yan P, Cerezo C, Jeffers BW. Effect of visit-to-visit blood pressure variability on cardiovascular events in patients with coronary artery disease and well-controlled blood pressure. *J Am Soc Hypertens*. 2016;10(10):799-810.
26. Havenon Ad, Fino NF, Johnson B, et al. Blood pressure variability and cardiovascular outcomes in patients with prior stroke. *Stroke*. 2019;50(11):3170-3176.
27. Wei F-F, Zhou Y, Thijs L, et al. Visit-to-visit blood pressure variability and clinical outcomes in patients with heart failure with preserved ejection fraction. *Hypertension*. 2021;77(5):1549-1558.
28. Pepine CJ. What is the optimal blood pressure and drug therapy for patients with coronary artery disease? *JAMA*. 2004;292(18):2271-2273.
29. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet*. 2016;388(10056):2142-2152.
30. Zang J, Liang J, Zhuang X, Zhang S, Liao X, Wu G. Intensive blood pressure treatment in coronary artery disease: implications from the Systolic Blood Pressure Intervention Trial (SPRINT). *J Hum Hypertens*. 2022;36:86-94.
31. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med*. 2006;144(12):884-893.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tsai T-Y, Leu H-B, Hsu P-F, et al. Association between visit-to-visit blood pressure variability and adverse events in coronary artery disease patients after coronary intervention. *J Clin Hypertens*. 2022;24:1327–1338. https://doi.org/10.1111/jch.14565