

Research Article



Arterial stiffness index and blood pressure phenotypes in patients undergoing percutaneous coronary intervention: prognostic implications for ischemic and bleeding events

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ABSTRACT

Background: The clinical implications of arterial stiffness in relation to hypertension remain unclear in patients undergoing percutaneous coronary intervention (PCI). This study aimed to determine whether the arterial stiffness index provides additional prognostic information regarding hypertension-related risks in this population.

Methods: Arterial stiffness was measured using brachial-ankle pulse wave velocity (baPWV) in 3,930 PCI patients before discharge. The primary outcome was net adverse clinical events (NACE), a composite of major adverse cardiac and cerebrovascular events (MACCE: all-cause death, myocardial infarction, stroke) and major bleeding over 4 years. The patients were categorized into four groups based on hypertensive status and baPWV phenotype (< 1,891 vs. ≥ 1,891 cm/s).

Results: Compared to hypertensive status, the baPWV phenotype showed a stronger association with clinical outcomes. Hypertensive status and baPWV phenotype showed an additive effect on risk stratification. The highest incidence rates of clinical events were observed in the hypertensives with high baPWV, followed by the normotensives with high baPWV, hypertensives with low baPWV, and normotensives with low baPWV groups. Specifically, the 4-year incidence of NACE was 14.8%, 12.4%, 7.1%, and 6.0%, respectively, and the corresponding incidences of MACCE were 12.7%, 9.5%, 6.2%, and 5.2%, respectively. The hypertensives with high baPWV group exhibited significantly higher risks for NACE (adjusted hazard ratio [aHR], 1.556; 95% confidence interval [CI], 1.132–2.138;

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Abbreviations

ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; aHR, adjusted hazard ratio; AUC, area under the curve; baPWV, brachial-ankle pulse wave velocity; BARC, Bleeding Academic Research Consortium; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GNUH, Gyeongsang National University Hospital; HDL, high-density lipoprotein; HR, hazard ratio; HTN, hypertension; IDI, integrated discrimination improvement; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NACE, net adverse clinical events; NRI, net reclassification improvement; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; ROC, receiver operating characteristic; SBP, systolic blood pressure; VIF, variance inflation factor; WBC, white blood cell.

$P = 0.006$), MACCE (aHR, 1.573; 95% CI, 1.113–2.223; $P = 0.010$), and major bleeding (aHR, 2.023; 95% CI, 1.029–3.978; $P = 0.041$) compared with the normotensive with low baPWV group. Findings were consistent across subgroups for NACE without significant interactions.

Conclusions: Arterial stiffness exhibited additive prognostic implications in patients undergoing PCI. The combined use of the baPWV and hypertension phenotype may enhance post-PCI risk stratification for clinical events.

Trial Registration: ClinicalTrials.gov Identifier: NCT04650529

Keywords: Coronary artery disease; Arterial stiffness; Pulse wave velocity; Hypertension; Percutaneous coronary intervention

BACKGROUND

Cardiovascular disease (CVD), the leading cause of death worldwide, makes a substantial contribution to health loss and excess healthcare costs. Coronary artery disease (CAD) is the leading cause of CVD mortality within the spectrum of CVDs, accounting for 9.44 million deaths in 2021 and 185 million disability-adjusted life years [1]. The rapid evolution of percutaneous coronary intervention (PCI) over the last 4 decades has yielded a safe, effective, and mainstay therapeutic option for patients with CAD worldwide [2]. Nevertheless, adverse post-PCI clinical outcomes, such as ischemic and bleeding complications, continue to pose a significant risk despite the advances in PCI techniques and associated guideline-directed medical therapies [3–6]. Therefore, identifying patients at high risk of developing complications in the future plays a crucial role in ensuring optimal outcomes.

Arterial stiffening, a sensitive marker of vascular pathology, can reflect atherosclerosis, vascular calcification, inflammation, and vascular aging [7]. The measured arterial stiffness index has shown a significant association with the occurrence of future cardiovascular (CV) events in the general population, as well as patients with various diseases, even after adjusting for traditional CV risk factors [8–10]. Increased arterial stiffness has also been linked to bleeding complications across several clinical settings, including stroke. By amplifying pulsatile hemodynamic stress and promoting endothelial dysfunction, arterial stiffening may increase vulnerability to bleeding [11–13]. Brachial-ankle pulse wave velocity (baPWV), a simple, non-invasive measure of arterial stiffness, has been widely used in clinical practice [14]. Notably, a high baPWV phenotype has been identified as a significant predictor of both future ischemic and bleeding outcomes in patients undergoing PCI [15].

Hypertension is a well-established traditional CV risk factor that makes a major contribution to the development of CAD. Hypertension is highly prevalent in patients with established CAD [16]. However, hypertension has shown inconsistent results as a prognostic factor in patients undergoing PCI, with some studies reporting its paradoxically protective effect [17]. Therefore, complementary biomarkers or surrogates (e.g., arterial stiffness index) are needed to facilitate appropriate risk stratification. High blood pressure (BP) aids in the development of atherosclerotic plaques via complex pathophysiological mechanisms, with damage to the arterial wall associated with increased arterial stiffness being a key factor [18]. Arterial stiffening and hypertension exhibit a bidirectional relationship [19,20]. However, studies specifically examining the combined effect of baPWV phenotype and hypertension on long-term clinical outcomes in patients undergoing PCI are lacking. Therefore, this study

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Competing interest

Dr. Gurbel has received grants and personal fees from Bayer HealthCare, Otopic, Amgen, and Janssen, US World-Meds; grants from Instrumentation Laboratory, Hikari Dx, Haemonetics, Medicure, and Idorsia Pharmaceuticals; and personal fees from UpToDate and has patents "Detection of Restenosis Risk in Patients Issued" and "Assessment of Cardiac Health and Thrombotic Risk in a Patient". Dr. Jeong has received honoraria for lectures from Daiichi Sankyo, Sanofi-Aventis, Amgen, Han-mi Pharmaceuticals, and Dae-woong Pharmaceuticals; and research grants or support from Yuhan Pharmaceuticals, Han-mi Pharmaceuticals, Sam-jin Pharmaceuticals, Biotronik, and U&I Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Availability of data and materials

Data will be shared on reasonable request to the corresponding author, if required.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the attending hospital (Gyeongsang National University Hospital Registry, GNUH) and the requirement for obtaining written informed consent for access to the institutional registry was waived (GNUH 2018-07-012). The study adhered to the Good Clinical Practice Guidelines and the Declaration of Helsinki.

Consent for publication

Not applicable.

Authors' contributions

Conceptualization: Hwang JY, Jeong YH; Data curation: Kim BS, Ahn JH, Kang MG, Kim KH, Cho YH, Koh JS, Cho EJ, Kim SW, Tantry US, Gurbel PA; Formal analysis: Kim BS, Shin JH; Methodology: Bae JS, Shin JH; Supervision:

investigated the combined effect of baPWV and hypertension on ischemic and bleeding clinical outcomes in these patients.

METHODS

Study design

The study population comprised eligible patients selected from the prospective Gyeongsang National University Hospital registry (NCT04650529) [21]. Consecutive patients who had undergone PCI for significant obstructive CAD at 2 tertiary referral hospitals (Jinju and Changwon) between January 2010 and November 2018 were included in the registry, regardless of presentation with acute coronary syndrome (ACS) or chronic coronary syndrome. Multiple vascular, hemostatic, and physiologic parameters were systematically evaluated in the registry, if possible.

Trained research personnel collected baseline demographic characteristics, CV risk factors, medical history, laboratory findings, and procedural profiles from the index hospitalization records or through patient interviews, under the supervision of the principal investigator. In addition, data were collected at the follow-up outpatient visits at 1, 6, and 12 months post-procedure, and annually thereafter. Additional data, if required, were obtained via telephone contact.

Patients who had undergone baPWV measurement during the index hospitalization were included in the current analysis. Among 4,676 eligible patients, 746 patients with an ankle-brachial index of ≤ 0.9 or > 1.4 and 123 patients with uncontrolled arrhythmia (such as atrial fibrillation) were excluded as these conditions reduce the accuracy of baPWV measurements. Therefore, 3,930 patients were included in the final analysis. The patients were categorized into four groups based on the presence of hypertension and baPWV phenotype ($< 1,891$ and $\geq 1,891$ cm/s): normotensive with low baPWV ($n = 1,570$, 39.9%); normotensive with high baPWV ($n = 242$, 6.2%); hypertensive with low baPWV ($n = 1,490$, 37.9%); and hypertensive with high baPWV ($n = 628$, 16.0%) (**Fig. 1**). The baPWV threshold of 1,891 cm/s was derived from time-dependent receiver operating characteristic (ROC) curves for the primary outcome, and the optimal cut-off was determined using the Youden index, which identifies the cutoff with the greatest sum of sensitivity and specificity (**Supplementary Fig. 1**).

Patient management

The patients received standard care at the respective hospital in accordance with the current guidelines [3,4]. The specific treatment strategy, including stent implantation and choice of medication, was selected at the discretion of the operator. Procedural characteristics were based on the index PCI. All patients were prescribed indefinite aspirin and/or a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) therapy. The duration of treatment and the P2Y₁₂ inhibitor were tailored by the operator according to the guidelines and the individual bleeding risks of each patient.

baPWV measurement and definition of hypertension

Arterial stiffness was assessed using baPWV before discharge from the index hospitalization. The measurements were conducted by well-trained technicians in accordance with a standardized protocol. The detailed methodology for measuring baPWV has been described in previous studies [14,22]. The patients were made to rest in a quiet, temperature-controlled

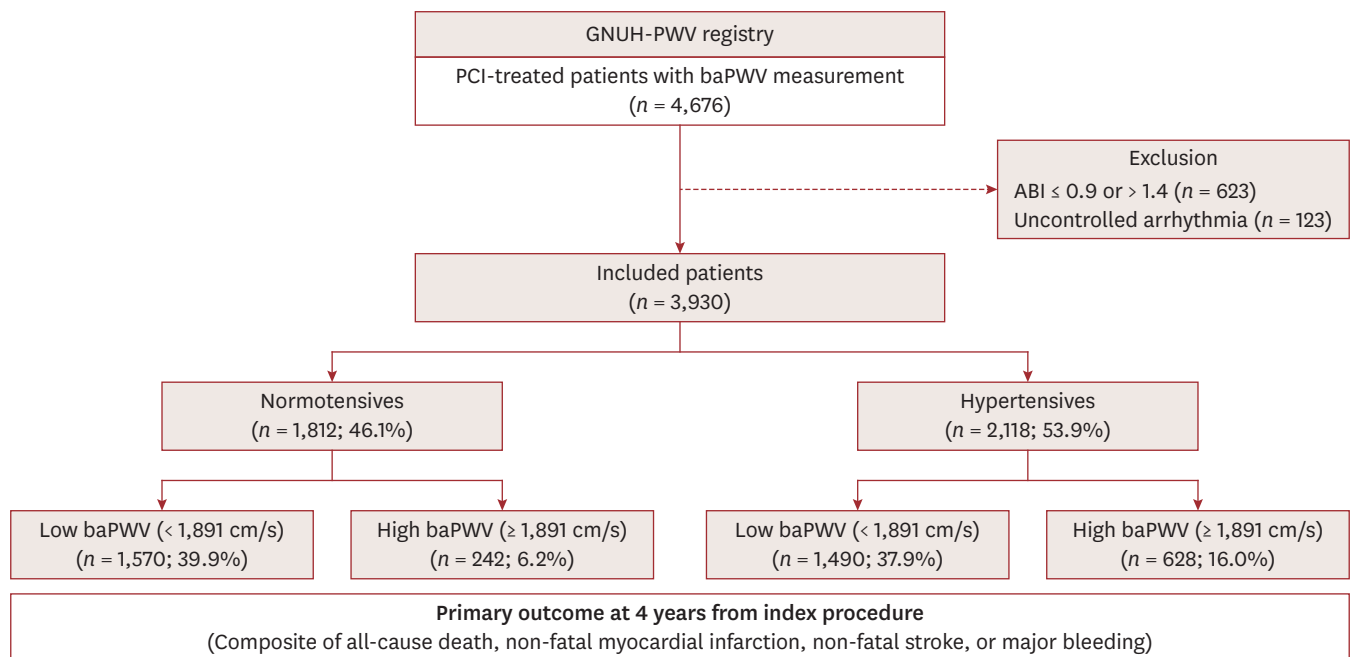


Fig. 1. Flow diagram of the study.

GNUH, Gyeongsang National University Hospital; PWV, pulse wave velocity; PCI, percutaneous coronary intervention; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index.

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room for at least 5 minutes before the measurement. In addition, the patients were instructed to avoid smoking, restrict the intake of caffeine and alcohol, and refrain from eating in the hours preceding the measurement. The patients were also instructed to refrain from speaking during the measurement. The baPWV was measured using a commercially available volume plethysmographic device (VP-1000; Colin Co. Ltd., Komake, Japan). Pneumatic BP cuffs were placed on the brachial site and ankle, electrocardiographic electrodes were attached to the wrists, and phonocardiographic electrodes were positioned at the optimal location on the sternum to facilitate accurate measurement. The index was calculated by dividing the estimated distance between the brachial and ankle sites, based on the height of the patient, by the transit time. The average baPWV value from the left and right sides was used in this study. Hypertension was defined as the use of antihypertensive drugs or a previously documented BP value of $\geq 140/90$ mmHg in a stable condition, as reported by the patient [23,24].

Study endpoint

The incidence of net adverse clinical events (NACE) over a 4-year period, encompassing a composite of all-cause mortality, non-fatal myocardial infarction (MI), non-fatal stroke, and major bleeding, was the primary outcome measure of this study. The secondary outcomes included major adverse cardiac and cerebrovascular events (MACCE) and major bleeding assessed within the same 4-year period. Additionally, each component of MACCE was assessed individually.

MACCE was defined as a combination of all-cause death, non-fatal MI, or non-fatal stroke. All clinical outcomes were defined in accordance with the recommendations set forth by the Academic Research Consortium [25]. Non-fatal MI was defined as the presence of symptoms of acute myocardial ischemia, new ischemic changes in electrocardiogram,

evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology detected via imaging, and an increase in the cardiac biomarker levels beyond the upper limit. Peri-procedural MI was not included in the clinical outcomes. Stroke was defined as a neurological deficit induced by an acute focal injury of the central nervous system caused by a vascular event requiring hospitalization and confirmed by a neurologist based on the imaging results. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) grade 3 or 5 bleeding. An independent event adjudication committee reviewed all clinical events.

Statistical analysis

Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as means with standard deviations or medians with interquartile ranges (IQRs), depending on their distribution. Continuous variables were assessed using the Kolmogorov–Smirnov test and via the examination of values of skew and kurtosis. One-way analysis of variance was performed to compare the baseline characteristics of the four groups and assess normally distributed continuous variables. Non-normally distributed continuous variables were assessed using the Kruskal–Wallis test. Post hoc comparisons were performed using Tukey’s test or Dunn’s multiple comparison test. Categorical variables were compared using the χ^2 test or Fisher’s exact test, as appropriate.

The cumulative event rates were estimated using Kaplan–Meier curves and compared using the log-rank test. Cox proportional hazard regression models based on the four groups defined according to the baPWV phenotype and the presence of hypertension were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary and secondary outcomes. Multivariable Cox proportional hazard models were constructed by incorporating the following clinically relevant variables: age, sex, body mass index, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), index presentation with ACS, smoking status, diabetes mellitus, dyslipidemia, chronic kidney disease (CKD), and potent P2Y₁₂ inhibitor, beta-blocker, angiotensin blockade, and statin. Backward elimination based on Akaike’s information criterion was performed to refine the models. The proportional hazard assumption for the variables in the model was tested using scaled Schoenfeld residuals. Multicollinearity was assessed by calculating variable inflation factors (VIFs), with all VIFs < 2 indicating no significant issues.

Time-dependent ROC curves at 4 years were constructed for 3 Cox models with sequential addition of variables: Model 1, clinical risk factors used in the multivariable adjusted model; Model 2, Model 1 + hypertensive status; and Model 3, Model 2 + baPWV phenotype. The corresponding area under the curves (AUCs) were compared to evaluate incremental discrimination. Furthermore, category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess the improvement in the predictive performance of the models. Sensitivity analysis was performed by redefining hypertension to include not only a history of hypertension or the use of antihypertensive medication but also presenting with SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg to assess the robustness of the findings. All statistical analyses were conducted using R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 2023.12.1; Posit, PBC, Boston, MA, USA), along with relevant packages such as *tableone*, *survminer*, *ggplot2*, *rms*, *survival*, *timeROC*, *survcomp*, and *survIDINRI*. All tests were 2-tailed, with a *P*-value of < 0.05 indicating statistical significance.

RESULTS

Baseline characteristics

Supplementary Table 1 summarizes the baseline characteristics of the enrolled patients ($n = 3,930$) according to the presence of hypertension. **Table 1** details the baseline characteristics of the enrolled patients according to the presence of hypertension and the baPWV levels ($< 1,891$ and $\geq 1,891$ cm/s). The overall mean age of the patients was 64.0 ± 11.5 years, and approximately 70% of the patients were males. Approximately 60% of the patients initially presented with ACS.

The patients with hypertension exhibited significantly higher baPWV values compared with those in the normotensive groups ($1,750.4 \pm 400.5$ vs. $1,550.5 \pm 330.9$ cm/s, $P < 0.001$). High baPWV phenotype ($\geq 1,891$ cm/s) was observed more frequently in patients in the hypertensive group (29.7%) than in those in the normotensive group (13.4%; odds ratio, 2.734; 95% CI, 2.320–3.223; $P < 0.001$). Compared with patients without hypertension, patients with hypertension were older, comprised a higher percentage of women, and had a higher body mass index (all $P < 0.001$). The prevalence of diabetes mellitus, CKD, and history of stroke was higher in this population (all $P < 0.001$). However, lesion complexity and the percentage of target lesions were similar across the groups (**Supplementary Table 1**).

Patients in the hypertensives with high baPWV phenotype group were generally older. Furthermore, the prevalence of comorbidities, such as diabetes mellitus, CKD, and previous stroke, was higher in these patients compared with that in those in the normotensives with baPWV phenotype group. Furthermore, the SBP and DBP, as well as the prevalence of multivessel disease, were higher in this group. The patients in the high baPWV groups (with and without hypertension) were older. The left ventricular ejection fraction of these patients was lower than those of the patients in the normotensive and low baPWV group. Laboratory findings indicated that patients in the hypertensive with high baPWV phenotype group had lower hemoglobin levels and estimated glomerular filtration rates, but higher HbA_{1c} values. The prescription of aspirin, beta-blockers, and statin was similar across the groups. Procedural characteristics indicated that the stent length and number in patients in the hypertensives with high baPWV phenotype group were greater than those of the patients in the normotensives with normal baPWV group (**Table 1**).

Prognostic implications of hypertensive status and baPWV levels

The median follow-up duration was 3.72 years (IQR, 1.56–6.47 years). A total of 323 patients (8.2%) experienced NACE during the follow-up period of up to 4 years. Hypertensive status had a modest effect on risk stratification (**Fig. 2A**). In contrast, the baPWV phenotype had a relatively higher predictive power (**Fig. 2B**). The incremental relationship between the baPWV index and the occurrence of clinical events was similar in the hypertensive and normotensive groups (**Supplementary Fig. 2**).

Hypertensive status and baPWV phenotype exhibited an additive effect on risk stratification. **Fig. 3** illustrates the Kaplan–Meier curves for the cumulative incidences of NACE, MACCE, and major bleeding stratified according to the baPWV phenotype and hypertensive status. The highest incidence rates of clinical events were observed in the hypertensives with high baPWV phenotype group (**Table 2**). The highest incidence of NACE was observed in the hypertensives with high baPWV group (14.8%), followed by the normotensives with high baPWV (12.4%), hypertensives with low baPWV (7.1%), and normotensives with low

Table 1. Baseline characteristics according to hypertensive status and baPWV phenotype (< 1,891 vs. ≥ 1,891 cm/s)

Characteristics	Normotension & low baPWV (n = 1,570)	Normotension & high baPWV (n = 242)	Hypertension & low baPWV (n = 1,490)	Hypertension & high baPWV (n = 628)	P-value
baPWV (cm/s)	1,455.2 ± 210.9	2,168.4 ± 301.0 ^a	1,546.7 ± 199.0 ^{ab}	2,233.5 ± 339.3 ^{abc}	< 0.001
Age (yr)	60.4 ± 11.0	70.7 ± 10.8 ^a	63.4 ± 10.7 ^{ab}	71.8 ± 9.5 ^{ac}	< 0.001
Women	283 (18.0)	94 (38.8)	451 (30.3)	326 (51.9)	< 0.001
Body mass index (kg/m ²)	24.3 ± 3.2	23.1 ± 3.4 ^a	25.2 ± 3.2 ^{ab}	23.7 ± 3.0 ^{ac}	< 0.001
SBP (mmHg)	123.8 ± 18.7	126.7 ± 20.6	133.8 ± 26.1 ^{ab}	135.9 ± 26.5 ^{ab}	< 0.001
DBP (mmHg)	76.4 ± 12.5	76.3 ± 13.7	79.8 ± 14.6 ^{ab}	79.2 ± 14.5 ^{ab}	< 0.001
Heart rate (/min)	73.6 ± 15.2	77.5 ± 15.7 ^a	74.6 ± 15.5 ^b	77.0 ± 16.1 ^{ac}	< 0.001
Index presentation with ACS	964 (61.4)	150 (62.0)	902 (60.5)	392 (62.4)	0.861
Risk factors					
Cigarette smoking	670 (42.7)	55 (22.7)	429 (28.8)	101 (16.1)	< 0.001
Diabetes mellitus	304 (19.4)	80 (33.1)	477 (32.0)	299 (47.6)	< 0.001
Dyslipidemia	918 (58.5)	123 (50.8)	835 (56.0)	320 (51.0)	0.005
Chronic kidney disease	84 (5.4)	35 (14.5)	189 (12.7)	186 (29.6)	< 0.001
Previous PCI	202 (12.9)	42 (17.4)	235 (15.8)	96 (15.3)	0.068
Previous stroke	48 (3.1)	15 (6.2)	101 (6.8)	55 (8.8)	< 0.001
Laboratory findings					
LVEF (%)	56.7 ± 8.2	54.9 ± 10.1 ^a	57.5 ± 8.3 ^{ab}	55.3 ± 9.4 ^{ac}	< 0.001
WBC (×10 ³ /mm ³)	9.07 ± 3.55	8.61 ± 3.75	8.57 ± 3.32 ^a	8.84 ± 3.45	0.001
Hemoglobin (g/dL)	14.0 ± 1.7	12.9 ± 1.8 ^a	13.6 ± 1.9 ^{ab}	12.6 ± 1.9 ^{ac}	< 0.001
Platelet (×10 ³ /mm ³)	238.7 ± 63.5	240.6 ± 70.3	242.6 ± 65.6	239.2 ± 71.7	0.419
eGFR (mL/min/1.73 m ²)	90.9 ± 24.5	83.9 ± 27.1 ^a	85.3 ± 27.6 ^a	72.5 ± 30.0 ^{abc}	< 0.001
Total cholesterol (mg/dL)	187.9 ± 48.8	175.1 ± 44.9 ^a	176.7 ± 45.6 ^a	174.4 ± 48.2 ^a	< 0.001
LDL cholesterol (mg/dL)	123.6 ± 43.3	110.7 ± 38.9 ^a	113.1 ± 40.8 ^a	110.7 ± 42.7 ^a	< 0.001
HDL cholesterol (mg/dL)	44.4 ± 12.3	46.6 ± 13.9	44.4 ± 12.8	46.8 ± 14.6 ^{ac}	< 0.001
Triglyceride (mg/dL)	169.0 ± 146.7	146.1 ± 80.9	164.2 ± 117.5	151.62 ± 134.0 ^{ac}	0.013 ^d
HbA _{1c} (%)	6.31 ± 1.29	6.62 ± 1.43 ^a	6.42 ± 1.23 ^a	6.62 ± 1.25 ^{ac}	< 0.001 ^d
Procedural characteristics					
AHA/ACC lesion: type B2/C	1,394 (88.8)	217 (89.7)	1,324 (88.9)	545 (86.8)	0.482
Multivessel PCI	242 (15.4)	48 (19.8)	280 (18.8)	122 (19.4)	0.031
Target lesion					0.340
Left main coronary artery	42 (2.7)	3 (1.2)	30 (2.0)	9 (1.4)	
Left anterior descending artery	883 (56.2)	141 (58.3)	821 (55.1)	346 (55.1)	
Left circumflex artery	358 (22.8)	66 (27.3)	404 (27.1)	182 (29.0)	
Right coronary artery	545 (34.7)	82 (33.9)	531 (35.6)	215 (34.2)	
Treatment method					< 0.001
Drug-eluting stent	1,383 (88.1)	223 (92.1)	1,336 (89.7)	556 (88.5)	
Bioresorbable scaffold	44 (2.8)	0 (0.0)	18 (1.2)	2 (0.3)	
Bare metal stent	6 (0.4)	3 (1.2)	10 (0.7)	2 (0.3)	
Drug-coated balloon	54 (3.4)	8 (3.3)	42 (2.8)	23 (3.7)	
POBA	83 (5.3)	8 (3.3)	84 (5.6)	45 (7.2)	
Numbers of stent	1.4 ± 0.7	1.4 ± 0.7	1.5 ± 0.8 ^a	1.5 ± 0.8 ^a	0.001
Total stent length (mm)	35.4 ± 20.8	37.1 ± 21.2	38.1 ± 22.4 ^a	38.6 ± 22.8 ^a	0.002
Stent diameter (mm)	3.2 ± 0.5	3.1 ± 0.5	3.2 ± 0.5	3.1 ± 0.5 ^{ac}	< 0.001
Discharge medications					
Aspirin	1,556 (99.1)	238 (98.3)	1,476 (99.1)	624 (99.4)	0.533
Type of P2Y ₁₂ inhibitor					0.058
Clopidogrel	1,197 (76.2)	197 (81.4)	1,206 (80.9)	512 (81.5)	
Prasugrel	79 (5.1)	11 (4.5)	71 (4.8)	23 (3.7)	
Ticagrelor	260 (16.6)	29 (12.0)	189 (12.7)	81 (12.9)	
Beta blocker	942 (60.0)	143 (59.1)	953 (64.0)	394 (62.7)	0.108
Angiotensin blockade	1,041 (66.3)	156 (64.5)	1,118 (75.0)	453 (72.1)	< 0.001
Statin	1,497 (95.4)	226 (93.4)	1,419 (95.2)	585 (93.2)	0.112

Data are presented as mean ± standard deviations or number (%).

baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; WBC, white blood cell; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AHA, American Heart Association; ACC, American College of Cardiology; POBA, plain old balloon angioplasty.

^aPost hoc *P*: Statistically significant difference *P* < 0.05 compared to the Normotension & low baPWV (< 1,891 cm/s) group.

^bPost hoc *P*: Statistically significant difference *P* < 0.05 compared to the Normotension & high baPWV (≥ 1,891 cm/s) group.

^cPost hoc *P*: Statistically significant difference *P* < 0.05 compared to the Hypertension & low baPWV (< 1,891 cm/s) group.

^dAssessed by nonparametric test.

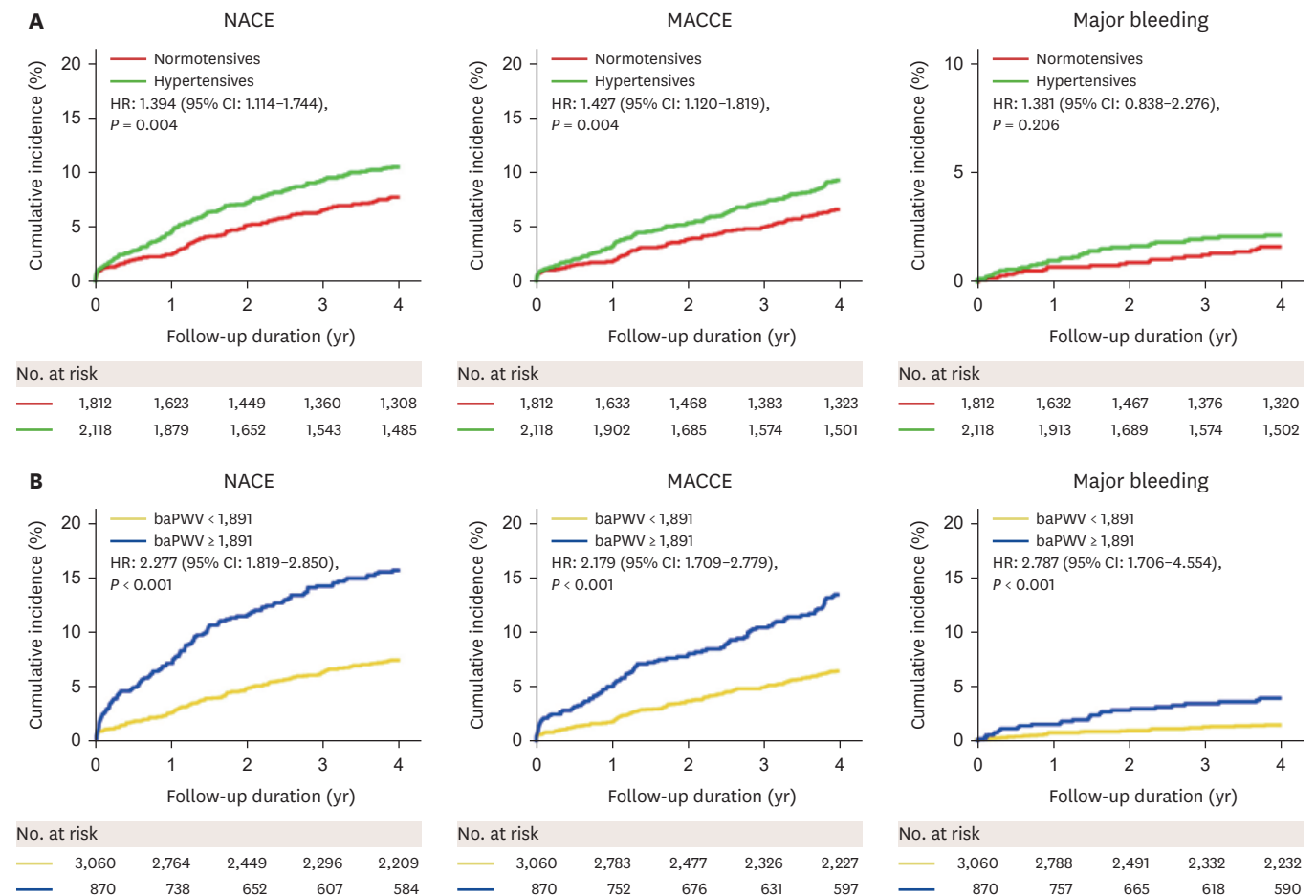


Fig. 2. Kaplan-Meier curves for the cumulative incidence of clinical outcomes. According to (A) hypertensive status and (B) baPWV phenotype ($< 1,891$ vs. $\geq 1,891$ cm/s). baPWV, brachial-ankle pulse wave velocity; NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; HR, hazard ratio; CI, confidence interval.

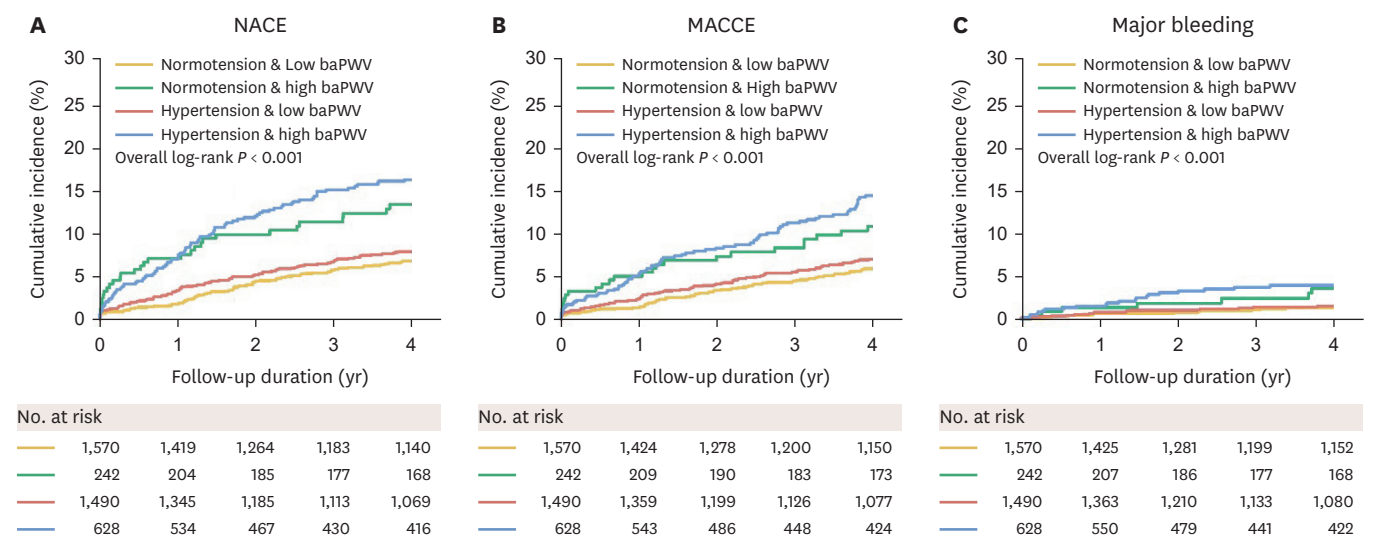


Fig. 3. Kaplan-Meier curves for the cumulative incidence. (A) NACE, (B) MACCE, and (C) major bleeding according to hypertensive status and baPWV phenotype ($< 1,891$ vs. $\geq 1,891$ cm/s). NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; baPWV, brachial-ankle pulse wave velocity.

Table 2. Clinical outcomes according to hypertensive status and baPWV phenotype (< 1,891 vs. ≥ 1,891 cm/s)

Outcomes	Overall (n = 3,930)	Normotension & low baPWV (n = 1,570)	Normotension & high baPWV (n = 242)	Hypertension & low baPWV (n = 1,490)	Hypertension & high baPWV (n = 628)	P-value
NACE ^a (MACCE ^b + major bleeding ^c)	323 (8.2)	94 (6.0)	30 (12.4)	106 (7.1)	93 (14.8)	< 0.001
MACCE (all-cause death, MI, stroke)	278 (7.1)	81 (5.2)	24 (9.5)	93 (6.2)	80 (12.7)	< 0.001
All-cause death	120 (3.1)	37 (2.4)	14 (5.8)	31 (2.1)	38 (6.1)	< 0.001
Non-fatal MI	92 (2.3)	24 (1.5)	5 (2.1)	34 (2.3)	29 (4.6)	< 0.001
Non-fatal stroke	61 (1.6)	16 (1.0)	7 (2.9)	20 (1.3)	18 (2.9)	0.004
Major bleeding	65 (1.7)	18 (1.1)	7 (2.9)	19 (1.3)	21 (3.3)	0.001

Data are presented as number (%).

baPWV, brachial-ankle pulse wave velocity; NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

^aNACE was defined as a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and major bleeding.

^bMACCE was defined as a composite of all-cause death, non-fatal myocardial infarction, and non-fatal stroke.

^cMajor bleeding was defined as Bleeding Academic Research Consortium 3 or 5 bleeding.

baPWV (6.0%) groups. Similar patterns were also observed for the occurrence of MACCE and major bleeding.

Compared with that observed in the normotensives with low baPWV group, a significant association with an increased risk of NACE, MACCE, and major bleeding was observed in the hypertensive with high baPWV group only (**Table 3**). The adjusted hazard ratios (aHRs) for NACE, MACCE, and major bleeding on comparing the hypertensives with high baPWV group with the normotensives with low baPWV group were 1.556 (95% CI, 1.132–2.138; $P = 0.006$), 1.573 (95% CI, 1.113–2.223; $P = 0.010$), and 2.023 (95% CI, 1.029–3.978; $P = 0.041$), respectively. Trends towards increased risks were observed in the normotensives with high baPWV and hypertensives with low baPWV groups compared with that in the normotensives with low baPWV group; however, these differences were not statistically significant.

Fig. 4 presents the incremental prognostic value of sequentially adding hypertensive status and baPWV to the clinical risk factor model for prediction of 4-year NACE. The clinical risk factor model (Model 1) yielded an AUC of 0.681 (95% CI, 0.648–0.714). Adding hypertensive status alone (Model 2) resulted in a small increase in AUC to 0.685 (95% CI, 0.652–0.717; $P = 0.049$ vs. Model 1), with no significant improvement in NRI or IDI. In contrast, further addition of baPWV (Model 3) increased the AUC to 0.695 (95% CI, 0.663–0.727; $P = 0.035$ vs. Model 2), with significant improvements in NRI (0.101; 95% CI, 0.035–0.174; $P = 0.020$ vs. Model 2) and IDI (0.004; 95% CI, 0.001–0.009; $P = 0.007$ vs. Model 2).

Subgroup analysis

Comparison of the hypertensives with high baPWV group with other groups revealed that “hypertension-high baPWV phenotype” showed significant associations with an increased risk of NACE (aHR, 1.389; 95% CI, 1.068–1.806). This finding was consistent across various subgroups, including age, sex, smoking status, diabetes mellitus, dyslipidemia, CKD, and index disease entity. The consistency of the effect across these subgroups was indicated by the interaction P -values (**Fig. 5A**). The clinical impact of “hypertension-high baPWV phenotype” on the occurrence of MACCE exhibited similar trends to those observed for NACE (**Fig. 5B**). **Fig. 5C** presents the results of the subgroup analysis for major bleeding, which also demonstrated similar trends, with significant interactions being observed in the smoking status and index disease entity.

Table 3. HRs for clinical outcomes according to hypertensive status and baPWV phenotype (< 1,891 vs. ≥ 1,891 cm/s)

Variables	Crude HR (95% CI)	P-value	Adjusted HR ^a (95% CI)	P-value
NACE ^b (MACCE ^c + major bleeding ^d)				
Normotension & low baPWV	Reference		Reference	
Normotension & high baPWV	2.167 (1.437–3.269)	< 0.001	1.458 (0.952–2.232)	0.083
Hypertension & low baPWV	1.196 (0.906–1.578)	0.207	1.115 (0.838–1.483)	0.455
Hypertension & high baPWV	2.620 (1.967–3.490)	< 0.001	1.556 (1.132–2.138)	0.006
MACCE (all-cause death, MI, and stroke)				
Normotension & low baPWV	Reference		Reference	
Normotension & high baPWV	1.974 (1.252–3.113)	0.003	1.340 (0.835–2.150)	0.225
Hypertension & low baPWV	1.216 (0.902–1.637)	0.199	1.141 (0.839–1.552)	0.400
Hypertension & high baPWV	2.577 (1.892–3.51)	< 0.001	1.573 (1.113–2.223)	0.010
Major bleeding				
Normotension & low baPWV	Reference		Reference	
Normotension & high baPWV	2.643 (1.104–6.328)	0.029	1.916 (0.794–4.622)	0.148
Hypertension & low baPWV	1.114 (0.585–2.122)	0.743	1.146 (0.593–2.216)	0.685
Hypertension & high baPWV	3.057 (1.629–5.737)	0.001	2.023 (1.029–3.978)	0.041
All-cause death				
Normotension & low baPWV	Reference		Reference	
Normotension & high baPWV	2.499 (1.351–4.623)	0.004	1.415 (0.745–2.686)	0.289
Hypertension & low baPWV	0.881 (0.547–1.42)	0.603	0.787 (0.484–1.279)	0.334
Hypertension & high baPWV	2.624 (1.669–4.126)	< 0.001	1.345 (0.810–2.234)	0.252
Non-fatal MI				
Normotension & low baPWV	Reference		Reference	
Normotension & high baPWV	1.355 (0.517–3.551)	0.537	1.154 (0.438–3.038)	0.772
Hypertension & low baPWV	1.494 (0.886–2.519)	0.132	1.240 (0.722–2.129)	0.437
Hypertension & high baPWV	3.088 (1.798–5.303)	< 0.001	2.039 (1.125–3.694)	0.019
Non-fatal stroke				
Normotension & low baPWV	Reference		Reference	
Normotension & high baPWV	2.891 (1.189–7.028)	0.019	1.667 (0.661–4.205)	0.279
Hypertension & low baPWV	1.316 (0.682–2.539)	0.413	1.075 (0.554–2.087)	0.830
Hypertension & high baPWV	2.854 (1.456–5.597)	0.002	1.421 (0.679–2.973)	0.351

HR, hazard ratio; baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

^aMultivariable analysis was performed after adjusting for clinically relevant covariates, including age, sex, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, presented with acute coronary syndrome, diabetes mellitus, dyslipidemia, chronic kidney disease, cigarette smoking, potent P2Y₁₂ inhibitor, angiotensin blockade, beta blocker, and statin.

^bNACE was defined as a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and major bleeding.

^cMACCE was defined as a composite of all-cause death, non-fatal myocardial infarction, and non-fatal stroke.

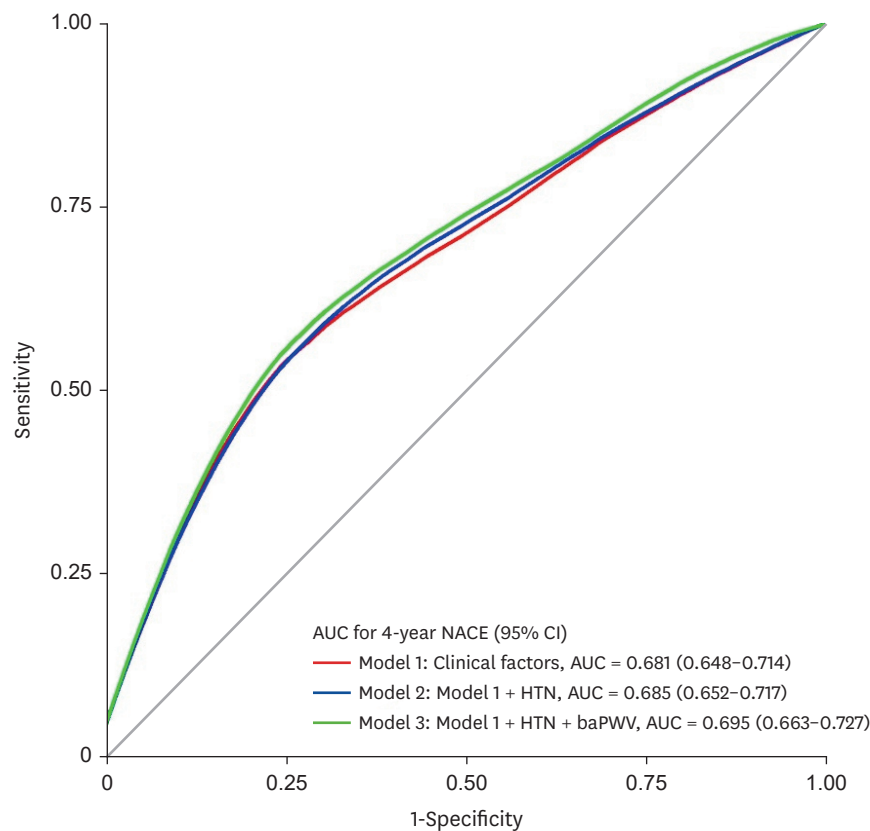
^dMajor bleeding was defined as Bleeding Academic Research Consortium 3 or 5 bleeding.

Sensitivity analysis

The results of a sensitivity analysis conducted using an alternative definition of hypertension, i.e., a history of hypertension or the presence of SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg [26], were consistent with those of the primary analysis. The highest cumulative incidence of NACE (14.7%) was observed in the hypertensives with high baPWV group. Notably, a significantly higher risk (aHR, 1.485; 95% CI, 1.066–2.068; *P* = 0.019) was observed in this group compared with that in the normotensives with low baPWV group. This group also exhibited a higher risk for MACCE and major bleeding; however, the higher risk for major bleeding was not statistically significant (**Supplementary Table 2**).

DISCUSSION

To the best of our knowledge, the present study is a largest analysis to evaluate the combined effect of arterial stiffness, measured using baPWV, and hypertensive status on the clinical outcomes in patients with CAD undergoing PCI. Importantly, this is also the first study to explore the association of these factors not only with ischemic outcomes but also with



	AUC for 4-year NACE (95% CI)	P-value		NRI (vs. model 1) (95% CI), P-value	NRI (vs. model 2) (95% CI), P-value	IDI (vs. model 1) (95% CI), P-value	IDI (vs. model 2) (95% CI), P-value
Model 1 ^a	0.681 (0.648–0.714)	Reference		Reference		Reference	
Model 2 ^a	0.685 (0.652–0.717)	0.049	Reference	0.047 (–0.031–0.095) P = 0.206	Reference	0.001 (–0.001–0.003) P = 0.465	Reference
Model 3 ^a	0.695 (0.663–0.727)	0.017	0.035	0.144 (0.048–0.187) P < 0.001	0.101 (0.035–0.174) P = 0.020	0.007 (0.002–0.016) P < 0.001	0.004 (0.001–0.009) P = 0.007

Fig. 4. Incremental prognostic value of hypertensive status and baPWV for predicting NACE over a 4-year period.

baPWV, brachial-ankle pulse wave velocity; NACE, net adverse clinical events; AUC, area under the curve; HTN, hypertension; NRI, net reclassification improvement; CI, confidence interval; IDI, integrated discrimination improvement.

^aModel 1 included the age and sex.

^bModel 2 included the clinical variables of age, sex, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, presented with acute coronary syndrome, diabetes mellitus, dyslipidemia, chronic kidney disease, cigarette smoking, potent P2Y₁₂ inhibitor, angiotensin blockade, beta blocker, and statin.

^cModel 3 included the variables in Model 2 plus hypertensive status and baPWV.

bleeding complications following PCI. The key findings from this analysis are as follows: 1) compared to hypertensive status, the baPWV phenotype showed a stronger association with clinical outcomes. The incidence rates of clinical events were highest in hypertensives with high baPWV, followed by normotensives with high baPWV, hypertensives with low baPWV, and finally normotensives with low baPWV groups; 2) compared with normotension and the low baPWV phenotype, the presence of hypertension and high baPWV phenotype resulted in a significant increase in the risks of adverse clinical outcomes, including NACE, MACCE, and major bleeding; 3) adjunctive use of baPWV phenotype and hypertensive status in addition to the clinical risk model significantly improved the predictive ability for NACE over a 4-year period, with baPWV providing a greater incremental improvement in risk discrimination than hypertensive status, indicating that arterial stiffness may reflect residual

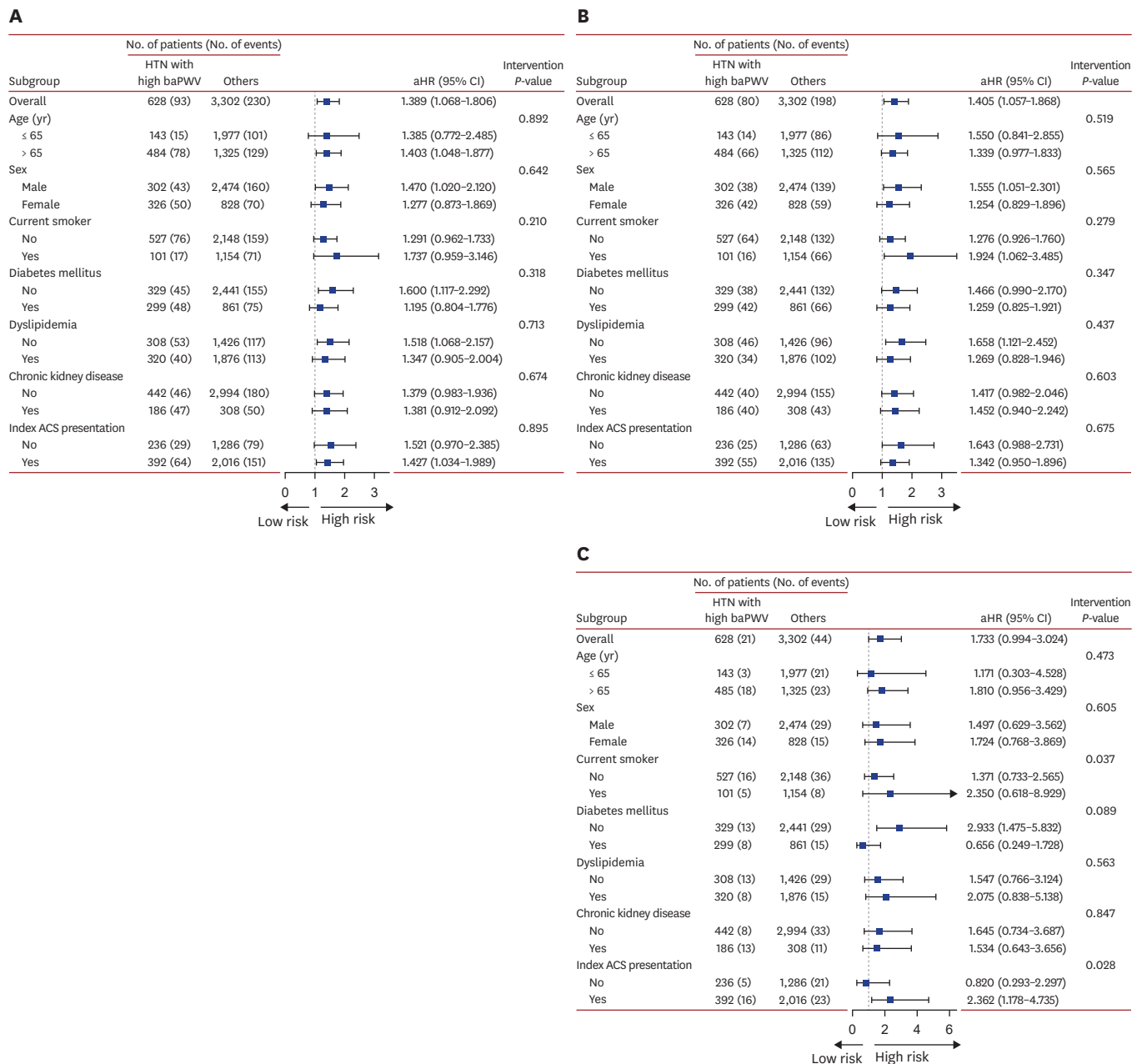


Fig. 5. Subgroup analysis of the risk. (A) NACE, (B) MACCE, and (C) major bleeding for the hypertension-high baPWV group compared with the other groups. NACE, net adverse clinical events; MACCE, major adverse cardiac and cerebrovascular events; baPWV, brachial-ankle pulse wave velocity; HTN, hypertension; aHR, adjusted hazard ratio; CI, confidence interval; ACS, acute coronary syndrome.

CV risk beyond BP control; and 4) the sensitivity analyses performed using alternative definitions of hypertension confirmed the robustness of these trends.

Strategies for secondary prevention play a crucial role in optimizing patient management and minimizing the risk of adverse events following PCI [27]. The cumulative risk for recurrent events during the long-term follow-up period following PCI persists even with the advent of state-of-the-art devices and the implementation of guideline-directed medical therapy and lifestyle interventions [1,28]. Therefore, further studies must be conducted in the future

to identify residual CV risk factors and identify patients susceptible to future CV events, in addition to established risk factor control.

Hypertension is an important risk factor for the development of CAD and is commonly observed in patients with established CAD [16]. Furthermore, the management of hypertension is a crucial element in the secondary prevention of CAD [23,29]. However, previous studies have reported differing effects of hypertension on the prognosis of patients who have undergone PCI, with some studies reporting neutral outcomes and others reporting adverse outcomes [30,31]. The pathophysiological interplay between hypertension and arterial wall damage contributes to increased arterial stiffness, thereby building a bidirectional relationship between hypertension and arterial stiffening [32]. Arterial stiffness is a type of hypertensive-mediated organ damage representing the arterial damage caused by hypertension [29]. Elevated arterial stiffness is a precursor to hypertension [33]. The effect of arterial stiffness in general populations has been studied extensively [8,9], with some studies reporting its correlation with the presence and severity of coronary atherosclerosis [10]. baPWV is a simple and non-invasive measure commonly used for risk assessment in patients with hypertension. Furthermore, it serves as a prognostic indicator in patients with CAD [15,23]. Over 50% of the patients in the present study had hypertension, and these patients had a significantly higher proportion of high baPWV phenotype compared with the patients who were normotensive (29.7% vs. 13.4%). Notably, only 16% of the entire cohort had concomitant hypertension and high baPWV, indicating that the concurrence of these risk factors is relatively uncommon.

An interesting finding of this study is that patients with normotension but elevated baPWV also exhibited a modestly increased clinical risk. Although causality cannot be inferred, this phenotype may reflect isolated vascular aging or masked hypertension, with increased arterial stiffness serving as a marker of subclinical target-organ damage that precedes overt hypertension [19,34]. Similar patterns have been reported previously [35], supporting the notion that elevated baPWV may identify a high-risk subgroup even in the absence of diagnosed hypertension. These observations suggest that reliance on office BP alone may underestimate future CV risk. Accordingly, assessment of arterial stiffness may help identify high-risk individuals without diagnosed hypertension and capture residual risk not fully explained by BP status in patients undergoing PCI.

Several studies have explored the combined effects of arterial stiffness and hypertension on CV outcomes. However, these studies primarily focused on general populations and hypertensives. Wu et al. demonstrated that the presence of the high baPWV phenotype coupled with hypertension resulted in a significant increase in the risk of CVD in the general population, indicating the superior predictive value of combining baPWV with BP over using either parameter alone [20]. Niiranen et al. [36] explored the combined effect of carotid-femoral PWV and BP in predicting CVD. Another study revealed an additive effect of combining baPWV and BP in predicting the incidence of peripheral arterial disease in the general population [35]. Furthermore, Song et al. [37] reported the combined effect of baPWV and BP control status on the risk of stroke in patients with hypertension. Compared with the findings of these studies, the findings of the present study specifically address the additive impact of baPWV phenotype and hypertensive status in high-risk patients with CAD undergoing PCI. These findings provide novel insights into their combined effect on the general population and high-risk patients such as those with established CAD. Furthermore, the present study is unique in that it examines the ischemic and bleeding outcomes.

The causes underlying the additive effect of arterial stiffness and hypertension on adverse clinical outcomes remain unclear; however, several hypotheses can be considered. First, hypertension enhances the development of atherosclerosis and destabilizes plaques [38]. Furthermore, arterial stiffness is also closely related to the progression of atherosclerosis [39]. Hypertension and arterial stiffness exhibit a bidirectional relationship; thus, these conditions reinforce each other and create a positive feedback loop, thereby increasing the risk of CVD. Second, hypertension and arterial stiffness share several pathophysiological mechanisms associated with the risk of CVD. For instance, reactive oxygen species, inflammation, and endothelial dysfunction are related to both conditions and may synergistically contribute to the occurrence of adverse clinical outcomes [40,41].

Beyond ischemic complications, a potential association between arterial stiffness and bleeding events also warrants consideration. Increased arterial stiffness is associated with reduced arterial wall compliance, degenerative changes in collagen and elastin, and widened pulse pressure; collectively, these alterations may heighten vascular fragility and increase susceptibility to bleeding events [11,42,43]. Consistent with these observations, prior studies have reported that greater aortic stiffness is associated with an increased risk of gastrointestinal bleeding in patients with left ventricular assist devices [44]. Moreover, increased arterial stiffness has been linked to a higher risk of aortic rupture in patients with aortic aneurysm, suggesting that advanced stiffness may coexist with structural weakening of the arterial wall [13]. Taken together, arterial stiffness may reflect a greater degree of vascular fragility. Because hypertension is also associated with chronic vascular injury and a higher risk of bleeding complications after PCI [45], the coexistence of hypertension and increased arterial stiffness may further amplify the risks of both ischemic and bleeding events.

The present study holds significant clinical implications. The combination of baPWV and hypertension could serve as a significant risk enhancer in the management of patients following PCI. Thus, incorporating baPWV measurements, which are simple and widely applied in daily practice, into routine clinical practice for high-risk patients with CAD could improve risk stratification and identify patients who may benefit from more aggressive therapeutic strategies. Clinicians could potentially reduce the incidence of ischemic and bleeding events by addressing arterial stiffness and hypertension, leading to better long-term outcomes for patients who have undergone PCI. Clinicians could consider implementing more intensive strategies for the management of BP and tailored antihypertensive +/- anti-thrombotic therapies based on baPWV and hypertensive status to achieve this. Patient education encouraging lifestyle changes, such as diet, exercise, and smoking cessation, should also be emphasized.

Nevertheless, this study has certain limitations that should be considered. First, the findings are primarily exploratory rather than establishing causality, given the observational nature of this study. Because this study was not designed to elucidate pathophysiologic mechanisms, the observed association between arterial stiffness and bleeding events should be interpreted as hypothesis-generating rather than causal. Second, although approximately 4,000 patients were included consecutively, there is still a possibility of selection bias as the patients were selected from a prospective, two-center registry. Third, residual confounding from clinical factors not captured in the registry cannot be fully excluded despite multivariable adjustment. In particular, data on key variables—such as antiplatelet adherence and smoking cessation during follow-up—were unavailable and may have influenced the results. However, the robustness of this study is bolstered by the large sample size and systematic

data collection conducted by well-trained coordinators. Moreover, this study only used baseline baPWV value and did not account for interchanges during the follow-up period.

CONCLUSIONS

In conclusion, this study underscores the additive effect of arterial stiffness index, measured using baPWV, in addition to hypertensive status on predicting the occurrence of long-term ischemic and bleeding events in high-risk patients with CAD undergoing PCI. The findings of the present study suggest that baPWV assessment and diligent management of blood pressure could improve the clinical outcomes in these patients.

ACKNOWLEDGEMENTS

Not applicable.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics according to hypertensive status

Supplementary Table 2

Sensitivity analysis of clinical outcomes based on alternative hypertension definition

Supplementary Fig. 1

Time-dependent ROC curve of baPWV for the prediction of 4-year NACE. The optimal cut-off of 1,891 cm/s was identified using the Youden index.

Supplementary Fig. 2

Restricted cubic spline analyses depicting the continuous association between baPWV and the risk of NACE over a 4-year period in patients. Patients who were (A) hypertensive and (B) normotensive.

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