Lower systolic blood pressure and cardiovascular event risk stratified by renal resistive index in hospitalized cardiovascular patients: J-VAS study

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Content

1. Introduction

The new US hypertension guideline recommends a lower blood pressure (BP) target compared with previous guidelines.[1] The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive BP control provided a benefit for the reduction of cardiovascular events compared with standard BP control[2], but a sub-analysis of the study revealed the J-shaped curve phenomenon of diastolic BP (DBP) and cardiovascular event.[3] Although it has been hypothesized that patients with greater progression of arterial stiffness would be more likely to exhibit the J-shaped curve phenomenon[4], it is not clear why this phenomenon was observed in the selected cardiovascular populations.[3,5,6] In part for this reason, the threshold of BP-lowering in hospitalized atherosclerotic-cardiovascular patients has been a matter of controversy. We hypothesized that to categorize the hospitalized atherosclerotic-cardiovascular patients by a renal Doppler parameter; renal resistive index (RRI), which has been proved to associate well with the arterial stiffness parameters, would demonstrate a discrepancy of the impact of the different BP level on the future cardiovascular event risk in these patients.

1.1 Renal resistive index

The RRI is generally measured by Doppler ultrasonography at the renal interlobar arteries.[7,8] Previous studies reported that the RRI provided more prognostic power for both renal and cardiovascular outcomes than did the conventional biomarkers of kidney function alone in the hypertensive patients[9], elderly patients[10], and heart failure patients.[11] Moreover, the RRI has been reported to reflect not only the intra-renal vascular atherosclerosis and tubulo-interstitial damage but also represent the systemic hemodynamic condition. It has been well correlated with arterial stiffness parameters such as pulse pressure and pulse wave velocity (PWV).[12,13]

1.1.1 Measurement technique

Anatomically, the main renal arteries originate from the aorta then divide into anterior and posterior branches, which subdivide into the segmental and interlobar arteries. The interlobar arteries further divide into arcuate arteries that run through the corticomedullary junction. (Figure 1) The RRI at the level of interlobar artery has been preferred for using in the clinical application.[14] By Doppler ultrasonography, systolic and diastolic blood flow velocities can be measured from the interlobar arteries. However, waveforms must be refined for measurement by using the proper probe (highest frequency), the lowest pulse repetition frequency to get rid of aliasing, the highest gain with the least background noise, and the lowest wall filter.[15]

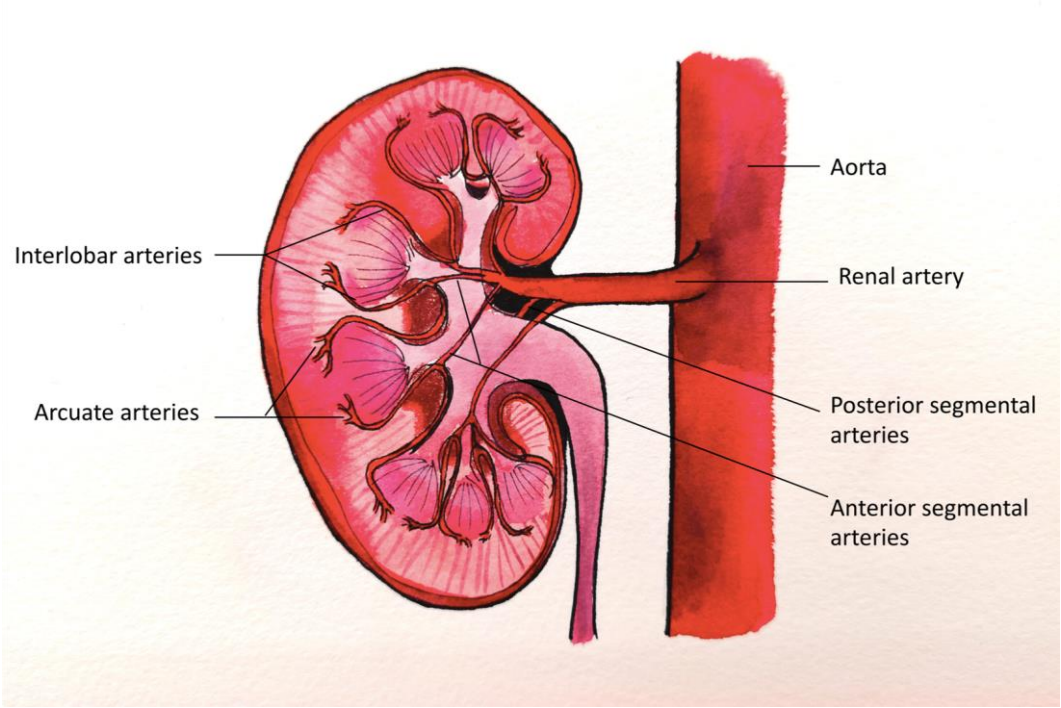

Figure 1: Anatomy of the renal arteries

The Doppler RRI is a traditional waveform index initially used as a measure of vascular resistance that was firstly introduced and described by Pourcelot ([peak systolic velocity - end diastolic velocity]/peak systolic velocity).[16] The RRI value is independent of the diameter of the vessels and of the angle between the ultrasound beam and blood flow. A

universal normal value for RRI was 0.60, whereas 0.70 is usually considered the upper threshold of normal RRI in adults.[7,17] As mentioned before, this index is initially adopted as a parameter for quantifying the changes in renal vascular resistance (RVR). However, the RRI is not only dependent on RVR, and it is also affected by other potentially influencing factors. Therefore, to correctly interpreting the RRI, clinician should take into account the factors that can confound it including central hemodynamics i.e. arterial stiffness, pulse pressure and heart rate[12], intra-abdominal pressure (IAP)[18], and other factors, including age[19] and underlying renal disease.[20]

In vitro experiments by Bude and Robin underlined the vital importance of vascular compliance in RRI analysis.[20,21] They found that when the compliance was normal, RRI was dependent on RVR. However, when the compliance decreased, there was change in the relationship between RRI and RVR. Furthermore, RRI was totally independent of RVR when compliance was down to zero. The author of the study suggested that the RRI is a misnomer and it should be named the "*impedance index*" because resistance and compliance both effect the change of Doppler arterial waveform.[20,21] This is very important because vascular compliance is often varied in vivo according to arterial pressure, age, treatments, and chronic diseases such as diabetes or hypertension.[22,23] With regard to pulse pressure, there was a significant positive linear correlation found between the RRI and the pulse pressure index ([systolic pressure - diastolic pressure]/systolic pressure).[12] Therefore, a patient with a high pulse pressure might have a higher RRI values, even without renal disease. Furthermore, the higher pulse pressure associates with a lower vascular compliance that can explain the increase in RRI according to age regardless of any renal disease.[19] (Figure 2)

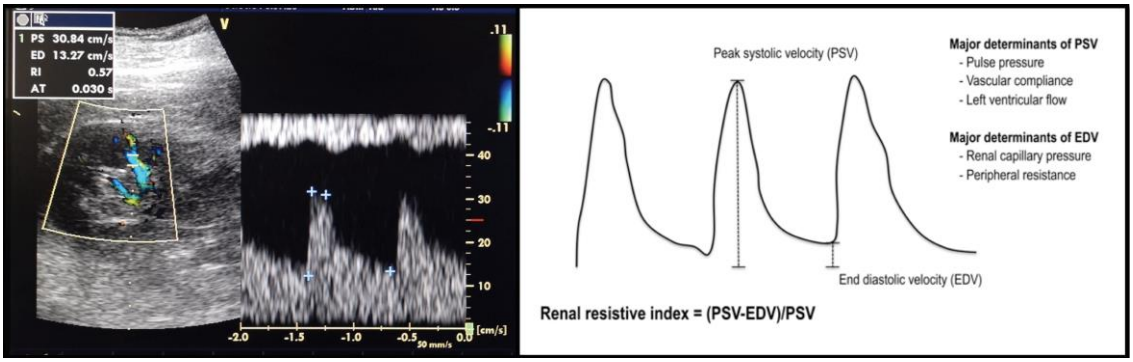

Figure 2: The Doppler ultrasonographic measurement of RRI and its influencing factors

1.1.2 Applications

From the recent evidences, RRI has been a promising marker of vascular damage and a predictor of poor cardiovascular outcome. However, the merit of RRI was found in selected group of patients. Apart from renal disease patients, RRI was found to have a predictive value in cardiovascular patients such as hypertension, and heart failure with preserved ejection fraction.

1.1.2.1 Hypertension

Hypertensive patients with higher morning BP surge (the morning BP minus the lowest nocturnal BP more than 32.5 mmHg) were found to have significantly higher RRI values[24], as well as those with high BP variability in visit-to-visit BP measurements.[25] Another studies of hypertensive patients also addressed a significant correlation between daytime systolic BP (SBP) variability[26], ambulatory arterial stiffness index (AASI)[26], PWV[27], aortic pulse pressure[27] and RRI. In a study of refractory hypertensive patients, the group of patients with RRI >0.7 had higher PWV, carotid intima media thickness (IMT) and coronary artery calcification compared with patients with normal RRI.[28] A previous study showed that strict BP control in patients with essential hypertension with captopril administration was associated with the improvement of RRI.[29] These studies demonstrated significant associations of RRI with the markers of cardiovascular damage in hypertensive patients.

Therefore, there is a possibility of the use of RRI in diagnosis of cardiovascular damage in hypertensive patients.

1.1.2.2 Cardiovascular outcome prediction

There are limited data regarding the role of RRI for prediction of all-cause and cardiovascular mortality. A previous study demonstrated an independent association between RRI and Framingham risk score, IMT and pulse pressure.[30] Ennezat et al. studied in a group of patients with pEF and found significantly higher RRI values in HFpEF patients even after adjusting for renal function, BP and anti-hypertensive medication.[11] Furthermore, higher RRI (>0.82) significantly associated with death and hospitalized HF events and were an independent predictor of poor outcome in HFpEF patients (HR 1.06; 95 % CI 0.16–0.62; p = 0.007). The authors addressed an important predictive value of this indicator. Likewise, there was a study by Tedesco et al, which found that left ventricular mass index (LVMI), an important pathophysiology of HFpEF, significantly and independently associated with the value of the RRI.[31] In a prospective study of 726 American elderlies, who were followed up for 4 years, the authors found that RRI together with renal artery peak systolic velocity (PSV) was significantly associated with all-cause mortality and cardiovascular event (hospitalized angina, congestive heart failure, myocardial infarction, coronary artery bypass grafting, stroke, transient ischemic attack), and only PSV was found to be a predictor of cardiovascular disease event.[10] However, post-hoc analysis of this study in 86 patients with atherosclerotic reno-vascular disease who were followed up for 5 years, showed that RRI >0.8 was the strongest predictor of death (HR, 6.7; 95 % CI, 2.6–17.0; $p < 0.001$).[32] This data suggests a promising role of RRI in prediction of mortality due to cardiovascular risk.

2. Objectives

We hypothesized that to categorize the relatively vulnerable subjects, namely, the hospitalized atherosclerotic-cardiovascular patients by RRI would demonstrate a discrepancy of the impact of the different BP level on the future cardiovascular event risk.

To test this hypothesis, we analyzed the association between BP at discharge and the risk of future cardiovascular events in hospitalized atherosclerotic-cardiovascular patients with lower vs. higher RRI at a single tertiary care center.

3. Methods

3.1 Study design

We analyzed data of the patients enrolled in the Jichi Vascular Hemodynamics in Hospitalized Cardiovascular Patients (J-VAS) study, which was a single center, retrospective cohort study of Japanese adults who were hospitalized from cardiovascular diseases at the cardiovascular unit of Jichi Medical University Hospital, a tertiary-care center. The patients in this cohort were performed non-invasive vascular hemodynamic measurements including clinic blood pressure, renal and carotid artery Doppler ultrasonography, ankle-brachial index and arterial pulse wave velocity and were followed to collect the prognostic data. The Institutional Review Board of Jichi Medical University approved the study with a waiver of consent.

3.2 Study subjects

For this study, 2390 patients of the J-VAS study who admitted between the 1st of January 2012 and 30th of September 2016 and were performed renal Doppler ultrasonography were recruited. The patients were diagnosed with acute coronary syndrome (ACS), acute decompensated heart failure (ADHF), acute aortic disease (AAD) or peripheral vascular disease (PAD). The diagnostic criteria of ACS, ADHF, AAD and PAD are shown below;

1. Acute coronary syndromes (ACS) was diagnosed according to the third universal definition of myocardial infarction.[33]

Detection of a rise and/or fall in the cardiac biomarker values with at least one value above the 99th upper reference limit and one of the following criteria;

1. Clinical symptoms of ischemia
2. New or presumed new ST-segment and/or T-wave abnormalities
3. New left bundle branch block
4. Pathological Q-waves
5. Radiologic evidence of new loss of viable myocardium or region wall motion abnormalities
6. Identification of new intracoronary occlusion on angiography

2. Acute decompensated heart failure (ADHF) was diagnosed based on a careful history and physical examination. The cardinal manifestations for ADHF diagnosis are acute dyspnea on exertion and signs of fluid retention (pulmonary and/or splanchnic congestion and/or peripheral edema) according to ACCF/AHA Guideline for the Management of Heart Failure.[34]

3. Acute aortic diseases (AAD) in this study included 1. aortic dissection, 2. intramural hematoma of aorta, and 3. penetrating atherosclerotic ulcer of aorta. The clinical manifestations and the investigations for making diagnosis have been defined in the ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease.[35]

4. Peripheral vascular disease (PAD) was diagnosed with clinical and diagnostic methods according to the management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations) [36]

<u>Clinical for diagnosis of PAD</u>

1. A history of walking impairment, claudication, ischemic rest pain, and/or non-healing wounds

2. Signs and symptoms of acute or critical limb ischemia

Diagnostic methods for diagnosis of PAD

Ankle- and Toe-Brachial Indices (ABI); ABI results reported values defined as greater than 1.40, normal values 1.00 to 1.40, borderline 0.91 to 0.99, and abnormal 0.90 or less.

Among this group, 160 patients who had ADHF due to non-atherosclerotic causes (dilated cardiomyopathy, valvular insufficiency, and arrhythmias) and 453 patients whose data were incomplete were excluded. There were thus 1777 patients included in the final analyses (Figure 3).

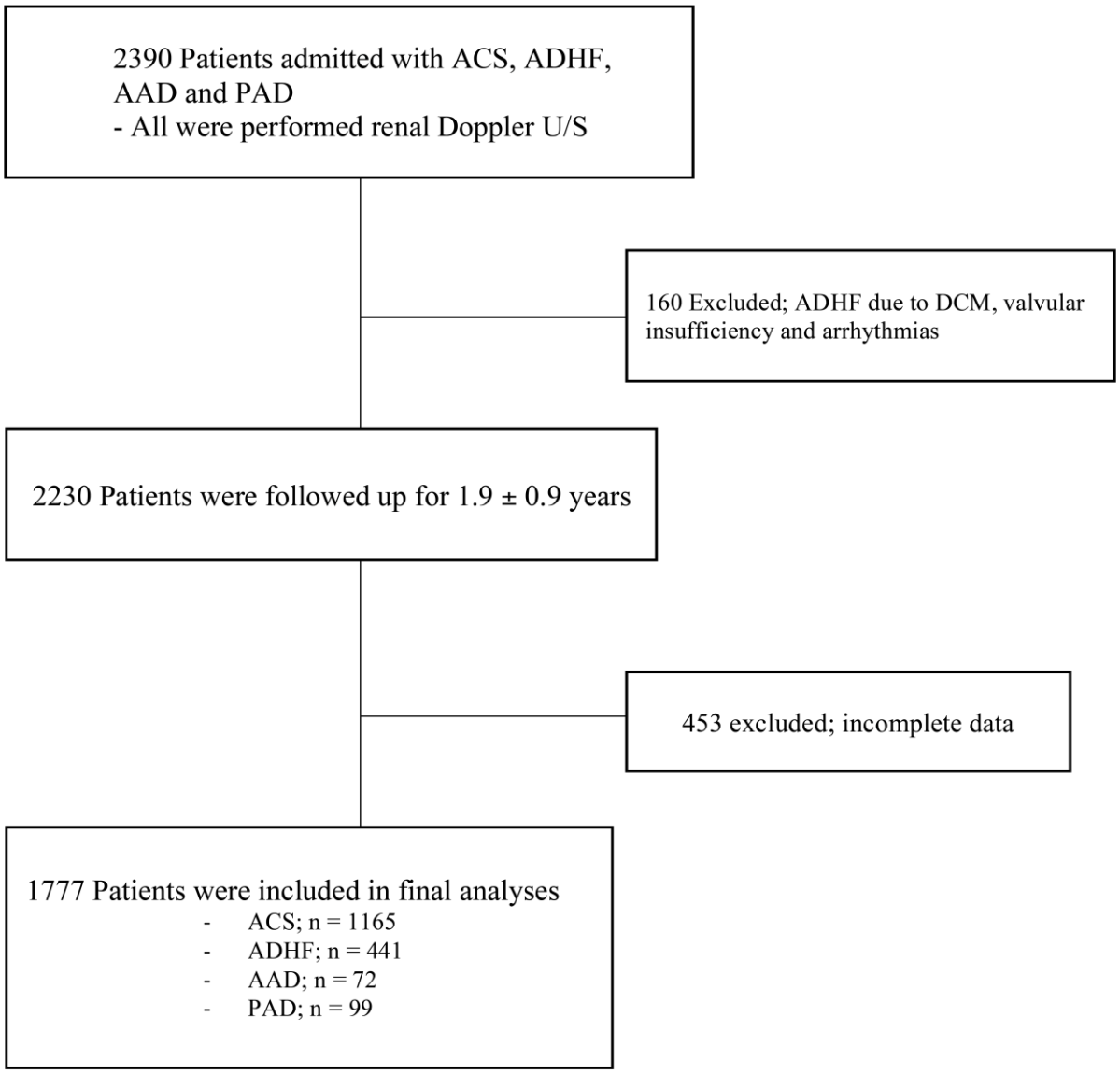

Figure 3 ***Flow of study patients*** A total of 2390 patients were hospitalized with the clinical diagnoses of acute coronary syndrome (ACS), acute decompensated heart failure (ADHF), acute aortic disease (AAD) or peripheral vascular disease (PAD). All patients underwent renal Doppler ultrasonography. We excluded 160 patients who had ADHF due to dilated cardiomyopathy, valvular insufficiency or arrhythmias and 453 patients whose data were incomplete. There were 1777 patients included in the final analyses.

3.3 Clinical characteristics

3.3.1 Blood pressure measurement

Systolic BP (SBP) and DBP were measured during the admission period and prior to discharge according to the standard-of-care time schedules, using an oscillometric BP device (H55D; Terumo, Tokyo) with an appropriate upper-arm cuff size for the individual arm circumference by an in-charge nurse. In this study, the BP readings taken just before the day of discharge with the patient in a sitting position were used for analyses.

3.3.2 Laboratory measurement

Blood samples were collected after overnight fasting and then assayed within 4 hours with an automatic clinical chemical analyzer at the hospital central laboratory. HbA1c was measured using the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160; Arkray, Kyoto, Japan). Serum levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL) and creatinine (Cr) were measured using enzymatic methods (Automated analyzer JCA-BM12; JEOL, Tokyo).

3.3.3 Renal Doppler ultrasonography

One experienced ultrasonographer who was blinded to the clinical data of the patients performed Doppler ultrasonographic examinations in all patients in the cohort. A Vivid S5 ultrasound machine (GE Healthcare, Chicago, IL) with a 2.5-MHz pulsed Doppler frequency and 3.5-MHz convex array transducer was used for the examinations. The patient was in a supine position during the examination. The transducer was placed on the lumbar region. The B-mode measurement was used to examine the contour and the size of the left and right kidneys. Intrarenal Doppler signals were obtained bilaterally from the three most manifest proximal segmental arteries. RRI was calculated using the following equation: (peak systolic velocity-end diastolic velocity)/peak systolic velocity. The average RRI of the left and right

kidneys was used for the statistical analyses. The cut-off point of RRI at 0.8 was based on previous evidence of the decreased event-free survival in selected cardiovascular patients.[10,11]

3.4 Follow up and cardiovascular outcomes

Patients were follow-up for 1.9±0.9 years (3365 person-years) with the standard-care hospital visits of 30-90 days intervals. The outcome of interest was the incidence of the first cardiovascular disease event from the time of discharge including;

(1) Fatal and non-fatal cardiovascular diseases included acute myocardial infarction, angina pectoris requiring percutaneous coronary intervention, acute decompensated heart failure, acute aortic diseases, acute arterial occlusion and sudden death within 24 hours of the abrupt onset of symptoms.

(2) Fatal and non-fatal stroke, defined as sudden onset of a neurological deficit persisting for ≥ 24 hours in the absence of any other disease that could account for the symptoms, with the findings of brain computed tomography or magnetic resonance imaging. Transient ischemic attack was not included.

(3) Sudden death without other specified causes other than cardiovascular cause

If events occurred on ≥ 2 occasions, the first occurrence was included in the analysis.

The attending physician, who was unaware of the renal ultrasonographic findings, determined the cardiovascular outcome. The cardiovascular outcome during the follow-up period was ascertained by cardiologists employed by Jichi Medical University Hospital and also by annual or more frequent reviewing of the patient's medical records. When patients failed to come to the hospital, we interviewed them and/or their families by telephone.

3.5 Statistical analysis

Baseline data on the patients' characteristics are shown as the mean ± SD or a percentage for continuous variables and categorical variables, respectively. The subjects were categorized into RRI ≥0.8 and <0.8 groups, and then each group was further subdivided according to the SBP quartiles. The chi-square test of independence was used to compare categorical variables among groups, and the analysis of variance was used to compare continuous variables. Cox proportional hazard analysis was used to examine the relationship between the primary composite endpoint and risk factors including SBP, DBP, age, sex and other conventional cardiovascular risk factors and presented as the unadjusted Hazard ratio (HR). Considering the clinical importance and using P <0.05 as a criterion, the parameters of age, sex, diabetes mellitus, hypertension, smoking, body mass index (BMI), Cr, LDL and HDL were included in the Cox regression models together with the SBP quartiles to examine the HR and 95% confidence interval (95%CI). Event-free survival analysis was done in both groups (RRI <0.8 and RRI ≥0.8), and the Kaplan-Meier curve of the cumulative incidence was plotted according to the SBP quartiles.

4. Results

4.1 Baseline characteristics

Table 1 shows the demographic data and clinical characteristics of the patients. The mean age was 64.7 ± 11.8 years, and 1348 (76%) of the patients were men. Mean BMI was 24.6 ± 4.0 kg/m^2. The admission diagnoses were ACS (65.6%), ADHF (24.8%), AAD (4.0%) and PAD (5.6%).

There were 296 and 1481 patients with RRI ≥0.8 and <0.8, respectively. Patients with RRI ≥0.8 were older and had higher prevalence of hypertension, diabetes mellitus, and chronic kidney disease (CKD); eGFR <60 mL/min/1.73 m^2, (all P <0.001). In addition, patients with

RRI ≥0.8 had higher Cr compared with the patients with RRI <0.8 (193.6±217.5 μmol/L vs. 90.2±91.1 μmol/L, *P* <0.001).

Tables 2 and 3 show the demographic data and clinical characteristics of the patients with RRI ≥0.8 and <0.8 subdivided by SBP quartiles. In both patients with RRI ≥0.8 and those with RRI <0.8, the lowest SBP quartile group had the lowest BMI and lowest prevalence of hypertension and diabetes mellitus, while the highest SBP quartile group had the highest Cr and highest prevalence of diabetes mellitus.

Table 1: Baseline characteristics by RRI categories

Measures	Total population (n=1777)	RRI group ≥ 0.8 (n=296)	RRI group < 0.8 (n=1481)	P-value
Age, years	64.7±11.8	73.5±10.4	66.1±11.7	<0.001
Men, n (%)	1348 (75.9)	197 (66.5)	1151 (77.7)	<0.001
BMI, kg/m^2	24.6±4.0	24.0±3.8	24.7±4.0	<0.005
Smoking, n (%)	522 (29.4)	63 (21.3)	459 (31.0)	0.001
Hypertension, n (%)	1326 (74.6)	245 (82.8)	1081 (73.0)	<0.001
Diabetes mellitus, n (%)	678 (38.2)	176 (59.4)	502 (33.9)	<0.001
Chronic kidney disease, n (%)	675 (38.0)	200 (67.6)	475 (32.1)	<0.001
ASCVD, n (%)				
- ACS	1165 (65.6)	135 (45.6)	1030 (69.5)	<0.001
- ADHF	441 (24.8)	123 (41.5)	318 (21.5)	<0.001
- AAD	72 (4.0)	4 (1.4)	68 (4.6)	0.008
- PAD	99 (5.6)	34 (11.5)	65 (4.4)	<0.001
HbA1c, %	6.2±1.2	6.4±1.2	6.2±1.2	0.018
LDL-cholesterol, mmol/L	2.65±0.91	2.48±0.81	2.69±0.92	<0.001
HDL-cholesterol, mmol/L	1.33±0.39	1.35±0.41	1.33±0.37	0.303
Creatinine, μmol/L	107.9±127.3	193.6±217.5	90.2±91.1	<0.001
Antiplatelet, n (%)	1346 (75.7)	218 (73.6)	1128 (76.2)	0.297
ACEI/ARB, n (%)	1150 (64.7)	191 (64.5)	959 (64.7)	0.947
CCB, n (%)	586 (33.0)	123 (41.5)	463 (31.3)	<0.001
B-blocker, n (%)	1152 (64.8)	179 (60.5)	973 (65.7)	0.083
Diuretics, n (%)	458 (25.8)	123 (41.5)	335 (22.6)	<0.001
Statin, n (%)	1129 (63.5)	156 (52.7)	973 (65.7)	<0.001
SBP, mmHg	130.2±23.1	134.2±25.9	129.4±22.4	0.001
DBP, mmHg	74.2±15.6	66.5±14.6	75.8±15.3	<0.001
Renal segmental artery PSV, cm/s	25.2±11.7	28.2±10.0	24.6±12.0	<0.001
Renal segmental artery EDV, cm/s	6.9±3.5	4.4±2.0	7.4±3.5	<0.001
RRI	0.72±0.08	0.84±0.05	0.69±0.06	<0.001
Primary endpoint*, n (%)	252 (14.2)	71 (24.0)	181 (12.2)	<0.001
Incidence rate per 1000-patient-years (95%CI)	74.7 (66.0-84.5)	132.6 (105.1-167.3)	63.7 (55.1-73.7)	N/A

Values indicate n (%) or mean±SD. RRI indicates renal resistive index; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AAD, acute aortic disease; PAD, peripheral vascular disease; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; B-blocker, beta-receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; PSV, peak systolic velocity; EDV, end diastolic velocity. *The primary endpoint included cardiovascular death and sudden death or the first subsequent non-fatal ACS, ADHF, AAD, acute arterial occlusion, and stroke during the follow-up period.

Table 2: Baseline characteristics by quartiles of SBP in the population with ≥0.8 of RRI

Measures	SBP quartiles				
	Q1 80-105 mmHg (n=69)	**Q2** 106-117 mmHg (n=69)	**Q3** 118-129 mmHg (n=66)	**Q4** 130-185 mmHg (n=92)	**P-value**
Age, years	73.6±9.9	74.8±10.4	74.1±9.1	72.2±11.5	0.431
Men, n (%)	43 (62.3)	48 (69.6)	42 (63.6)	64 (69.6)	0.691
BMI, kg/m^2	22.9±3.9	24.0±3.7	23.9±3.6	24.9±3.7	0.011
Smoking, n (%)	11 (15.9)	19 (27.5)	15 (22.7)	18 (19.6)	0.387
Hypertension, n (%)	53 (76.8)	60 (87.0)	53 (80.3)	79 (85.9)	0.325
Diabetes mellitus, n (%)	35 (50.7)	39 (56.5)	38 (57.6)	64 (69.6)	0.093
Chronic kidney disease, n (%)	45 (65.2)	45 (65.2)	42 (63.6)	59 (64.1)	0.235
ASCVD					
- ACS	28 (40.6)	36 (52.2)	25 (37.9)	46 (50.0)	0.242
- ADHF	36 (52.2)	29 (42.0)	26 (39.4)	32 (34.8)	0.168
- AAD	2 (2.9)	1 (1.4)	0 (0)	1 (1.1)	0.536
- PAD	3 (4.3)	3 (4.3)	15 (25.8)	13 (14.1)	0.001
HbA1c, %	6.3±1.4	6.4±1.2	6.4±1.2	6.4±1.2	0.960
LDL-cholesterol, mmol/L	2.47±0.91	2.39±0.02	2.55±0.64	2.47±0.85	0.730
HDL-cholesterol, mmol/L	1.27±0.44	1.35±0.43	1.39±0.41	1.39±0.42	0.316
Creatinine, μmol/L	197.2±196.3	160.9±176.0	179.5±216.6	224.6±258.2	0.302
Antiplatelet, n (%)	46 (66.7)	50 (72.4)	48 (72.7)	74 (80.4)	0.264
ACEI/ARB, n (%)	45 (65.2)	50 (72.4)	39 (59.1)	57 (62.0)	0.390
CCB, n (%)	10 (14.5)	30 (43.5)	30 (45.5)	53 (57.6)	<0.001
B-blocker, n (%)	47 (68.1)	42 (60.9)	43 (65.2)	47 (51.1)	0.129
Diuretics, n (%)	32 (46.4)	30 (43.5)	29 (43.9)	32 (34.8)	0.451
Statin, n (%)	31 (44.9)	40 (58.0)	34 (51.5)	51 (55.4)	0.434
SBP, mmHg	117.0±21.2	129.8±20.8	138.6±24.8	147.3±25.7	<0.001
DBP, mmHg	61.6±13.9	66.4±13.1	66.1±13.5	70.4±15.8	0.002
Renal resistive index	0.843±0.049	0.838±0.045	0.849±0.050	0.845±0.043	0.596
Primary endpoint*,	24 (34.7)	18 (26.1)	13 (19.7)	16 (17.4)	0.059
n (%)	214.3	146.3	101.6	92.5	N/A
Incidence rate per 1000-patient-years (95%CI)	(144.0-318.9)	(92.6-231.3)	(59.4-173.8)	(56.9-150.2)	

Values indicate n (%) or mean±SD. SBP indicates systolic blood pressure; RRI, renal resistive index; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AAD, acute aortic disease; PAD, peripheral vascular disease; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; B-blocker, beta-receptor blockers; DBP, diastolic blood pressure. *The primary endpoint included cardiovascular death and sudden death or the first subsequent non-fatal ACS, ADHF, AAD, acute arterial occlusion, and stroke during the follow-up period.

Table 3: Baseline characteristics by quartiles of SBP in the population with <0.8 of RRI

Measures	**SBP quartiles**				***P-value***
	Q1 60-105 mmHg (n=356)	**Q2** 106-117 mmHg (n=370)	**Q3** 118-129 mmHg (n=409)	**Q4** 130-180 mmHg (n=346)	
Age, years	66.9±12.1	65.3±12.3	66.1±10.9	66.3±11.6	0.306
Men, n (%)	262 (73.6)	300 (80.1)	317 (73.9)	272 (78.6)	0.108
BMI, kg/m^2	23.7±3.8	25.1±4.0	25.0±3.8	25.0±4.2	<0.001
Smoking, n (%)	106 (29.8)	115 (31.1)	131 (32.0)	107 (30.9)	0.937
Hypertension, n (%)	214 (60.1)	258 (69.7)	315 (77.0)	294 (84.9)	<0.001
Diabetes mellitus, n (%)	95 (26.7)	127 (34.3)	141 (34.5)	139 (40.2)	0.003
Chronic kidney disease, n (%)	114 (32.0)	106 (28.6)	132 (32.3)	123 (35.5)	0.275
ASCVD					
- ACS	228 (64.0)	252 (68.1)	306 (74.8)	244 (70.5)	0.012
- ADHF	98 (27.5)	87 (23.5)	65 (16.0)	66 (19.1)	0.001
- AAD	23 (6.5)	16 (4.3)	18 (4.4)	9 (2.6)	0.104
- PAD	6 (1.7)	14 (3.8)	19 (4.6)	24 (6.9)	0.007
HbA1c, %	6.1±1.1	6.2±1.1	6.1±1.2	6.4±1.4	0.003
LDL-cholesterol, mmol/L	2.66±0.92	2.70±1.04	2.69±0.80	2.70±0.93	0.912
HDL-cholesterol, mmol/L	1.34±0.39	1.31±0.40	1.34±0.36	1.32±0.34	0.717
Creatinine, μmol/L	90.2±87.5	86.7±80.5	83.1±69.8	103.5±122.0	0.018
Antiplatelet, n (%)	250 (70.2)	278 (75.1)	331 (80.9)	269 (77.7)	0.005
ACEI/ARB, n (%)	241 (67.7)	246 (66.5)	261 (63.8)	211 (61.0)	0.211
CCB, n (%)	60 (16.9)	98 (26.5)	149 (36.4)	156 (45.1)	<0.001
B-blocker, n (%)	249 (69.9)	247 (66.7)	270 (66.0)	207 (59.8)	0.030
Diuretics, n (%)	122 (34.3)	79 (22.2)	75 (18.3)	60 (17.3)	<0.001
Statin, n (%)	226 (63.5)	244 (68.5)	279 (68.2)	224 (64.7)	0.573
SBP, mmHg	117.6±20.5	127.0±20.3	132.7±21.3	140.4±21.6	<0.001
DBP, mmHg	70.8±15.4	75.6±14.6	76.7±15.0	80.0±15.0	<0.001
Renal resistive index	0.687±0.063	0.689±0.060	0.695±0.057	0.692±0.061	0.184
Primary endpoint*, n (%)	50 (13.7)	43 (12.1)	49 (12.0)	39 (11.3)	0.674
Incidence rate per 1000-patient-years (95%CI)	74.9 (56.8-98.7)	61.0 (45.3-82.2)	60.4 (45.7-79.9)	59.5 (43.5-81.3)	N/A

Values indicate n (%) or mean±SD. SBP indicates systolic blood pressure; RRI, renal resistive index; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AAD, acute aortic disease; PAD, peripheral vascular disease; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; B-blocker, beta-receptor blockers; DBP, diastolic blood pressure. **The primary endpoint included cardiovascular death and sudden death or the first subsequent non-fatal ACS, ADHF, AAD, acute arterial occlusion, and stroke during the follow-up period.

4.2 Cardiovascular outcomes

A total of 252 cardiovascular events occurred throughout the study period. Detailed outcomes are demonstrated in Table 4. Patients with RRI ≥0.8 had a higher incidence of primary composite endpoints compared with those with an RRI <0.8 (24.0% vs. 12.2%, *P* <0.001) (Table 1). When categorized by the SBP quartiles, patients who belonged to the lowest SBP quartile were found to have the highest incidence of primary composite endpoint in both patients with RRI ≥0.8 (34.7%) and <0.8 (13.7%) (Tables 2 and 3).

4.3 The impact of RRI and BP at discharge on the primary composite endpoint

In the total population, Cox regression models adjusted for age, sex, diabetes mellitus, hypertension, smoking, BMI, Cr, LDL and HDL were performed. RRI as a continuous variable (per 1-SD) was associated with the primary composite endpoint (HR, 1.15; 95%CI 1.01-1.33; P =0.045), as well as the SBP at discharge (per 1-SD; HR, 0.84; 95%CI 0.73-0.97; P =0.014).

The survival curves were constructed after dividing the patients into 2 groups, RRI ≥0.8 and <0.8, and then each group was stratified by the SBP quartiles. Figure 4 depicts the significantly lower event-free survival from the primary composite endpoint in the patients with RRI ≥0.8 who belonged to the lowest SBP quartile category compared with the highest quartile category. However, in the patients with RRI <0.8, the plot of the event-free survival showed no significant difference among SBP quartiles.

To examine the association between the lower SBP and the risk of the primary composite endpoint, Cox regression models adjusted for age, sex, diabetes mellitus, hypertension, smoking, BMI, Cr, LDL and HDL were generated using the highest SBP quartile as a reference. In the patients with RRI ≥0.8, the lowest SBP quartile was significantly associated with the risk of primary composite endpoint (HR, 2.42; 95%CI, 1.17-5.03; *P* =0.017) (Figure 5A), while this association was not observed in the patients with RRI

<0.8 (HR, 1.22; 95%CI 0.78-1.89, *P* =0.388) (Figure 5B). Regarding the DBP, the same Cox regression analysis was done using the highest DBP quartile as a reference, but no significant association was observed between the lowest DBP quartile and the primary composite endpoint in either patients with RRI ≥0.8 (HR, 1.11; 95%CI 0.53-2.31; *P* =0.788) or those with RRI <0.8 (HR, 1.12; 95%CI 0.71-1.77; *P* =0.615) (Figure 6).

Table 5 shows the association between conventional cardiovascular risk factors or SBP and DBP per 1 SD and primary composite endpoint using unadjusted Cox proportional-hazard model in the total population. Age, Cr and diabetes mellitus were the significant risk factors for the primary composite endpoint in the total population. There was also an inverse association between SBP and the risk for the primary composite endpoint (HR per 1 SD, 0.86; 95%CI 0.75-0.98; *P* =0.023), and this association was independent of age, sex, diabetes mellitus, hypertension, smoking, BMI, Cr, LDL, and HDL (adjusted HR per 1 SD, 0.84; 95%CI 0.73-0.97; *P* =0.016). An inverse association was observed between DBP and the risk for the primary composite endpoint (HR per 1 SD, 0.88; 95%CI 0.77-1.00; P =0.045), but it was not significant after adjusting for the conventional cardiovascular risk factors (HR per 1 SD, 0.97; 95%CI 0.84-1.11; P =0.655).

Table 5 also shows the association between conventional cardiovascular risk factors or SBP and DBP per 1 SD and the primary composite endpoint according to RRI levels. In the group with RRI ≥0.8, age was a significant risk factor for the primary composite endpoint (HR per 1 SD, 1.03; 95%CI 1.01-1.06; P =0.011). Moreover, consistent with the findings in the total population, there was a significant inverse association between SBP and the primary composite endpoint (HR per 1 SD, 0.75; 95%CI 0.59-0.95; *P* =0.013), and this association was still significant after adjusting by age, sex, diabetes mellitus, hypertension, smoking, BMI, Cr, LDL and HDL (adjusted HR per 1 SD, 0.73; 95%CI 0.57-0.94; *P* =0.015). In the group with RRI <0.8, age, Cr, and hypertension were the significant risk factors for the

primary composite endpoint, while SBP showed no significant association. There was no interaction between SBP and the primary composite endpoint according to the absence or presence of higher RRI (*P* for interaction =0.110).

As a sensitivity analysis, after we categorized the subjects into two groups based on their RRI values (RRI ≥0.75 and <0.75), we performed a Cox proportional hazard analysis for the association between SBP or DBP and the primary composite endpoint. Discharge SBP was significantly associated with the primary composite endpoint in the RRI ≥0.75 group (HR 0.83, 95%CI 0.69–0.99, p=0.045) but not in the RRI <0.75 group. (Table 6)

Table 4: Summary of the cardiovascular events

Causes	**Number of event** (n=252)	**Percent of event in total population** (n=1777)	**Percent of event in total events** (n=252)
Sudden death	**15**	**0.84**	**5.95**
Cardiovascular death	**77**	**4.33**	**30.55**
- ADHF	48	2.70	19.05
- ACS	8	0.45	3.17
- AAD	3	0.17	1.19
- Acute arterial occlusion	2	0.11	0.79
- Strokes	16	0.90	6.35
Non-fatal CV events	**160**	**9.00**	**63.49**
- ADHF	83	4.67	32.94
- ACS	52	2.93	20.63
- AAD	5	0.28	1.98
- Acute arterial occlusion	1	0.05	0.40
- Strokes	19	1.07	7.54

Abbreviation: ADHF, acute decompensated heart failure; ACS, acute coronary syndrome; AAD, acute aortic disease.

Table 5: Unadjusted Hazard ratio of the primary composite endpoint by using Cox's proportional hazards model

Covariates	**Total population** (n=1777)		**RRI ≥0.8** (n=296)		**RRI <0.8** (n=1481)	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Age, per 1 year	1.03 (1.02-1.05)	<0.001	1.03 (1.01-1.06)	0.011	1.03 (1.01-1.04)	<0.001
Sex, (Men=1, Women =0)	0.90 (0.68-1.19)	0.459	0.66 (0.41-1.06)	0.082	1.19 (0.82-1.71)	0.358
BMI, per 1 kg/m^2	0.96 (0.93-0.99)	0.011	0.97 (0.91-1.03)	0.325	0.96 (0.92-0.99)	0.038
Creatinine, per 1 mg/dL	1.14 (1.08-1.20)	<0.001	1.02 (0.94-1.11)	0.614	1.19 (1.10-1.28)	<0.001
Diabetes mellitus, (1=Yes, 0=No)	1.47 (1.15-1.88)	0.002	1.21 (0.75-1.96)	0.435	1.35 (1.00-1.82)	0.052
Hypertension, (1=Yes, 0=No)	1.36 (1.00-1.84)	0.050	0.79 (0.44-1.42)	0.450	1.46 (1.02-2.09)	0.035
Smoking, (1=Yes, 0=No)	0.77 (0.58-1.02)	0.061	0.89 (0.49-1.59)	0.685	0.79 (0.57-1.10)	0.158
LDL-cholesterol, per 1 mg/dL	1.00 (0.99-1.00)	0.989	1.00 (0.99-1.01)	0.746	1.00 (0.99-1.00)	0.656
HDL-cholesterol, per 1 mg/dL	0.99 (0.98-1.01)	0.168	1.00 (0.99-1.02)	0.949	0.99 (0.98-1.00)	0.071
dSBP, per 1 SD	0.86 (0.75-0.98)	0.023	0.75 (0.59-0.95)	0.013	0.89 (0.76-1.05)	0.166
dDBP, per 1 SD	0.88 (0.77-1.00)	0.045	0.85 (0.66-1.09)	0.204	0.98 (0.84-1.14)	0.810

One SD increment of each BP measure was as follows: dSBP, per 17.5 mmHg; dDBP, per 11.9 mmHg. HR indicates the hazard ratio; RRI, renal resistive index; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; dSBP, systolic blood pressure at discharge; dDBP, diastolic blood pressure at discharge.

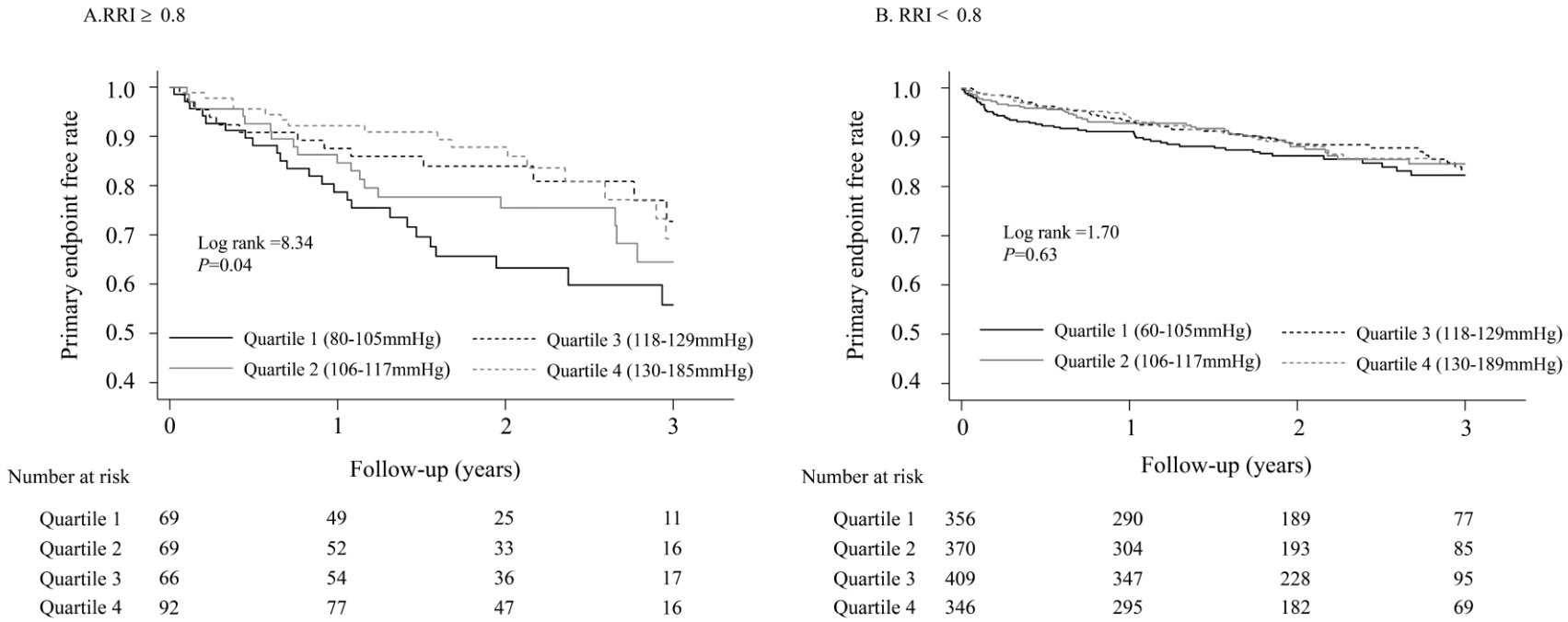

Figure 4 ***Kaplan-Meier curves*** depict the lower event-free survival from the primary composite endpoint in the group of patients with RRI ≥0.8 who belonged to the lowest SBP quartile category compared with the highest quartile category (A). However, in the group of patients with RRI <0.8, the plots of the event-free survival were similar among the SBP quartiles (B).

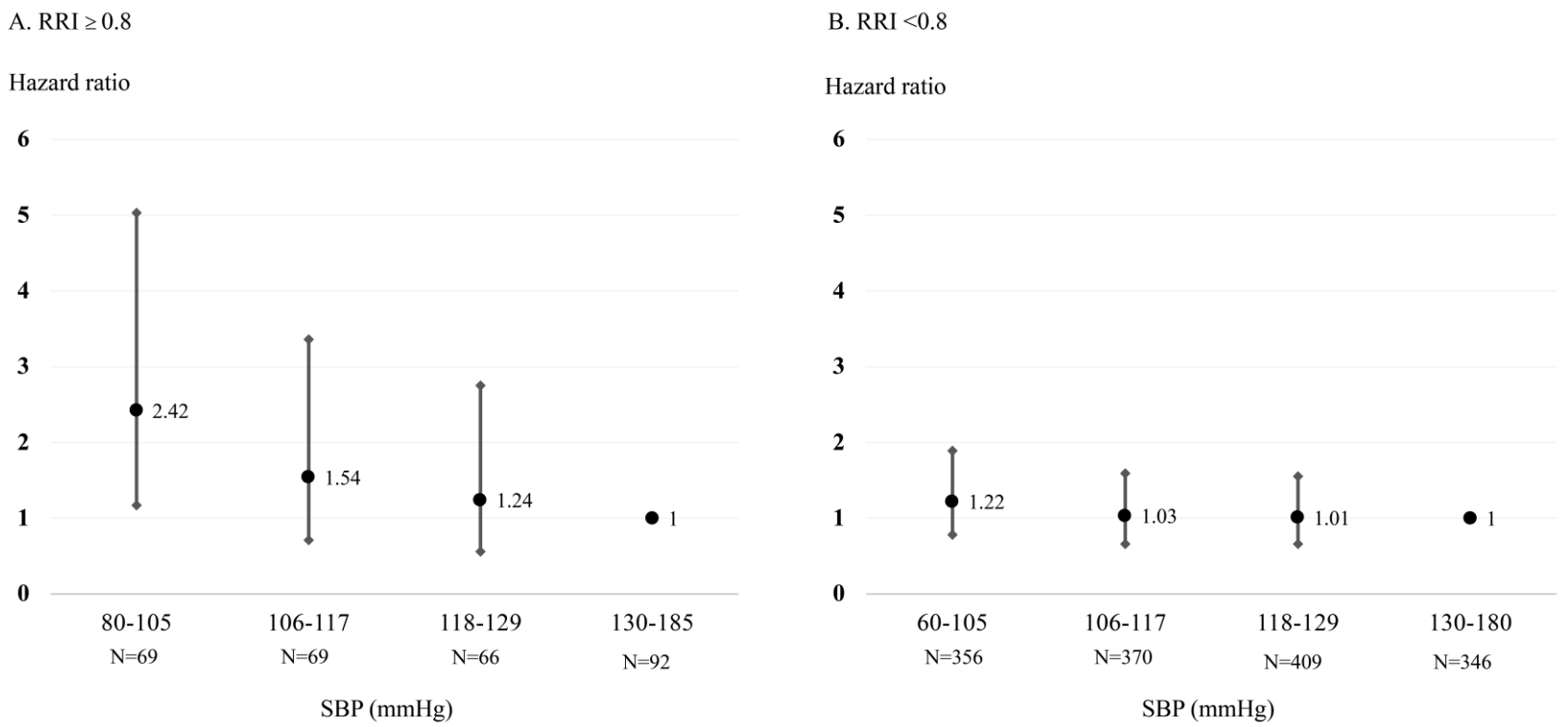

Figure 5 ***Systolic blood pressure (SBP) and primary endpoint*** Hazard ratio (95%CI) adjusted for age, sex, diabetes mellitus, hypertension, smoking, body mass index, Cr, LDL and HDL of the primary composite endpoint in patients with RRI ≥0.8 (A) and RRI <0.8 (B). In the patients with RRI ≥0.8, membership in the lowest SBP quartile was significantly associated with a risk of primary composite endpoint (HR, 2.42; 95%CI, 1.17-5.03; P =0.017), while this association was not observed in the patients with RRI <0.8 (HR, 1.22; 95%CI 0.78-1.89, P =0.388)

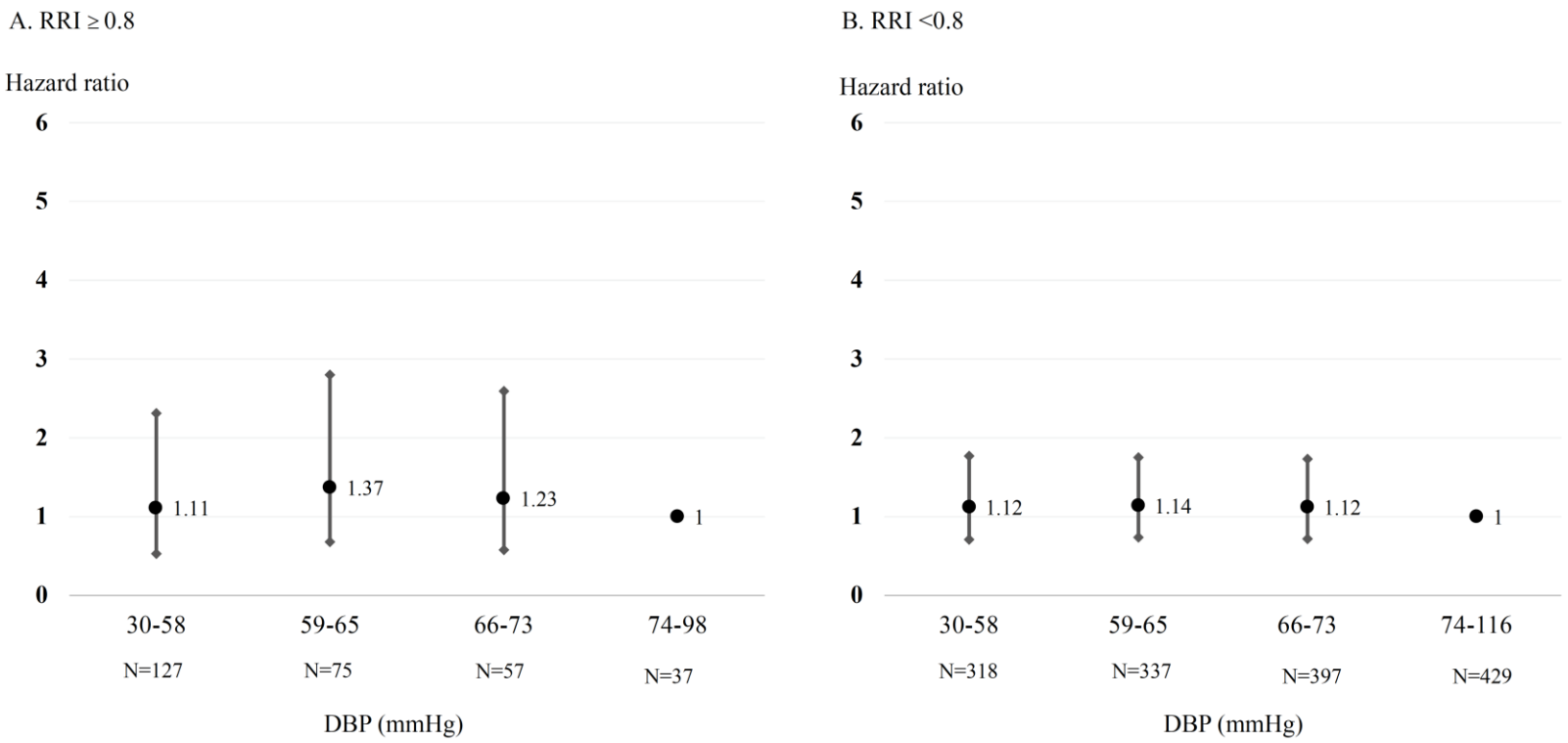

Figure 6 ***Diastolic blood pressure (DBP) and primary endpoint*** Hazard ratio (95%CI) adjusted for age, sex, diabetes mellitus, hypertension, smoking, body mass index, Cr, LDL and HDL showed no significant association between blood pressure quartiles and a risk of primary composite endpoint in both patients with RRI ≥0.8 (A) and RRI <0.8 (B)

Table 6: Unadjusted Hazard ratio of the primary composite endpoint by using Cox's proportional hazards model

Covariates	**RRI ≥0.75** (n=590)		**RRI <0.75** (n=1187)	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Age, per 1 year	1.03 (1.02-1.05)	<0.001	1.03 (1.01-1.04)	0.002
Sex, (Men=1,Women =0)	0.78 (0.53-1.15)	0.214	1.19 (0.77-1.83)	0.433
BMI, per 1 kg/m^2	0.97 (0.92-1.02)	0.237	0.95 (0.91-0.99)	0.042
Creatinine, per 1 mg/dL	1.10 (1.03-1.17)	0.004	1.32 (1.01-1.28)	0.043
Diabetes mellitus, (1=Yes, 0=No)	1.53 (1.06-2.23)	0.024	1.19 (0.84-1.69)	0.344
Hypertension, (1=Yes, 0=No)	1.59 (0.95-2.65)	0.064	1.14 (0.77-1.68)	0.500
Smoking, (1=Yes, 0=No)	0.66 (0.42-1.06)	0.083	0.91 (0.63-1.31)	0.595
LDL-cholesterol, per 1 mg/dL	1.00 (1.00-1.01)	0.213	1.00 (1.00-1.01)	0.870
HDL-cholesterol, per 1 mg/dL	1.00 (0.99-1.01)	0.773	0.99 (0.98-1.00)	0.081
dSBP, per 1 SD	0.83 (0.69-0.99)	0.045	0.86 (0.72-1.04)	0.117
dDBP, per 1 SD	0.93 (0.78-1.11)	0.437	0.93 (0.76-1.14)	0.470

One SD increment of each BP measure was as follows: dSBP, per 17.5 mmHg; dDBP, per 11.9 mmHg. HR indicates the hazard ratio; RRI, renal resistive index; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; dSBP, systolic blood pressure at discharge; dDBP, diastolic blood pressure at discharge.

5. Discussion

The present study examined the association between the blood pressure at discharge and future cardiovascular event in hospitalized atherosclerotic-cardiovascular patients. An inverse linear association between SBP and the risk of future cardiovascular event was observed. When patients were further stratified by the level of RRI, the lowest SBP quartile had a significant impact on future cardiovascular event compared with the highest SBP quartile in the subgroup with RRI ≥0.8, while this association was not observed in the subgroup with RRI <0.8.

According to a previously published meta-analysis of 123 randomized controlled trial (RCT)[37] and the landmark RCT, SPRINT[2], intensive SBP control was associated with less mortality and fewer cardiovascular events compared with standard SBP control. Accordingly, the BP target was set lower in the latest hypertension guidelines than in the previous ones.[1] However, the sub-analysis of the SPRINT trial revealed the J-shaped curve phenomenon of DBP. The risk of cardiovascular events was significantly increased when DBP fell below 55 mmHg.[3] This result reveals the downside of over-reduction of blood pressure based on the data from a large RCT.

Sub-analyses of anti-hypertensive trials have demonstrated that low therapeutic BP levels are disadvantageous in terms of cardiovascular event risk. In a further analysis of the data of 25,588 patients with high-cardiovascular risk from the ONTARGET study, a relationship was found between the lowest quartile of SBP and total mortality and fatal or non-fatal cardiovascular events, with a nadir of 130 mmHg.[38] Other researchers explored the data from the PROVE IT-TIMI 22 study, which enrolled hospitalized ACS patients. They found a relationship between low therapeutic BP and cardiovascular event and concluded that a combined SBP/DBP level of less than 110/70 mmHg was associated with an increased risk of worsening cardiovascular outcome.[6] A large cohort study in patients with stable coronary

artery disease also reported an increased risk of cardiovascular event in patients with SBP below 120 mmHg (HR, 1.56; 95%CI 1.36-1.81) and DBP below 60 mmHg (HR, 1.41; 95%CI 1.24-1.61).[39] The results of the present study substantiate the previous findings on the risk of low SBP for future cardiovascular events in high-risk cardiovascular patients. That is, we observed a significant inverse association between SBP and the primary composite endpoint in the hospitalized atherosclerotic-cardiovascular patients, independent of other conventional cardiovascular risk factors.

Clinical characteristics or cardiovascular risk profiles are the main considerations when determining the optimal therapeutic BP for each patient. The renal resistive index (RRI) measured at the renal segmental interlobar arteries can be obtained quickly and non-invasively.[7,8] This method has been shown to provide stronger prognostic power for the renal and cardiovascular outcomes than the conventional biomarkers of kidney function.[9,10,11] Prior histological studies reported associations between RRI and both atherosclerotic renal pathology and tubulo-interstitial damage.[40,41] RRI was also found to correlate well with systemic hemodynamic parameters such as pulse pressure and pulse wave velocity, which represent arterial stiffness.[12,13] The present study showed an inverse linear association between the SBP at discharge and future cardiovascular event in the subgroup of patients with RRI $\geq$0.8, but not in those with RRI <0.8. These results support the role of RRI as a parameter for the stratification of atherosclerotic-cardiovascular patients and reflect that it might be used as a tool for guiding the choice of optimal BP threshold. Namely, in patients with RRI $\geq$0.8, the lowest SBP quartile (<105 mmHg) exhibited a significant association with the risk for the primary composite endpoint even after adjusting for conventional cardiovascular risk factors.

It is not widely understood why lower BP is more harmful in some cardiovascular patients than others. The progression of arterial stiffness is believed to be associated with a

greater risk of the J-shaped curve phenomenon due to the widening of pulse pressure that accounted for the late systolic-phase retrograde aortic wave instead of the diastolic phase and eventually decreased coronary blood flow.[4] Our study confirms this association, since the impact of low SBP was observed only in the group with higher RRI, which represented the progressive arterial stiffness, while in the group with lower RRI, no impact of SBP on future cardiovascular events was observed. Moreover, the SBP levels in the lowest quartile were relatively low (<105 mmHg). Very low blood pressure was reported to be associated not only with brain damage and cognitive impairment[42] but also with complications such as syncope and falling that also lead to poorer outcomes.[43] In addition, the results of the SPRINT study raised the concern that intensive BP control leads to worsening kidney function, which may worsen the prognosis of cardiovascular outcome during a long-term follow up.[2] Our study found that patients with higher RRI had significantly higher serum creatinine and may also have had worse long-term outcomes, especially when the BP was kept too low. Although a clear risk of cardiovascular events was observed in the patients with high RRI values who belonged to the lowest SBP quartile, we were unable to eliminate the impact of the dissimilarity of disease distribution between the two RRI groups on the risk of cardiovascular events. The higher-RRI group was more likely to have ADHF than the lower-RRI group, and there was evidence that low blood pressure in ADHF patients is associated with poorer cardiovascular outcomes.[44,45] Therefore, the disease status (i.e., ADHF) *per se* might influence the inverse association between SBP and the risk of cardiovascular events in patients with a high RRI.

Although several previous studies reported that low SBP conferred a risk of cardiovascular events, some of them were limited by a selection bias caused by the selected group of studied patients—e.g., elderly patients or patients with diabetes mellitus or CKD.[46, 47, 48] Therefore, their results may have been impacted by reverse causality. The present study

differs from the prior studies in several respects. First, the population in this study consisted of hospitalized atherosclerotic-cardiovascular patients who were relatively vulnerable to extreme changes of BP. In order to avoid reverse causality, we studied the BP obtained before discharge, which represented the treated BP in patients considered safe for discharge from the viewpoint of their physicians. The BP prior to discharge was more clinically relevant for assessing the risk of over-reduction and the J-shaped curve issue after receiving the treatment, while the initial BP merely reflected the severity of the disease. Second, in contrast to the sub-analysis of the SPRINT trial, which found the J-shaped curve phenomenon only in DBP,[3] we did not observe a relationship between future cardiovascular event and lower DBP (data presented in the online-supplemental material). The mean DBPs of the lowest quartile were 50.3 ± 6.3 mmHg and 52.3 ± 4.5 mmHg in the groups of patients with RRI ≥0.8 and <0.8, respectively, which were lower than the DBPs of patients at risk for cardiovascular event described in the sub-analysis of SPRINT (<55 mmHg). However, an inverse linear association was observed between DBP per 1 SD and the primary composite endpoint in the total population.

The strengths of the present study include its enrollment of a large number of hospitalized atherosclerotic-cardiovascular patients. In addition, because the results were derived from patients with ACS, ADHF, AAD and PAD, they are useful for generalization. Finally, the renal Doppler ultrasonography and BP measurement were carefully done during admission in all patients so as to limit the possible environmental confounders.

However, the present findings should be interpreted in the context of a number of potential limitations. First, the renal Doppler ultrasonography was not performed immediately upon admission; therefore, some patients may have been exposed to a treatment that could have confounded the ultrasonographic study results. Second, the BP data were derived from a clinic BP measurement, which was inevitably affected by the white-coat

effect in some patients; moreover, the BP readings used in the analyses were obtained from a single time point without any follow-up BP data, and thus they cannot be taken as definitive evidence of a causal relationship. Moreover, there were a much higher number of men than women in this study (76% vs. 24%), which might have led to a sex bias, although this has been adjusted as one of the covariates. Finally, since this was a study in Japanese patients, among whom both the biological and cultural background tends to differ from those of other populations, care should be taken when extrapolating these results.

6. Conclusion

The SBP target should be individualized in each hospitalized atherosclerotic-cardiovascular patient according to his or her clinical characteristics. From the results of the present study, the patients with RRI ≥0.8 had a significant risk for developing future cardiovascular event when the SBP before discharge was under 105 mmHg. RRI measurement is feasible, harmless and inexpensive. Therefore, it may be a useful tool for stratifying atherosclerotic-cardiovascular patients and guiding the choice of optimal BP threshold.

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