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Impact of multivessel versus single-vessel disease on the association between low diastolic blood pressure and mortality after acute myocardial infarction with revascularization

Min Kim et al., Prognosis of low average on-treatment DBP in multivessel AMI

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Abstract

Background: Previous studies demonstrated a J-shaped relationship between low diastolic blood pressure (DBP) and adverse clinical outcomes in patients with acute myocardial infarction (AMI) that was sensitive to revascularization. Hypothesized herein, was that this relationship differs between patients with multivessel disease (MVD) and those with single-vessel disease due to differing degrees of myocardial ischemic burden.

Methods: Among 9,983 AMI patients from the Korea Acute Myocardial Infarction Registry

database who underwent percutaneous coronary intervention and were followed up for a median duration of 3.2 years, average on-treatment DBP was calculated at admission, discharge, and every scheduled visit and divided into these parameters: < 70 mmHg, 70–74 mmHg, 75–79 mmHg, and ≥ 80 mmHg. The relationship between average on-treatment DBP and clinical outcomes including all-cause death, cardiovascular (CV) death, non-CV death, and hospitalization for heart failure was analyzed using the Cox regression models adjusted for clinical covariates.

Results: In patients with MVD, all-cause death (hazard ratio [HR]: 1.47; 95% confidence interval [CI]: 1.06–2.04, p = 0.012) and CV death (HR: 1.59; 95% CI: 1.02–2.46, p = 0.027) were significantly increased in patients with a DBP < 70 mmHg, showing a J-shaped relationship. However, these findings were not significant for single-vessel disease. On a sensitivity analysis excluding subjects with a baseline SBP < 120 mmHg, an increased risk of a low DBP < 70 mmHg remained in MVD.

Conclusions: The J-shaped relationship between low DBP and adverse clinical outcomes in AMI patients who underwent revascularization persisted in MVD, which has a high ischemic burden. These high-risk patients require cautious treatment.

Key words: acute myocardial infarction, all-cause death, cardiovascular death, diastolic blood pressure, multivessel disease, revascularization

Introduction

Although the beneficial effect of lowering blood pressure (BP) on cardiovascular (CV) morbidity and mortality is undeniable [1–3], aggressive lowering of diastolic BP (DBP) can lead to an increase in adverse events, especially in patients with CV risk; the so-called J-shaped relationship. The J-shape theory, which emerged over the past four decades, suggests a non-linear relationship between DBP and CV events based on many observational analyses [4–16]. This background can be explained by coronary blood flow perfusion occurring mainly during cardiac diastole. Therefore, intensive lowering of DBP may reduce cardiac perfusion by decreasing coronary perfusion and aggravate myocardial ischemia. In patients with acute coronary syndrome who have more complicated obstructive coronary artery disease (CAD), a J-shaped relationship between DBP and clinical outcomes was reported [17], but it was abolished with reperfusion therapy [18]. However, many patients with acute myocardial infarction (AMI) have multivessel disease (MVD), which adversely affects

clinical outcomes and has a high ischemic burden [19–21]; thus, the existence of such an abolished J-shaped relationship depending on the number of stenotic vessels is unclear.

Therefore, the present study investigated the J-shaped relationship between average on-treatment DBP and clinical outcomes including all-cause death and CV death in AMI patients who underwent revascularization according to the number of stenotic vessels during long-term follow-up using data from a large multicenter AMI registry. Also under investigation was the same relationship using average on-treatment SBP. The aim was to explore the impact of the number of stenotic vessels on the association between DBP and clinical outcomes in patients with AMI who underwent percutaneous coronary intervention (PCI) with the fact that MVD has a higher ischemic burden than single-vessel disease (SVD) [21].

Methods

Data were collected from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) database, a prospective open observational online registry of a nationwide multicenter cohort that evaluated the prognosis and surveillance index of post-AMI patients from 20 tertiary university hospitals capable of PCI. Patients were consecutively enrolled between November 2011 and October 2015. The detailed study protocol was published elsewhere [22]. Initially, AMI was defined as type 1 myocardial infarction (MI) based on the criteria of the Third Universal Definition of Myocardial Infarction. Consequently, the current study confirmed that this definition of type 1 MI is consistent with the criteria of the Fourth Universal Definition of Myocardial Infarction without patient dropout [24]. MVD was defined as ≥ 70% stenosis of two or more major coronary arteries with a diameter ≥ 2.5 mm or a fractional flow reserve ≤ 0.8 with visual stenosis of ≥ 50% in at least one major non-infarct-related artery [25]. The KAMIR-NIH protocol was approved by the institutional review board and ethical committee of each participating center and written informed consent was provided by all participants upon enrollment.

Study population

Among the 13,104 patients enrolled in the KAMIR-NIH registry, those meeting the following criteria were excluded (n = 3,121): 1) in-hospital death, stent thrombosis, and cerebrovascular events (n = 670); 2) having undergone permanent pacemaker implantation (n = 14); 3) having undergone coronary artery bypass graft (n = 258) or not undergone PCI (n = 1,008); and 4) lack of available follow-up BP data since hospital discharge (n = 1,171).

Finally, 9,983 patients were included with AMI who underwent PCI and for whom follow-up BP data were available. Patients were divided into subgroups according to number of stenotic vessels: MVD (n = 4,545) and SVD (n = 5,438) (Fig. 1).

BP measurements

Hemodynamic measurements were obtained at each institution where the patient was hospitalized and attended an outpatient clinic. These institutions were certified as medical health examination centers by the Korean National Health Insurance Corporation. Brachial BP was measured by qualified medical personnel at each institution following at least 5 min of rest with the patient in the sitting position. An automatic, semiautomatic, or manual mercury sphygmomanometer was used for BP measurements. The preferred recommendations specified the use of manual mercury sphygmomanometers until 2015, when the sale of mercury sphygmomanometers was banned. BP was measured at admission, discharge, and on every outpatient clinic visit. The mean number of follow-up BP measurements for each patient was 3.9 ± 0.7. Average on-treatment DBP and SBP were calculated and divided into subgroups in 5-mmHg increments for DBP (< 70 mmHg, 70–74 mmHg, 75–79 mmHg, and ≥ 80 mmHg) and 10-mmHg increments for SBP (< 110 mmHg, 110–119 mmHg, 120–129 mmHg, and ≥ 130 mmHg).

Clinical outcomes and follow-up protocol

The relevant medical records of all clinical events were reviewed and adjudicated by an external clinical event adjudication committee using a web-based case report form on the Internet-based Clinical Research and Trial Management System (iCReaT), a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT study no. C110016). The primary clinical outcome was all-cause mortality. The secondary clinical outcomes were cardiovascular death, non-cardiovascular death, and hospitalization for heart failure (HF). Clinical outcomes were monitored by the Standardized Data Collection for Cardiovascular Trials Initiative [26]. After discharge, regular follow-up was performed at an outpatient clinic at 6, 12, 24, and 36 months based on patient availability. Follow-up data were collected from the patients by the attending physicians. If patients did not visit the hospital, outcome data were assessed via telephone interviews.

Statistical analysis

The patients' baseline characteristics were compared using descriptive statistics and are presented as median (interquartile range) for continuous variables and number

(percentage) for categorical variables. To compare the clinical outcomes, the Cox regression analysis we used based on average on-treatment DBP and SBP as categorical variables, which were also adjusted for age, sex, body mass index, history of smoking, hospital stay, symptom-to-door time, the Killip classification, previous history of HF, MI, ischemic stroke, intracerebral hemorrhage, hypertension, diabetes mellitus, dyslipidemia, MI type, left ventricular (LV) systolic impairment, the location of infarction (anterior vs. non-anterior), newly developed atrial fibrillation (AF), peak cardiac troponin level, and discharge medications including antiplatelet agents, beta-blockers, renin–angiotensin–aldosterone system blockers, statins, and calcium-channel blockers. The proportional hazards assumption was tested based on Schoenfeld residuals [27]. Restricted cubic spline functions presented with a hazard ratio (HR) curve and an area of 95% confidence interval (CI) based on average on-treatment DBP and SBP as continuous variables. In the sensitivity analyses, we additionally censored patients with a baseline SBP < 120 mmHg to avoid unmeasured confounding factors affecting BP level. We also analyzed the same model using baseline BP levels. Two-sided p values < 0.05 were considered statistically significant. The statistical analyses were performed using R (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the total population and by subgroups of average on-treatment DBP and SBP are reported in Tables 1 and **Suppl. Table S1**, respectively. The median age was 63 (54–73) years, 75.8% were male, and the median hospital stay duration was 5 (4–7) days in the total population. All patients were prescribed antiplatelet agents, and 87.5%, 83.4%, and 95.5% were taking beta-blockers, renin–angiotensin–aldosterone system blockers, and statins, respectively, at hospital discharge. Among the study population, 25.3% (n = 2,531), 19.4% (n = 1,938), 21.1% (n = 2,111), and 34.2% (n = 3,403) had an average on-treatment DBP < 70, 70–74, 75–79, and ≥ 80 mmHg, respectively. Patients with a low DBP were older; more likely to be female, have a low body mass index, have elevated peak cardiac enzyme levels, be never smokers, have a high Killip classification, have a high GRACE risk score, have ST-segment elevated MI, have a previous history of MI, have a previous history of ischemic stroke, have diabetes, have chronic kidney disease, have newly developed AF, and have LV systolic impairment; and were less likely to have anterior wall infarction and a previous history of hypertension than those with a higher DBP. They also had lower

prescription rates of beta-blockers, renin–angiotensin–aldosterone system blockers, and calcium-channel blockers than those with a higher DBP.

BP and clinical outcomes in MVD and SVD

Figure 2 depicts the spline curves based on average on-treatment DBP and SBP for patients with MVD and SVD, which showed a J-shaped relationship with the risk of all-cause death or hospitalization for HF. Patients with MVD and a low DBP showed a pronounced increased risk of all-cause death or hospitalization for HF compared to those with SVD and a low DBP. However, patients with a low SBP showed a similar increased risk for all-cause death or hospitalization for HF regardless of MVD or SVD.

Over a median follow-up duration of 3.2 years, 697 deaths were observed that were classified into 413 CV deaths and 284 non-CV deaths. The number of events and adjusted HR of clinical outcomes are shown in Figure 3. In MVD, after multivariable adjustment for clinical variables as described in the material and methods section, patients with a low DBP (< 70 mmHg) had a 53% increase in all-cause death (HR: 1.53; 95% CI: 1.10–2.14, p = 0.012) and a 65% increase in CV death (HR: 1.65; 95% CI: 1.06–2.56, p = 0.027) compared to patients with an average DBP (75–79 mmHg). Increased risks of all-cause death and CV death were also observed in patients with a DBP ≥ 80 mmHg (HR: 1.39; 95% CI: 0.99–1.96, p = 0.061; and HR: 1.36; 95% CI: 0.86–2.17, p = 0.191), but these differences were not statistically significant. The risk of non-CV death and hospitalization for HF did not increase in patients with a low DBP (< 70 mmHg) (HR: 1.41; 95% CI: 0.85–2.32, p = 0.184; and HR: 1.37; 95% CI: 0.82–2.28, p = 0.225) compared to patients with a DBP 75–79 mmHg. In patients with SVD, a low DBP (< 70 mmHg) was not associated with an increased risk of all-cause death (HR: 1.14; 95% CI: 0.81–1.61, p = 0.457), CV death (HR: 1.25; 95% CI: 0.81–1.96, p = 0.312), non-CV death (HR: 0.98; 95% CI: 0.59–1.63, p = 0.931), or hospitalization for HF (HR: 0.90; 95% CI: 0.59–1.35, p = 0.613), respectively.

Based on the average on-treatment SBP, although an increased risk of all-cause death and CV death was observed in patients with an SBP < 110 mmHg regardless of MVD or SVD, only the rate of CV death was significantly higher among those with MVD (HR: 1.81; 95% CI: 1.15–2.79, p = 0.007) versus patients with an SBP of 120–129 mmHg (**Suppl. Fig. 1**).

Sensitivity analysis

The data was analyzed after excluding patients with a baseline SBP < 120 mmHg. The risks of all-cause death and CV death (HR: 1.67; 95% CI: 1.15–2.44, p = 0.008; and HR: 1.78; 95% CI: 1.02–2.89, p = 0.041) was unchanged and significantly increased in patients

with a low DBP (< 70 mmHg) compared to those of patients with a DBP of 75–79 mmHg and MVD. Patients with a low DBP (< 70 mmHg) and SVD were not at an increased risk of clinical outcomes as in the primary analysis (Fig. 4).

The spline curves based on baseline DBP and SBP at hospital admission were analyzed to address non-detected background morbidities affecting BP levels, and the results showed no J-shaped relationship with all-cause death or hospitalization for HF (**Suppl. Fig. 2**).

Effect of multivessel revascularization strategies

Procedural profiles were analyzed based on revascularization strategies in MVD (**Suppl. Table 2**). Of patients in MVD PCI, 1,235 (27.1%) patients underwent complete revascularization. Of these, 62% did non-IRA PCI immediately after culprit lesion PCI during the index procedure. According to revascularization strategies, the location of the culprit lesion, pre-PCI thrombolysis in myocardial infarction flow, and the number of diseased vessels were significantly different.

The effect of complete revascularization on clinical outcomes was also evaluated in patients with MVD. Whether or not complete revascularization was performed did not show a statistically significant effect on the risk of all-cause death, cardiovascular death, non-CV death, and hospitalization for HF (**Suppl. Fig. 3**).

Discussion

In this nationwide cohort study, it was demonstrated that a low average on-treatment DBP was associated with higher risks of all-cause death and CV death among patients with MVD compared to those with SVD, especially a DBP lower than 70 mmHg, among AMI patients who underwent PCI. An average on-treatment SBP of < 110 mmHg was associated with a higher risk of CV death in patients with MVD. Furthermore, these results are based on a J-shaped relationship, which was not observed based on baseline DBP and SBP. These findings suggest that the adverse effect of a low BP in patients with AMI who underwent revascularization through PCI is affected by the number of stenotic vessels with or without complete revascularization and associated with increased risks of all-cause death and CV death in patients with MVD, which has a high ischemic burden on the myocardium compared with SVD. These relationships were more emphasized by DBP, which is associated with coronary perfusion distal to the vessels.

Several studies have investigated the effects of low BP management on CV outcomes in CAD, and increasingly poor outcomes with a low BP have been reported with the presence of a J-shaped curve [4, 9, 14, 16–18]. Among the 54% of patients who underwent angioplasty

among 10,001 patients with clinically evident CAD [16], a J-shaped relationship between BP management and CV events was demonstrated with an exponentially increased risk in patients with a low BP (< 110–120/< 60–70 mmHg). The same investigators [17] showed similar results in 4,162 ACS patients who underwent PCI. Among them, 26.7% showed a plateau curve for BP at 110–130/70–90 mmHg. Böhm et al. [18] recently reported that the more frequent adverse outcomes associated with a low DBP (< 70 mmHg) were restricted to AMI patients with signs and symptoms of HF or to those with a low LV ejection fraction (< 40%) who did not undergo revascularization. In terms of SBP, there was an increase in the incidence of clinical outcomes at a low SBP (< 130 mmHg) irrespective of revascularization. Patients who underwent revascularization seemed to be at an increased risk of clinical outcomes at a low DBP, potentially due to improved coronary perfusion.

In the present study, an abolished J-shaped relationship between a low DBP and all-cause death and CV death in SVD was observed, concordant with a previous study and demonstrated that the association between low DBP and all-cause death and CV death appears pronounced in MVD with a J-shaped relationship despite revascularization. The effect of complete revascularization was also evaluated, which was expected to be superior to incomplete revascularization in preventing a major adverse cardiac event [25]. However, the present study showed no differences in clinical outcomes between revascularization strategies in MVD. The results herein, suggest that the association between a low DBP and clinical outcomes was not affected by reperfusion in patients with MVD due to the high ischemic burden compared to SVD. However, the association between a low SBP and poor outcomes was not affected by the number of stenotic vessels in the current study. These results are concordant with those of a prior study showing that reperfusion did not impact outcomes at a low SBP. Specific high-risk patients who required management with special attention to the low DBP during follow-up despite revascularization were found.

Myocardial blood flow depends on myocardial perfusion pressure during diastole [28]. Moreover, a low DBP is associated with increased arterial stiffness, which impairs the reservoir function of the aorta. This mechanism might be more pronounced in patients with complicated obstructive CAD, particularly those with MVD. This suggestion is reinforced by a previous study that showed a wide pulse pressure in patients with a low DBP, and more than 60% of patients with MVD had worse long-term mortality rates [29].

Although a low SBP appeared to increase adverse outcomes in both MVD and SVD, only an increased CV death rate was associated with MVD in the present study. A low SBP suggests more severe myocardial damage and could affect under-treatment. In an analysis of

MI patients over 75 years of age, a low SBP within the first 48 hours of hospitalization was associated with increased incidence of all-cause death and CV death [30]. However, the fact that the current study population consisted of 53% of patients under 65 years of age should be considered, also the average on-treatment SBP were analyzed.

To address non-detectable background comorbidities affecting BP, patients with a baseline SBP < 120 mmHg were excluded from the sensitivity analysis. Also under evaluation, was the association between baseline BP level and clinical outcomes. Primary results were unchanged, indirectly suggesting that low DBP management might contribute to poor outcomes, especially in patients with MVD.

This study has several strengths, including its large AMI population derived from a nationwide multicenter registry. Long-term follow-up events were investigated using the average on-treatment BP. Due to the potential impact of reverse causality, results of the sensitivity analysis were compared. This study provides plausible explanations for the current results and is in line with previous studies. However, further studies are needed to determine whether more careful DBP management is necessary in AMI patients with MVD after revascularization

Limitations of the study

The present study has several limitations. This was a retrospective analysis of a preexisting registry and not a prospective trial. Therefore, the results cannot be extrapolated to other populations. Data regarding adverse events related to antihypertensive management are lacking, and adverse events might occur more frequently in subjects with a low BP. Due to insufficient data, no investigation was done into whether medication changes during follow-up could have affected the outcomes. Finally, BP was measured using different instruments across the hospital and clinical visits, which may have affected the relationship between BP and outcomes. However, the preferred recommendations specified the use of manual mercury sphygmomanometers during the study period. Finally, patients with in-hospital death and major adverse cardiac events were excluded from the analysis. Therefore, the results of the present study suggest that this association is possibly the result of selection confounders. Despite these limitations, this study was a large and comprehensive investigation that evaluated the impact of MVD on the association between BP and clinical outcomes in patients with AMI who underwent revascularization through PCI. The study used data from a nationwide registry and reported some novel findings in addition to showing a trend similar to that observed in previous studies.

Conclusions

Among patients with AMI who underwent PCI, a low average on-treatment DBP was associated with increased risks of all-cause death and CV death, especially in patients with MVD. Thus, clinicians may need to exercise caution when treating specific individuals with a low DBP.

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Conflict of interest: None declared

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Table 1. Baseline characteristics of study population by average on-treatment diastolic blood pressure categories (n = 9,983).

	Overall (n = 9,983)	**Average diastolic blood pressure during follow-up [mmHg]**				
		< 70 (n = 2,531)	**70–74 (n = 1,938)**	**75–79 (n = 2,111)**	**≥ 80 (n = 3,403)**	**P**
Demographic						
Age [years]	63 (54, 73)	69 (58, 76)	65 (56, 74)	63 (54, 72)	59 (51, 69)	< 0.001
Male	7,569 (75.8%)	1,767 (69.8%)	1,450 (74.8%)	1,616 (76.6%)	2,736 (80.4%)	< 0.001
Body mass index [kg/m^2]	24.1 (22.1, 26.0)	23.4 (21.4, 25.2)	23.8 (21.9, 25.8)	24.1 (22.2, 25.9)	24.5 (22.9, 26.6)	< 0.001
Smoking:						< 0.001
Never	3,761 (38.6%)	1,042 (42.2%)	768 (40.5%)	791 (38.2%)	1,160 (35.0%)	
Former	1,904 (19.5%)	488 (19.8%)	399 (21.0%)	392 (18.9%)	625 (18.9%)	
Current	4,085 (41.9%)	939 (38.0%)	730 (38.5%)	888 (42.9%)	1,528 (46.1%)	
Clinical						
Hospital stays [days]	5 (4, 7)	6 (4, 8)	6 (4, 7)	5 (4, 7)	5 (4, 7)	< 0.001
Symptom to door time [h]	3.8 (1.5, 13.4)	3.8 (1.5, 13.3)	4.0 (1.6, 15.6)	3.7 (1.6, 12.9)	3.8 (1.5, 12.5)	0.142
Killip classification:						< 0.001
Ⅰ	8,298 (83.1%)	1,949 (77.0%)	1,627 (84.0%)	1,805 (85.5%)	2,917 (85.7%)	
Ⅱ	830 (8.4%)	209 (8.3%)	179 (9.2%)	172 (8.1%)	270 (7.9%)	
Ⅲ	613 (6.1%)	195 (7.7%)	115 (5.9%)	116 (5.5%)	187 (5.5%)	
Ⅳ	242 (2.4%)	178 (7.0%)	17 (0.9%)	18 (0.9%)	29 (0.9%)	
GRACE risk score*:						< 0.001
Low	1,067 (10.7%)	49 (1.9%)	75 (3.9%)	159 (7.5%)	784 (23.0%)	
Intermediated	2,945 (29.5%)	392 (15.5%)	503 (26.0%)	746 (35.3%)	1,304 (38.3%)	

High	5,971 (59.8%)	2,090 (82.6%)	1,360 (70.2%)	1,206 (57.1%)	1,315 (38.6%)	
Previous heart failure	112 (1.1%)	37 (1.5%)	21 (1.1%)	17 (0.8%)	37 (1.1%)	0.203
Previous MI	699 (7.0%)	226 (8.9%)	154 (7.9%)	142 (6.7%)	177 (5.2%)	< 0.001
Previous ischemic stroke	543 (5.5%)	157 (6.2%)	121 (6.3%)	115 (5.5%)	150 (4.4%)	0.006
Previous ICH	50 (0.5%)	15 (0.6%)	10 (0.5%)	6 (0.3%)	19 (0.6%)	0.449
Hypertension	4,982 (49.9%)	1,165 (46.0%)	938 (48.4%)	1,039 (49.2%)	1,840 (54.1%)	< 0.001
Diabetes mellitus	2,708 (27.1%)	737 (29.1%)	546 (28.2%)	563 (26.7%)	862 (25.3%)	0.008
Dyslipidemia	1,164 (11.7%)	267 (10.5%)	219 (11.3%)	253 (12.0%)	425 (12.5%)	0.124
Chronic kidney disease	1,777 (17.8%)	613 (24.2%)	347 (17.9%)	315 (14.9%)	502 (14.8%)	< 0.001
Myocardial infarction:						< 0.001
NSTEMI	5,031 (50.4%)	1,120 (44.3%)	972 (50.2%)	1,105 (52.3%)	1,834 (53.9%)	
STEMI	4,952 (49.6%)	1,411 (55.7%)	966 (49.8%)	1,006 (47.7%)	1,569 (46.1%)	
Multivessel disease	4,545 (45.5%)	1,175 (46.4%)	902 (46.5%)	957 (45.3%)	1,511 (44.4%)	0.334
Anterior wall infarction	4,864 (48.7%)	1,031 (40.7%)	958 (49.4%)	1,083 (51.3%)	1,792 (52.7%)	< 0.001
LVEF < 40% in hospital	998 (10.0%)	328 (13.0%)	188 (9.7%)	183 (8.7%)	299 (8.8%)	< 0.001
Atrial fibrillation in hospital	189 (1.9%)	67 (2.6%)	40 (2.1%)	35 (1.7%)	47 (1.4%)	0.004
Hemodynamics at admission						
Systolic BP [mmHg]	130 (114, 150)	110 (100, 120)	120 (110, 135)	130 (120, 144)	150 (140, 169)	< 0.001
Diastolic BP [mmHg]	80 (70, 90)	60 (60, 70)	76 (70, 80)	80 (80, 88)	95 (90, 100)	< 0.001
Heart rate [bpm]	77 (66, 88)	72 (60, 84)	76 (66, 86)	78 (68, 88)	80 (70, 91)	< 0.001
Hemodynamics at discharge						
Systolic BP [mmHg]	110 (100, 120)	107 (100, 115)	110 (100, 120)	110 (100, 120)	120 (110, 130)	<

						0.001
Diastolic BP [mmHg]	70 (60, 75)	60 (60, 70)	65 (60, 70)	70 (60, 74)	70 (66, 80)	< 0.001
Heart rate [bpm]	70 (64, 76)	70 (64, 76)	70 (64, 76)	70 (64, 77)	70 (64, 77)	0.363
Cardiac enzyme, peak level						
Troponin I [ng/mL]	19 (4, 50)	23 (6, 58)	19 (4, 47)	16 (3, 48)	16 (3, 49)	< 0.001
CK-MB [ng/mL]	52 (10, 169)	65 (14, 189)	49 (10, 164)	46 (9, 162)	47 (9, 162)	< 0.001
Medication*						
Antiplatelet agents	9,983 (100.0%)	2,531 (100.0%)	1,938 (100.0%)	2,111 (100.0%)	3,403 (100.0%)	1.000
Beta-blockers	8,734 (87.5%)	2,123 (83.9%)	1,669 (86.1%)	1,857 (88.0%)	3,085 (90.7%)	<0.001
≥ 25% of optimal dose	1,353 (15.5%)	227 (10.7%)	210 (12.6%)	285 (15.3%)	631 (20.5%)	< 0.001
ACEI or ARBs	8,324 (83.4%)	2,024 (80.0%)	1,571 (81.1%)	1,756 (83.2%)	2,973 (87.4%)	< 0.001
Statins	9,534 (95.5%)	2,401 (94.9%)	1,845 (95.2%)	2,028 (96.1%)	3,260 (95.8%)	0.166
Moderate to high intensity	9,387 (98.4%)	2,355 (98.1%)	1,812 (98.2%)	1,996 (98.4%)	3,219 (98.7%)	0.223
Calcium channel blockers	610 (6.1%)	98 (3.9%)	93 (4.8%)	145 (6.9%)	274 (8.1%)	< 0.001

The data are presented as the number (%), and median (interquartile interval). Non-parametric continuous variables as assessed by the Kolmogorov-Smirnov method and were analyzed by Mann-Whitney U test. *GRACE risk score classification: 108 ≥: low, 109–140: intermediate, > 140: high; **Defined as a prescription at hospital discharge after acute coronary syndrome; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin Ⅱ receptor blocker; BP — blood pressure; ICH — intracranial hemorrhage; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST segment elevation myocardial infarction

Figure 1. Flow diagram of the study population; AMI — acute myocardial infarction; KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institutes of Health; PCI — percutaneous coronary intervention

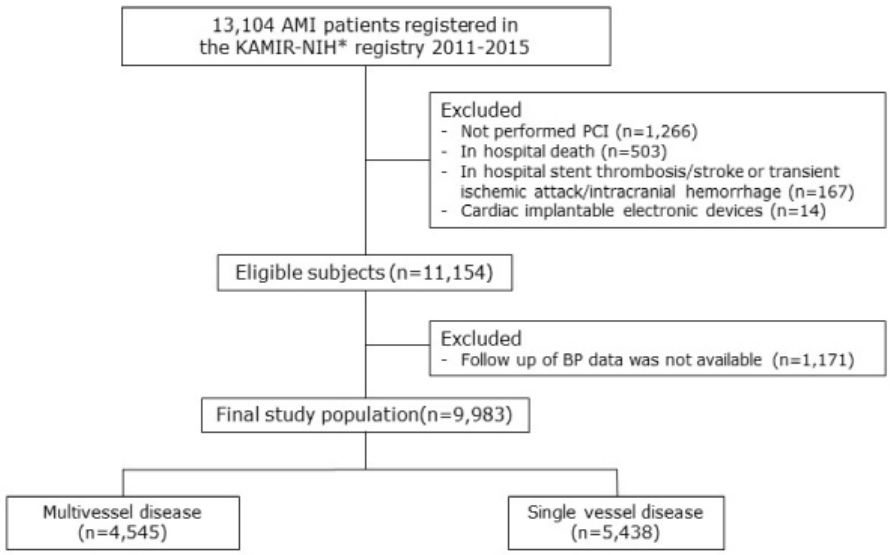
Figure 2. Restricted cubic spline model of all-cause death or hospitalization for heart failure (HF) in patients with multivessel disease (**A**) or

single-vessel disease (**B**) during a 3-year follow-up according to on-treatment blood pressure (BP). The dashed black horizontal lines indicate a hazard ratio (HR) of 1 and the painted areas indicate the 95% confidence interval (CI) (red line: diastolic BP [DBP]; blue line: systolic BP [SBP]).

Figure 3. Forest plots of Cox regression analysis of clinical outcomes by multivessel disease (**A**) or single-vessel disease (**B**) of diastolic blood pressure (DBP) during a 3-year follow-up period; HF — heart failure; HR — hazard ratio; CI — confidence interval.

Figure 4. Sensitivity analysis: Forest plots of the Cox regression analysis for clinical outcomes by multivessel disease (**A**) and single-vessel disease (**B**) of diastolic blood pressure (DBP) during a 3-year follow-up period after excluding patients with baseline systolic blood pressure < 120 mmHg; HR — hazard ratio; CI — confidence interval.

Figure 1



* Korean Acute Myocardial Infarction Registry-National Institutes of Health

Figure 2

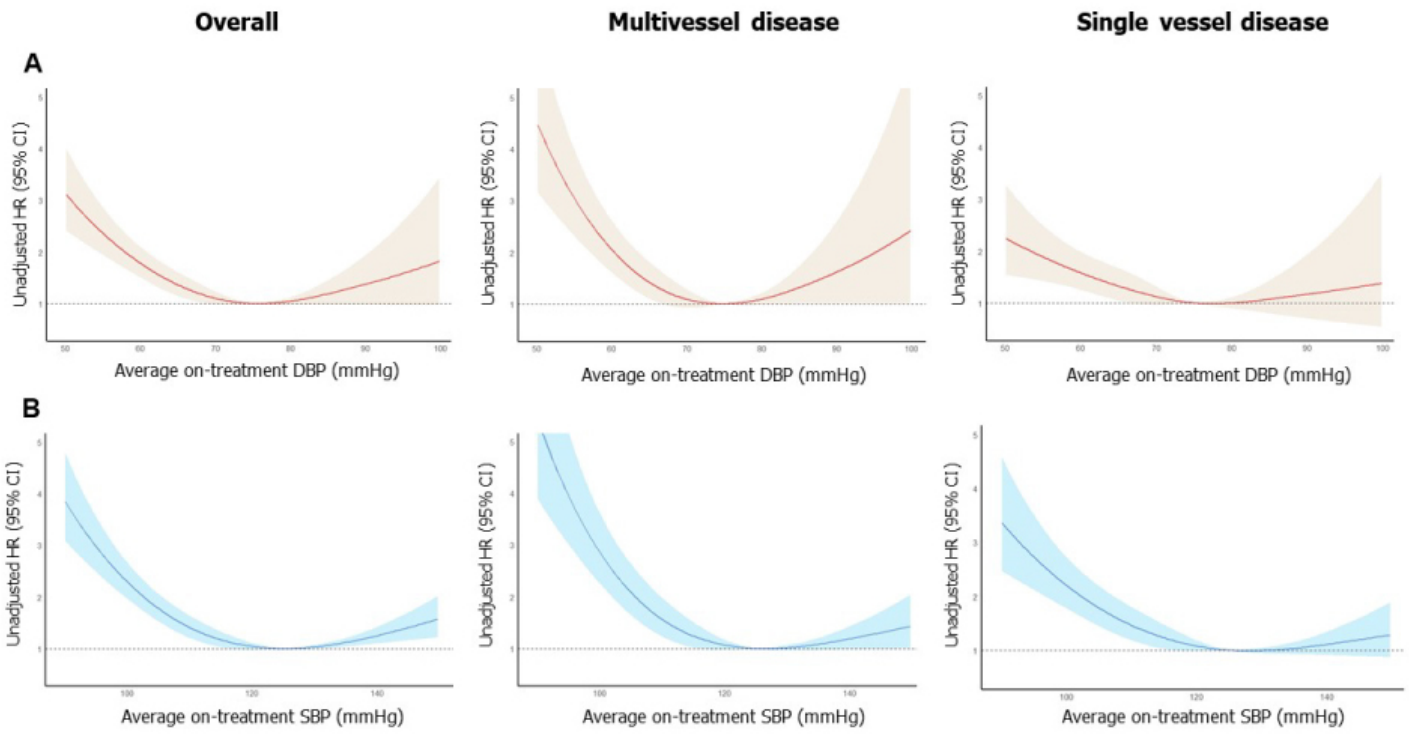

Overall
Multivessel disease
Single vessel disease
A
Unadjusted HR (95% CI)
Average on-treatment DBP (mmHg)
B
Unadjusted HR (95% CI)
Average on-treatment SBP (mmHg)

Figure 3

A: Multivessel disease

All-cause death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	118	2.28 (1.66-3.14)	1.53 (1.10-2.14)	0.012
70 to 74 mmHg	902	76	1.40 (0.97-2.01)	1.11 (0.76-1.61)	0.601
75 to 79 mmHg	957	59	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	90	1.19 (0.85-1.66)	1.39 (0.99-1.96)	0.061

Cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	71	2.46 (1.61-3.76)	1.65 (1.06-2.56)	0.027
70 to 74 mmHg	902	50	1.39 (0.85-2.26)	1.07 (0.64-1.77)	0.801
75 to 79 mmHg	957	34	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	54	1.20 (0.77-1.88)	1.36 (0.86-2.17)	0.191

Non-cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	47	2.04 (1.25-3.33)	1.41 (0.85-2.32)	0.184
70 to 74 mmHg	902	26	1.41 (0.82-2.44)	1.16 (0.66-2.03)	0.601
75 to 79 mmHg	957	25	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	36	1.17 (0.70-1.93)	1.41 (0.84-2.35)	0.193

HF hospitalization

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	69	1.85 (1.14-3.00)	1.37 (0.82-2.28)	0.225
70 to 74 mmHg	902	51	1.41 (0.82-2.40)	1.26 (0.73-2.19)	0.402
75 to 79 mmHg	957	42	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	49	1.15 (0.70-1.88)	1.38 (0.83-2.29)	0.222

*Adjusted by clinical covariates listed in method section

B: Single-vessel disease

All-cause death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	136	1.68 (1.23-2.30)	1.14 (0.81-1.61)	0.457
70 to 74 mmHg	1,036	65	1.40 (0.99-1.96)	1.01 (0.73-1.40)	0.950
75 to 79 mmHg	1,154	52	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	101	0.97 (0.70-1.34)	1.03 (0.73-1.44)	0.879

Cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	82	1.75 (1.16-2.63)	1.25 (0.81-1.96)	0.312
70 to 74 mmHg	1,036	36	1.59 (1.03-2.46)	1.02 (0.66-1.58)	0.932
75 to 79 mmHg	1,154	29	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	57	1.01 (0.65-1.54)	1.04 (0.68-1.59)	0.856

Non-cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	54	1.58 (0.97-2.56)	0.98 (0.59-1.63)	0.931
70 to 74 mmHg	1,036	29	1.13 (0.65-1.95)	0.97 (0.55-1.70)	0.919
75 to 79 mmHg	1,154	23	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	44	0.91 (0.55-1.52)	1.05 (0.62-1.77)	0.868

HF hospitalization

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	51	1.37 (0.94-2.01)	0.90 (0.59-1.35)	0.613
70 to 74 mmHg	1,036	30	1.31 (0.87-1.98)	1.14 (0.75-1.75)	0.534
75 to 79 mmHg	1,154	24	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	45	0.73 (0.49-1.11)	0.74 (0.48-1.14)	0.168

*Adjusted by clinical covariates listed in method section

Figure 4

A: Multivessel disease

All-cause death

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	2.65 (1.77-3.97)	1.67 (1.15-2.44)	0.008
70 to 74 mmHg	1.59 (1.07-2.36)	1.21 (0.82-1.79)	0.331
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1.21 (0.86-1.71)	1.47 (1.03-2.11)	0.032

Cardiovascular death

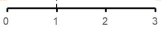
Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	2.79 (1.62-4.81)	1.78 (1.02-2.89)	0.041
70 to 74 mmHg	1.49 (0.86-2.58)	1.28 (0.72-2.27)	0.396
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1.29 (0.80-2.06)	1.44 (0.85-2.42)	0.176

Non-cardiovascular death

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	2.47 (1.36-4.50)	1.59 (0.95-2.68)	0.078
70 to 74 mmHg	1.70 (0.96-3.00)	1.16 (0.68-1.98)	0.583
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1.12 (0.67-1.88)	1.49 (0.92-2.41)	0.108

HF hospitalization

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	2.20 (1.17-4.13)	1.58 (0.90-2.77)	0.110
70 to 74 mmHg	1.58 (0.87-2.85)	1.29 (0.74-2.27)	0.371
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1.21 (0.72-2.03)	1.38 (0.83-2.31)	0.216

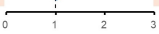


*Adjusted by clinical covariates listed in method section

B: Single-vessel disease

All-cause death

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1.40 (0.91-2.15)	0.99 (0.69-1.40)	0.949
70 to 74 mmHg	1.40 (0.97-2.04)	1.15 (0.78-1.69)	0.476
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	0.92 (0.66-1.29)	1.01 (0.58-1.75)	0.725

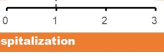


Cardiovascular death

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1.33 (0.74-2.38)	0.98 (0.58-1.69)	0.829
70 to 74 mmHg	1.57 (0.97-2.56)	1.27 (0.77-2.09)	0.341
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	0.98 (0.63-1.54)	1.00 (0.63-1.59)	0.997

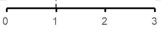
Non-cardiovascular death

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1.48 (0.79-2.79)	1.09 (0.61-2.32)	0.885
70 to 74 mmHg	1.19 (0.66-2.13)	1.08 (0.54-2.03)	0.861
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	0.85 (0.50-1.42)	0.92 (0.51-1.63)	0.863



HF hospitalization

Average DBP	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1.31 (0.77-2.22)	1.01 (0.58-1.74)	0.998
70 to 74 mmHg	1.31 (0.83-2.07)	1.19 (0.74-1.92)	0.480
75 to 79 mmHg	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	0.75 (0.49-1.15)	0.76 (0.48-1.20)	0.231



*Adjusted by clinical covariates listed in method section