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ORIGINAL ARTICLE
Ischemic Heart Disease

Impact of Low Diastolic Blood Pressure on Risk of Cardiovascular Death in Elderly Patients With Coronary Artery Disease After Revascularization

– The CREDO-Kyoto Registry Cohort-1 –

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on behalf of CREDO-Kyoto Investigators

Background: We investigated the effects of age and low diastolic blood pressure (DBP) on cardiovascular death in patients with coronary artery disease (CAD) after coronary revascularization.

Methods and Results: Stable, chronic CAD patients after coronary revascularization in the CREDO-Kyoto registry cohort-1 were allocated to the Young (≤64 years, n=2,619), Young-Old (65–74 years, n=2,932), and Old-Old (≥75 years, n=1,629) groups. Kaplan-Meier analysis showed that the crude cumulative incidence of cardiovascular death was higher in Young-Old patients with DBP <70 mmHg (P<0.001) and in Old-Old patients with DBP <60 mmHg (P=0.017), but not <70 mmHg (P=0.629), compared with each counterpart. Low DBP did not increase cardiovascular death in young patients. After adjustments with independent predictors, DBP <60 mmHg did not increase the cardiovascular death in the Old-Old group (HR=1.579 [95% CI, 0.944–2.642], P=0.082) and DBP <70 mmHg remained a predictor in the Young-Old group (HR=1.665 [1.094–2.532], P=0.017). On multivariate stepwise Cox proportional hazard regression analysis, independent predictors for cardiovascular death in low DBP patients were creatinine clearance (CCr; inversely), prior cerebrovascular disease, and aortic disease in the Young-Old group and CCr (inversely) and malignancy in the Old-Old group.

Conclusions: DBP <60 mmHg was not an independent factor for predicting cardiovascular death in Old-Old revascularized CAD patients, whereas DBP <70 mmHg remained a predictor in the Young-Old. (*Circ J* 2016; **80:** 1232–1241)

Key Words: Blood pressure; Cardiovascular risks; Coronary artery disease; Elderly; J-shaped curve phenomenon

Whether low diastolic blood pressure (DBP) increases cardiovascular events in patients with coronary artery disease (CAD) remains controversial.[1,2] There is concern that low diastolic coronary perfusion pressure reduces coronary blood flow, which may lead to myocardial ischemia and cardiac events (the so-called J-shaped curve phenomenon). The INVEST post hoc analysis demonstrated that the unadjusted hazard ratio (HR) for the composite of all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke was increased in hypertensive CAD patients with excessively low DBP (ie, <70 mmHg).[3] However, that analysis also showed that coronary revascularization reduced the increased risk for cardiovascular events in low DBP patients to less than half.[3] This finding indicates that myocardial ischemia related to residual significant epicardial coronary stenosis would account for up to one-half of the increased risk of cardiovascular events in CAD patients with extremely low DBP. Moreover, we have shown that low DBP (<70 mmHg)

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is not an independent factor predicting cardiovascular death in stable, chronic CAD patients after coronary revascularization after adjustments with significant factors such as age, male sex, low creatinine clearance (CCr), prior heart failure (HF), prior MI, low left ventricular ejection fraction (LVEF), prior cerebrovascular disease, and large pulse pressure.[4]

DBP becomes lower with age in the elderly, because aging, hypertension, and dyslipidemia accelerate arteriosclerosis and subsequently increase the stiffness of large conduit arteries.[5] Current guidelines for the management of hypertension or chronic CAD do not clearly state whether further systolic blood pressure (SBP) lowering should be pursued or withheld when CAD patients show isolated systolic hypertension associated with excessively low DBP.[1,6–8] In general, there is consensus that particular attention should be paid during the treatment of elderly hypertensive patients because of the high incidence of impairment of vital organ perfusion or autoregulation.[7,9] However, little is known about whether low DBP is actually an independent risk factor for excess cardiovascular death in elderly CAD patients.

Accordingly, in the present study, the effects of age and low DBP on cardiovascular death were examined in revascularized CAD patients. For this purpose, stable, chronic CAD patients were investigated in a large-scale cohort of the CREDO-Kyoto registry cohort-1 enrolling 9,877 consecutive CAD patients who underwent first coronary bypass surgery (CABG) or percutaneous coronary intervention (PCI).

Methods

CREDO-Kyoto Registry Cohort-1

The CREDO-Kyoto registry cohort-1 was a multicenter registry that enrolled 9,877 consecutive patients undergoing their first PCI or CABG in 30 institutions in Japan during 2000–2002.[10] The institutional review board or ethics committee of each participating institution approved this study. Because the study subjects were retrospectively enrolled, written, informed consent was waived according to the guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare of Japan.

The study design, methods, and principal results of the CREDO-Kyoto registry cohort-1 have been described in detail elsewhere.[10] Briefly, independent clinical research coordinators collected the data of the study patients from hospital charts or databases in each institution according to prespecified definitions. BP was measured in the seated position on admission by auscultation method using a mercury or aneroid sphygmomanometer. LVEF was assessed by either echocardiography or contrast left ventriculography. Left ventricular (LV) dysfunction was defined as LVEF <0.40. Hypertension, diabetes mellitus, peripheral vascular disease, atrial fibrillation (any class of paroxysmal, persistent, or permanent atrial fibrillation), prior MI, prior cerebrovascular disease, prior HF, malignancy, chronic obstructive pulmonary disease (COPD), aortic disease (aortic aneurysm and aortic dissection), and current smoking status were defined as present when these diagnoses were recorded in the hospital chart. Prior cerebrovascular disease included asymptomatic stroke detected by noninvasive imaging modalities, as well as symptomatic hemorrhagic and ischemic stroke. Metabolic syndrome (MetS)-like risk factor accumulation was defined when a body mass index (BMI) ≥25 kg/m^2 was accompanied by at least 2 of the following factors: BP ≥130/85 mmHg; serum triglycerides ≥150 mg/dl; high-density lipoprotein cholesterol <40 mg/dl for men and <50 mg/dl for women; and fasting blood glucose ≥110 mg/dl.

An independent clinical events committee adjudicated the events.[10] All deaths were confirmed on the basis of medical records or telephone interviews of the patients' families. Death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified. MI was adjudicated according to the definition in the Arterial Revascularization Therapy Study.[11] Only Q-wave MI was regarded as MI. Stroke during follow-up included only symptomatic stroke, as the etiology of stroke was not determined. Follow-up was terminated when a patient experienced a first event.

Study Population

This subanalysis enrolled 7,180 patients with stable, chronic CAD in the CREDO-Kyoto registry cohort-1. The patients were allocated to the Young (age <65 years, n=2,619), Young-Old (65–74 years, n=2,932), and Old-Old groups (≥75 years, n=1,629). Exclusion criteria were as follows: emergency procedure, in-hospital major cardiovascular events (death, recurrent MI, stroke, or urgent revascularization), MI within 28 days prior to the index procedure, symptomatic HF on admission, unstable angina on admission, lack of BP data, and age <20 years.

Statistical Analysis

Continuous variables are expressed as mean±SD. All analyses were performed using IBM SPSS Statistics version 21 (IBM Japan Inc, Tokyo, Japan). P values (2-sided) <0.05 were considered significant. For statistical comparisons of baseline demographics and characteristics among the 3 groups, analysis of variance followed by post hoc analysis using Scheffé's test for continuous variables with equal variance or Tamhane's test for those with possible unequal variance and the chi-squared test for categorical data was used. A Cox proportional hazards model was used to determine the cut-off BP level below which the maximum HR and the minimum P value for increasing cardiovascular death were obtained. Survival curves were analyzed using the Kaplan-Meier method and the log-rank test. To determine predictors for cardiovascular death, the following baseline variables were used for Cox proportional hazards model: male sex, BMI, SBP, DBP <70 mmHg (for the Young-Old group) or DBP <60 mmHg (for the Old-Old group), pulse pressure, CCr, hemoglobin, mode of revascularization (PCI), LV dysfunction, current smoking, hypertension, diabetes mellitus, dyslipidemia, MetS-like risk accumulation, peripheral vascular disease, valvular heart disease, atrial fibrillation, aortic disease, malignancy, COPD, prior MI, prior cerebrovascular disease, prior HF, family history of CAD, complete revascularization, and number of coronary lesions after revascularization, as well as potential risk-affecting drug therapies at hospital discharge: angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), calcium-channel blockers, β-blockers, statins, antiplatelet drugs, warfarin, oral hypoglycemic drugs and/or insulin, and antiarrhythmic agents. A multivariate stepwise Cox proportional hazards model was used to identify independent factors for predicting cardiovascular death using the significant variables obtained on univariate analyses. Finally, a Cox proportional hazards model was used to determine the crude and independent predictor-adjusted HRs for cardiovascular death.

Results

Table 1 shows the baseline demographics and characteristics of the Young, Young-Old, and Old-Old groups of CAD patients after coronary revascularization. The average SBP/DBP val-

Table 1. Baseline Demographics and Characteristics of the CAD Patients

	Young (≤64 years)	Young-Old (65–74 years)	Old-Old (≥75 years)	P value
n	2,619	2,932	1,629	–
Male, n (%)	2,136 (81.6)	2,060 (70.3)***	963 (59.1)***,†††	0.000
Blood pressure				
SBP, mmHg	134.4±20.4	136.1±19.6***	136.7±21.1***,†††	0.000
DBP, mmHg	76.6±12.6	74.2±11.8***	71.9±11.9***,†††	0.000
Pulse pressure, mmHg	57.8±16.0	62.0±16.3***	64.8±17.5***,†††	0.000
BMI, kg/m²	24.4±3.3	23.7±3.1***	23.0±3.2***,†††	0.000
Hemoglobin, mg/dl	13.8±1.9	13.1±1.8***	12.5±1.8***,†††	0.000
CCr, mg/ml/min	87.1±33.6	65.1±22.2***	51.0±17.7***,†††	0.000
LV dysfunction (LVEF <0.40), n (%)	117 (4.8)	129 (4.7)	65 (4.4)	0.832
Major coronary risks				
Hypertension, n (%)	1,696 (64.8)	2,108 (71.9)***	1,209 (74.2)***	0.000
Diabetes mellitus, n (%)	1,062 (40.6)	1,148 (39.2)	521 (32.0)***,†††	0.000
Dyslipidemia, n (%)	1,524 (58.2)	1,496 (51.1)***	717 (44.2)***,†††	0.000
Smoking, n (%)	1,608 (62.3)	1,384 (48.0)***	622 (39.0)***,†††	0.000
Family history, n (%)	523 (20.9)	402 (14.4)***	154 (10.1)***,†††	0.000
MetS-like risk factor accumulation, n (%)	593 (23.9)	501 (17.8)***	181 (11.6)***,†††	0.000
Past history				
MI, n (%)	518 (19.8)	571 (19.5)	337 (20.7)	0.613
HF, n (%)	113 (4.3)	138 (4.7)	98 (6.0)*	0.037
Cerebrovascular disease, n (%)	289 (11.0)	546 (18.6)***	333 (20.5)***	0.000
Coexisting disease				
Aortic disease, n (%)	58 (2.2)	175 (6.0)***	181 (11.1)***,†††	0.000
Atrial fibrillation, n (%)	97 (3.7)	189 (6.4)***	143 (8.8)***,††	0.000
COPD, n (%)	79 (3.0)	151 (5.2)***	130 (8.0)***,†††	0.000
Malignancy, n (%)	76 (2.9)	255 (8.7)***	180 (11.1)***,†	0.000
Coronary revascularization therapy				
PCI, n (%)	1,914 (73.1)	2,022 (69.0)***	1,207 (74.1)†††	0.000
Complete revascularization, n (%)	966 (50.5)	902 (44.6)***	509 (42.2)***	0.000
Coronary lesions after revascularization	2.2±1.3	2.4±1.4***	2.5±1.5***	0.000
Medication on discharge				
Antihypertensives, n (%)	2,011 (76.9)	2,310 (78.9)	1,277 (78.5)	0.176
ACEIs/ARBs, n (%)	720 (27.5)	891 (30.4)*	526 (32.3)**	0.002
β-blockers, n (%)	420 (16.1)	495 (16.9)	225 (13.8)†	0.025
Calcium-channel blockers, n (%)	1,579 (60.4)	1,855 (63.5)	1,016 (62.5)	0.069
Statins, n (%)	884 (33.8)	849 (29.0)***	366 (22.5)***,†††	0.000
Oral hypoglycemic and/or insulin, n (%)	454 (17.4)	494 (16.9)	223 (13.7)**,††	0.005
Antiplatelet agent, n (%)	2,521 (96.4)	2,793 (95.4)	1,556 (95.7)	0.167

Data are described as mean±SD. *P<0.05, **P<0.01, and ***P<0.001 vs. Young group. †P<0.05, ††P<0.01, and †††P<0.001 vs. Young-Old group. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CCr, creatinine clearance; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; MetS, metabolic syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

ues were 134.4/76.6, 136.1/74.2, and 136.7/71.9 mmHg in the Young, Young-Old, and Old-Old groups, respectively. Although the distribution of SBP was similar among the age groups (Figure S1A), the prevalence of patients with DBP <70 mmHg increased with age, from 26.3% in the Young group to 39.2% in the Old-Old group (Figure S1B). Hypertension, especially isolated systolic hypertension, was more common in the older age groups (Table 1, Figure S1C). Other conventional coronary risk factors, such as male sex, dyslipidemia, smoking, diabetes, family history, and MetS-like risk factor accumulation, decreased with age. Cardiovascular comorbidities (aortic dissection and atrial fibrillation) and systemic illnesses (COPD, malignancy, low BMI, reduced CCr, and low hemoglobin) became more common with age. The prevalence of prior cerebrovascular disease and of prior HF was higher in older age groups. However, the prevalence of LV dysfunction and of prior MI did not differ among the 3 groups. The complete revascularization rate was lower and the number of coronary lesions after revascularization was greater in the Young-Old and Old-Old groups than in the Young group. The prevalence of antihypertensive drug use was similar among the 3 groups. However, the use of ACEIs or ARBs was more common in the Young-Old and Old-Old groups than in the Young group, and the incidence of β-blocker use was lower in the Old-Old group than in the other groups.

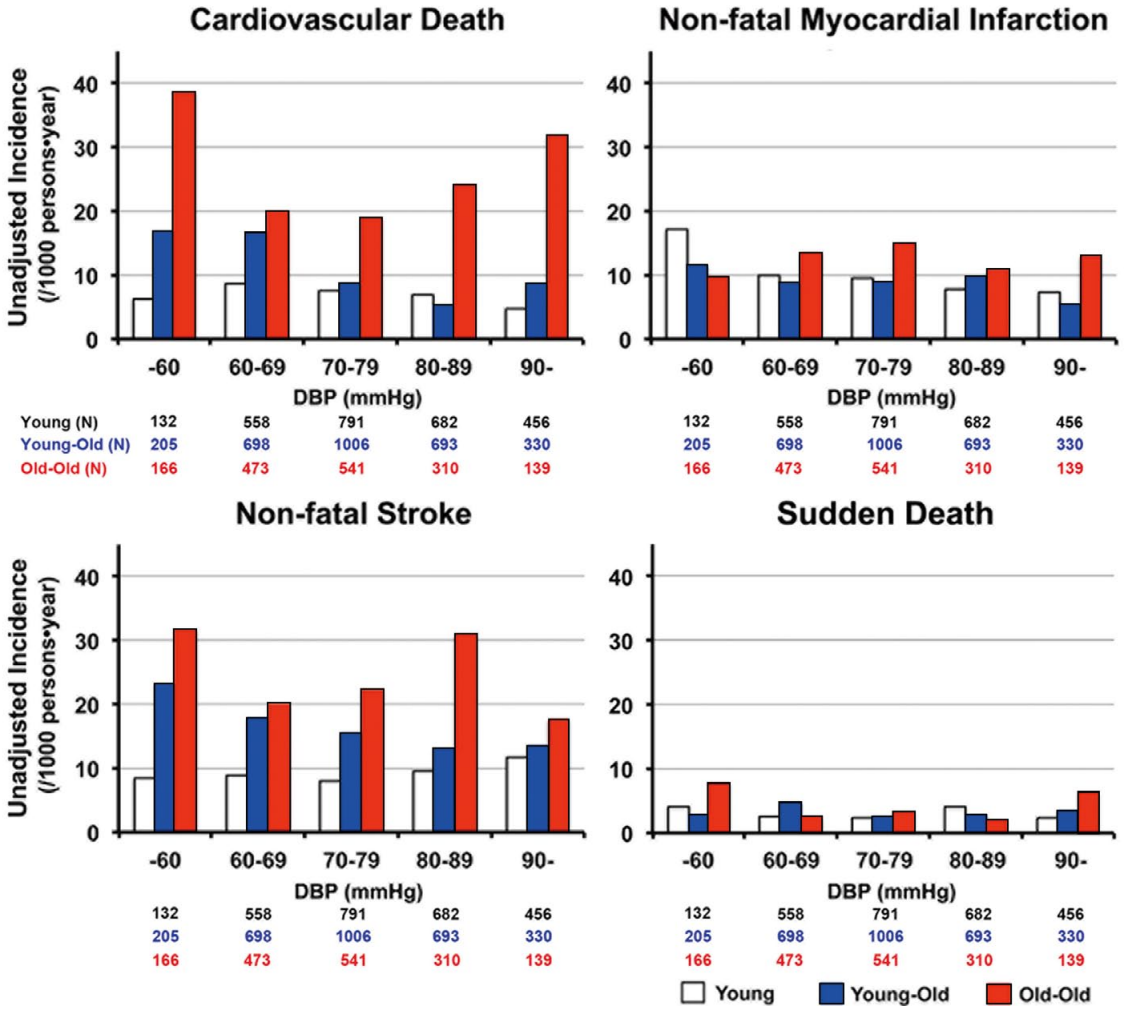

Figure 1. Unadjusted incidence (per 1,000 patients/year) of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and sudden death stratified by diastolic blood pressure (DBP) categories in the Young, Young-Old, and Old-Old groups of coronary artery disease patients.

Cut-Off BP Level for Increased Cardiovascular Death in Low DBP Patients

A total of 103 (3.9%) of 2,609 patients in the Young group, 213 (7.3%) of 2,932 in the Young-Old group, and 246 (7.8%) of 1,629 in the Old-Old group died during the follow-up period (median follow-up period 3.6 years). Cardiovascular deaths occurred in 67 (2.6%), 108 (3.7%), and 127 (7.8%) of the Young, Young-Old, and Old-Old groups, respectively. As shown in Figure 1, the crude incidence of cardiovascular death showed a U-shaped relationship with an inflection point, not a linear relationship, in the Young-Old and Old-Old groups. Furthermore, DBP <60 mmHg and DBP 60–69 mmHg had significantly greater odds ratios (ORs) for cardiovascular death than DBP 80–89 mmHg (as the reference) in the Young-Old group (Figure 2). Next, the inflection point (ie, the cut-off point below which the maximum HR for cardiovascular death was obtained) was investigated. In the Young-Old group, the risk of cardiovascular death was significantly higher in patients with DBP <80 mmHg and patients with DBP <70 mmHg, as compared with each counterpart (Table 2). DBP of 70 mmHg was determined to be the cut-off level of low DBP in the Young-Old group, because this DBP value gave the maximum HR and the minimum P value. Similarly, the cut-off DBP was found to be 60 mmHg in the Old-Old group. DBP categories had no effect on the HRs for cardiovascular death in the Young group.

DBP categories did not affect the incidence and OR of nonfatal MI, nonfatal stroke, and sudden death in the 3 age groups (Figures 1,2). There were no cut-off levels of low DBP for increasing nonfatal stroke, nonfatal MI, and sudden death in each age group (Tables S1–S3). There were no cut-off SBP levels below which significant increases in the HRs for cardiovascular death, nonfatal stroke, nonfatal MI, and sudden death were seen in the age groups (data not shown).

Unadjusted Cumulative Incidence of Cardiovascular Death

In the Young-Old group, Kaplan-Meier analysis demonstrated that the unadjusted cumulative incidence of cardiovascular death was significantly higher in patients with DBP <70 mmHg than in those with DBP ≥70 mmHg (P<0.001, log-rank test)

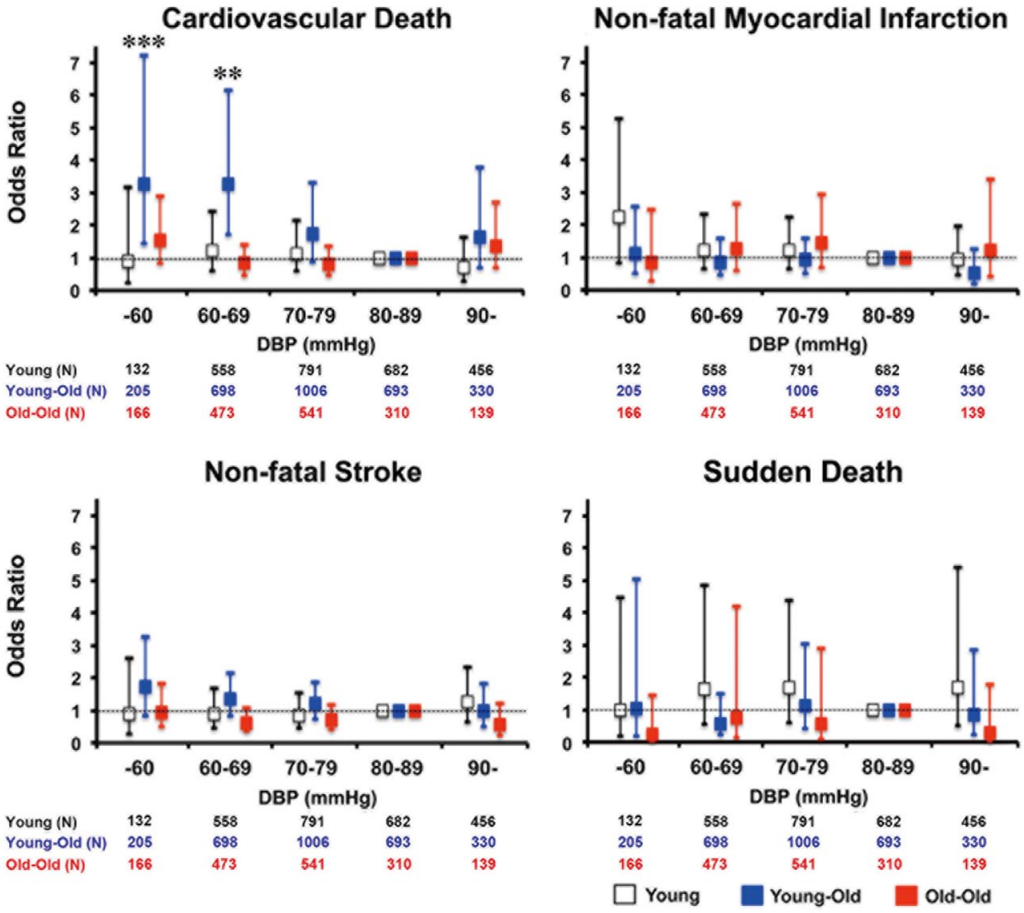

Figure 2. Odds ratios for cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and sudden death stratified by diastolic blood pressure (DBP) categories in the Young, Young-Old, and Old-Old groups of coronary artery disease patients. **P<0.01 and ***P<0.001 vs. DBP 80–89 mmHg (as the reference).

Table 2. Cut-Off Levels of Low DBP for Increasing Cardiovascular Death in CAD Patients After Revascularization

DBP level	Young			Young-Old			Old-Old		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Cardiovascular death									
≥60 mmHg	1.000	(Reference)	–	1.000	(Reference)	–	1.000	(Reference)	–
<60 mmHg	0.880	0.273–2.840	0.831	1.704	0.919–3.160	0.091	1.736	1.046–2.883	0.033
≥70 mmHg	1.000	(Reference)	–	1.000	(Reference)	–	1.000	(Reference)	–
<70 mmHg	0.837	0.492–1.422	0.510	2.238	1.522–3.291	0.000	1.081	0.748–1.562	0.680
≥80 mmHg	1.000	(Reference)	–	1.000	(Reference)	–	1.000	(Reference)	–
<80 mmHg	0.770	0.466–1.270	0.306	2.026	1.270–3.232	0.003	0.814	0.550–1.204	0.302
≥90 mmHg	1.000	(Reference)	–	1.000	(Reference)	–	1.000	(Reference)	–
<90 mmHg	0.637	0.302–1.342	0.235	1.252	0.647–2.425	0.505	0.672	0.380–1.187	0.171

Unadjusted Cox proportional hazards model was used to determine the cut-off level of DBP below which the maximum HR and the minimum P value for increasing cardiovascular death were obtained in each age group. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

(Figure 3). In the Old-Old group, the incidence of cardiovascular death was significantly greater in patients with DBP <60 mmHg (P=0.017), but not in those with DBP <70 mmHg (P=0.629), compared with each counterpart. In contrast, the incidence of cardiovascular death did not differ between DBP <70 mmHg and DBP ≥70 mmHg (P=0.461) and between DBP <60 mmHg and DBP ≥60 mmHg (P=0.826) in the Young group (data not shown).

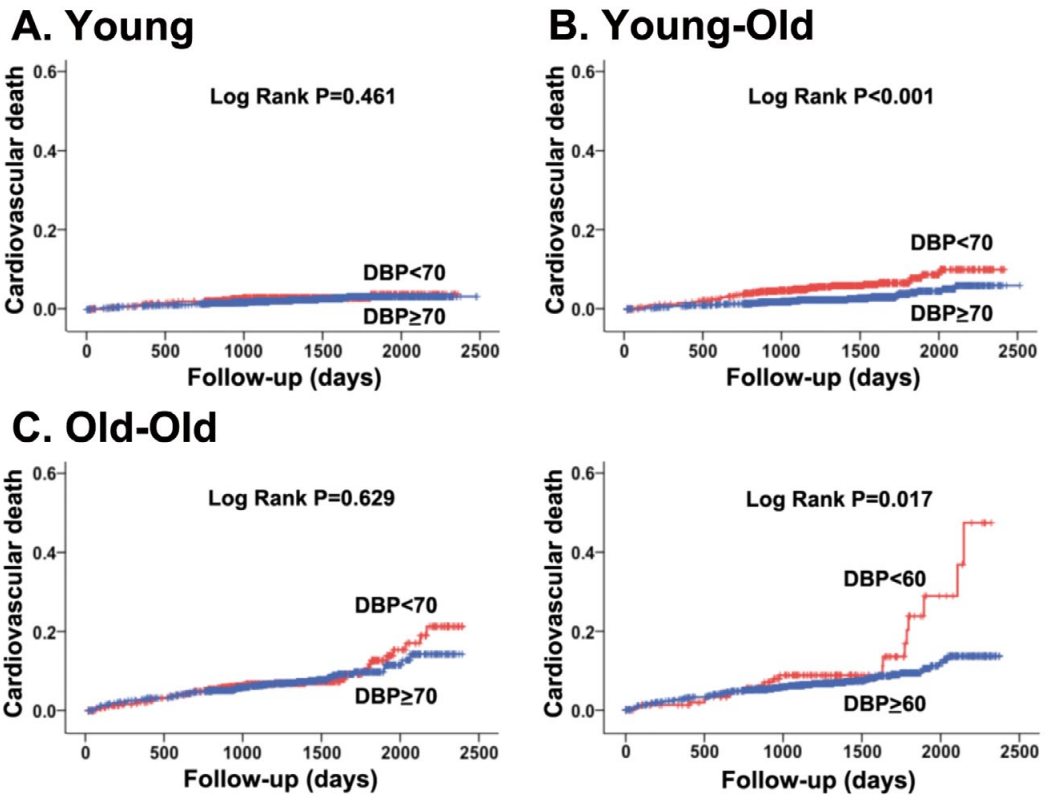

Figure 3. (**A**–**C**) Kaplan-Meier analyses for the cumulative incidence of cardiovascular death in the Young, Young-Old, and Old-Old groups of coronary artery disease patients. DBP, diastolic blood pressure.

Predicting Factors for Cardiovascular Death in the Young-Old Group

As shown in Table 3A, multivariate stepwise Cox proportional hazards model demonstrated that CCr (inversely), aortic disease, prior cerebrovascular disease, pulse pressure, DBP <70 mmHg, LV dysfunction, and use of statins (inversely) were the independent factors predicting cardiovascular death among all patients of the Young-Old group. Predicting factors were also investigated separately among patients with low DBP and among patients without low DBP. Significant predicting factors were CCr (inversely), prior cerebrovascular disease, and aortic disease among patients with DBP <70 mmHg (Table 3B) and CCr (inversely), aortic disease, pulse pressure, LV dysfunction, atrial fibrillation, and prior cerebrovascular disease among patients with DBP ≥70 mmHg (Table 3C).

Predicting Factors for Cardiovascular Death in the Old-Old Group

Among all patients of the Old-Old group, the independent predictive factors for cardiovascular death were CCr (inversely), prior HF, prior cerebrovascular disease, LV dysfunction, and coronary lesions after revascularization on multivariate stepwise Cox proportional hazards model (Table 4A). In patients with DBP <60 mmHg, CCr (inversely) and malignancy were significant predicting factors (Table 4B). In patients with DBP ≥60 mmHg, the independent factors were CCr (inversely), prior HF, LV dysfunction, prior cerebrovascular disease, and aortic disease (Table 4C).

HR for Cardiovascular Death Adjusted by Independent Predictive Factors

Finally, whether low DBP itself would be an independent predictor of increased cardiovascular death in revascularized CAD patients was investigated (Table 5). In the Young-Old group, the risk of DBP <70 mmHg for increasing cardiovascular death remained significant, but it was reduced to a marginal level after adjustments with the independent predictive factors among all patients (model 2; adjusted HR 1.665 [1.094–2.532], P=0.017) or those among patients with DBP <70 mmHg (model 3; adjusted HR 1.720 [1.165–2.540], P=0.013). In the Old-Old group, however, DBP <60 mmHg was not a significant factor after adjustments with independent predictors among all patients (model 2; adjusted HR 1.579 [95% CI, 0.944–2.642], P=0.082) and those among patients with DBP <60 mmHg (model 3; adjusted HR 1.527 [95% CI, 0.939–2.483], P=0.088).

Discussion

The present study demonstrated that the crude incidence of cardiovascular death was increased in revascularized CAD patients with DBP <70 mmHg in the Young-Old group and in those with DBP <60 mmHg in the Old-Old group, whereas low DBP did not affect the risk of cardiovascular death in the Young group (Figures 1–3). After adjustments with other independent predictors for cardiovascular death among each age group, DBP <60 mmHg was not a significant factor

Table 3. Risks for Cardiovascular Death in Young-Old CAD Patients

	Univariate*			Multivariate†		
	β	HR (95% CI)	P value	β	HR (95% CI)	P value
A. All patients						
CCr	−0.052	0.949 (0.942–0.957)	0.000	−0.046	0.955 (0.946–0.963)	0.000
Aortic disease	1.202	3.327 (1.980–5.590)	0.000	1.175	3.240 (1.896–5.536)	0.000
Prior cerebrovascular disease	0.728	2.072 (1.380–3.110)	0.000	0.842	2.321 (1.485–3.628)	0.000
Pulse pressure	0.018	1.018 (1.008–1.029)	0.001	0.014	1.014 (1.002–1.026)	0.017
DBP <70 mmHg	0.784	2.188 (1.502–3.195)	0.000	0.488	1.629 (1.070–2.481)	0.023
LV dysfunction	1.133	3.104 (1.693–5.688)	0.000	0.688	1.989 (1.061–3.728)	0.032
Use of statins	−0.972	0.378 (0.219–0.653)	0.000	−0.666	0.514 (0.277–0.952)	0.034
BMI	−0.137	0.872 (0.818–0.930)	0.000	–	–	–
Prior MI	0.678	1.970 (1.316–2.948)	0.001	–	–	–
Prior HF	1.481	4.398 (2.618–7.389)	0.000	–	–	–
Hemoglobin	−0.458	0.632 (0.575–0.696)	0.000	–	–	–
Diabetes	0.588	1.801 (1.234–2.630)	0.002	–	–	–
PCI	−0.632	0.531 (0.364–0.776)	0.001	–	–	–
Coronary lesions after revascularization	0.132	1.141 (1.019–1.277)	0.022	–	–	–
B. DBP <70 mmHg						
CCr	−0.046	0.955 (0.944–0.966)	0.000	−0.046	0.955 (0.944–0.966)	0.000
Prior cerebrovascular disease	0.656	1.928 (1.072–3.466)	0.000	0.815	2.258 (1.246–4.094)	0.007
Aortic disease	1.197	3.311 (1.492–7.345)	0.003	0.995	2.705 (1.213–6.033)	0.015
Pulse pressure	0.015	1.015 (1.001–1.029)	0.042	–	–	–
Hemoglobin	−0.440	0.644 (0.560–0.741)	0.000	–	–	–
BMI	−0.103	0.902 (0.826–0.986)	0.023	–	–	–
Prior HF	1.192	3.294 (1.654–6.558)	0.001	–	–	–
C. DBP ≥70 mmHg						
CCr	−0.055	0.947 (0.936–0.957)	0.000	−0.050	0.951 (0.939–0.963)	0.000
Aortic disease	1.304	3.684 (1.855–7.320)	0.000	1.405	4.077 (1.974–8.420)	0.000
Pulse pressure	0.020	1.020 (1.004–1.036)	0.012	0.023	1.024 (1.006–1.042)	0.008
LV dysfunction	1.537	4.650 (2.176–9.935)	0.000	1.484	4.410 (2.002–9.716)	0.000
Atrial fibrillation	0.900	2.460 (1.162–5.207)	0.019	1.079	2.941 (1.336–6.476)	0.007
Prior cerebrovascular disease	0.789	2.202 (1.254–3.868)	0.006	0.713	2.041 (1.107–3.765)	0.022
Use of statins	−1.330	0.265 (0.113–0.618)	0.002	−0.952	0.386 (0.151–0.988)	0.047
Male sex	0.872	2.392 (1.130–5.064)	0.023	–	–	–
BMI	−0.148	0.862 (0.786–0.946)	0.002	–	–	–
Prior MI	0.749	2.115 (1.204–3.715)	0.009	–	–	–
Prior HF	1.571	4.813 (2.173–10.662)	0.000	–	–	–
Hemoglobin	−0.440	0.644 (0.563–0.737)	0.000	–	–	–
Diabetes	0.678	1.970 (1.160–3.345)	0.012	–	–	–
Dyslipidemia	−0.738	0.478 (0.274–0.833)	0.009	–	–	–
PCI	−0.710	0.492 (0.289–0.838)	0.009	–	–	–
Coronary lesions after revascularization	0.191	1.210 (1.040–1.408)	0.013	–	–	–

*The following variables were used for Cox proportional hazard model: male sex, BMI, SBP, DBP <70 mmHg, pulse pressure, CCr, hemoglobin, PCI, LV dysfunction, current smoking, hypertension, diabetes mellitus, dyslipidemia, MetS-like risk accumulation, peripheral vascular disease, valvular heart disease, atrial fibrillation, aortic disease, malignancy, COPD, prior MI, prior cerebrovascular disease, prior HF, family history of CAD, complete revascularization, coronary lesions after revascularization, ACEIs or ARBs, calcium-channel blockers, β-blockers, statins, antiplatelet drugs, warfarin, oral hypoglycemic drugs and/or insulin, and antiarrhythmic agents. Only significant variables with P<0.05 are presented. †The significant variables in univariate analyses were used in the multivariate stepwise Cox proportional hazard model. β, regression coefficient; LV, left ventricular. Other abbreviations as in Tables 1,2.

predicting cardiovascular death in the Old-Old group, whereas DBP <70 mmHg was a predictor in the Young-Old group (Table 5).

It remains an open question whether extremely low DBP is a causal risk for increasing cardiovascular events in CAD patients, especially in elderly patients. It has been shown that the cardiovascular risk of low DBP is reduced to less than half by coronary revascularization.[3] Over the past decade, CABG and PCI have been increasingly offered to elderly patients, even Old-Old patients.[12–18] Therefore, to address the issue, CAD patients after revascularization in the cohort of a prospective, large-scale, multicenter registry, the CREDO-Kyoto registry cohort-1 were investigated.

It is interesting to note that low DBP affected cardiovascular

Table 4. Risks for Cardiovascular Death in Old-Old CAD Patients

	Univariate*			Multivariate†		
	β	HR (95% CI)	P value	β	HR (95% CI)	P value
A. All patients						
CCr	−0.044	0.957 (0.947–0.967)	0.000	−0.036	0.964 (0.951–0.978)	0.000
Prior HF	1.405	4.074 (2.166–7.663)	0.000	1.413	4.108 (2.190–7.706)	0.000
Prior cerebrovascular disease	0.640	1.897 (1.163–3.094)	0.010	0.674	1.962 (1.202–3.203)	0.007
LV dysfunction	1.203	3.330 (1.868–5.393)	0.000	1.041	2.833 (1.332–6.025)	0.007
Coronary lesions after revascularization	0.111	1.117 (1.012–1.233)	0.028	0.207	1.230 (1.040–1.454)	0.015
Use of statins	−0.657	0.518 (0.307–0.876)	0.014	–	–	–
DBP <60 mmHg	1.776	1.101 (1.046–2.864)	0.019	–	–	–
Age	0.082	1.085 (1.038–1.135)	0.000	–	–	–
BMI	−0.160	0.852 (0.802–0.905)	0.000			
Aortic disease	0.736	2.088 (1.347–3.237)	0.001	–	–	–
Hemoglobin	−0.284	0.752 (0.684–0.828)	0.000	–	–	–
Dyslipidemia	−0.621	0.537 (0.367–0.787)	0.001	–	–	–
Mets-like risk accumulation	−2.807	0.060 (0.008–0.432)	0.005	–	–	–
Complete revascularization	−0.514	0.518 (0.386–0.927)	0.021			
B. DBP <60 mmHg						
CCr	−0.054	0.947 (0.922–0.974)	0.000	−0.054	0.948 (0.923–0.972)	0.000
Malignancy	1.797	6.030 (2.310–15.740)	0.000	1.823	6.188 (2.308–16.587)	0.000
Prior HF	1.129	3.093 (1.090–8.783)	0.034	–	–	–
LV dysfunction	1.812	6.121 (1.959–19.121)	0.002	–	–	–
C. DBP ≥60 mmHg						
CCr	−0.042	0.959 (0.947–0.970)	0.000	−0.034	0.966 (0.952–0.981)	0.000
Prior HF	1.495	4.460 (2.710–7.343)	0.000	1.327	3.770 (1.880–7.562)	0.000
LV dysfunction	1.042	2.836 (1.426–5.642)	0.003	1.181	3.259 (1.338–7.939)	0.009
Prior cerebrovascular disease	0.642	1.901 (1.267–2.851)	0.002	0.682	1.977 (1.160–3.370)	0.012
Aortic disease	0.868	2.382 (1.512–3.754)	0.000	0.700	2.014 (1.055–3.848)	0.034
Dyslipidemia	−0.695	0.499 (0.328–0.759)	0.001	–	–	–
Age	0.082	1.085 (1.033–1.140)	0.001	–	–	–
BMI	−0.161	0.852 (0.796–0.910)	0.000	–	–	–
Hemoglobin	−0.284	0.753 (0.678–0.835)	0.000	–	–	–
Mets-like risk accumulation	−2.622	0.073 (0.010–0.521)	0.009	–	–	–
Complete revascularization	−0.658	0.518 (0.320–0.838)	0.007	–	–	–
Use of statins	−0.688	0.503 (0.281–0.898)	0.020	–	–	–

*The same variables listed in the footnote of Table 3 were used for the Cox proportional hazard model, except DBP <60 mmHg was included instead of DBP <70 mmHg. Only the significant variables with P<0.05 are presented. †The significant variables on the univariate analyses were used for multivariate stepwise Cox proportional hazard model. Abbreviations as in Tables 1–3.

death in revascularized CAD patients differently among the age groups. In the Young group, the risk of cardiovascular death did not increase at least until DBP reached 60 mmHg (Table 2). It might be expected that the Old-Old group would be more susceptible to a low DBP than the Young-Old group, as cardiovascular risk is considered higher in older patients because of the greater incidence of advanced atherosclerosis and organ damage,[12,14] and the incidence of low DBP was higher in the Old-Old group than in the Young-Old group (Figure S1B). However, this was not the case, because the cut-off DBP below which increased cardiovascular death was 60 mmHg in the Old-Old group but it was 70 mmHg in the Young-Old group (Table 2, Figure 3). This is consistent with the epidemiological finding that the cut-off level of low DBP to increase cardiovascular events was 60 mmHg in cardiovascular disease patients older than 70 years.[19]

The present study investigated for the first time in detail the predictive factors for cardiovascular death in elderly revascularized CAD patients with low DBP. In the Young-Old group, low CCr, prior cerebrovascular disease, and aortic disease were the independent factors for predicting cardiovascular death in low DBP patients (Table 3). These factors were also the common predictors among the low DBP patients and all patients of the Young-Old group. In the low DBP patients of the Old-Old group, the independent predictors were low CCr and malignancy (Table 4). The common predictor among the low DBP patients and all patients was low CCr in the Old-Old group. It is interesting to note that low CCr was the common predictor for cardiovascular death in the low DBP patients of the Young-Old and Old-Old groups. Accordingly, renal dysfunction, coexisting cardiovascular disease, and poor general condition rather than low DBP itself were important factors of cardiovascular death in the low DBP patients of the Young-Old and Old-Old groups.

The most important finding of this study was that, after adjustments with other independent predictors, DBP <60 mmHg was not an independent factor for predicting cardiovascular death in the Old-Old group, whereas DBP <70 mmHg was a

Table 5. Adjusted HRs for Cardiovascular Death in Low DBP Patients of the Young-Old and Old-Old Groups of CAD Patients

	Unadjusted		Adjusted					
			Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Young-Old group								
DBP ≥70 mmHg	1.000 (Reference)	–	1.000 (Reference)	–	1.000 (Reference)	–	1.000 (Reference)	–
DBP <70 mmHg	2.190 (1.502–3.194)	0.000	2.256 (1.544–3.295)	0.000	1.665 (1.094–2.532)	0.017	1.720 (1.165–2.540)	0.013
Old-Old group								
DBP ≥60 mmHg	1.000 (Reference)	–	1.000 (Reference)	–	1.000 (Reference)	–	1.000 (Reference)	–
DBP <60 mmHg	1.776 (1.101–2.864)	0.019	1.694 (1.049–2.738)	0.031	1.579 (0.944–2.642)	0.082	1.527 (0.939–2.483)	0.088

Adjustments of HRs for cardiovascular death in patients with low DBP were performed using Model 1 (age and male sex), Model 2 (model 1 plus the independent predictors on multivariate stepwise regression analysis among all patients), and Model 3 (model 1 plus the independent predictors on multivariate stepwise regression analysis among low DBP patients) of each age group. In the Young-Old group, Model 2 included age, male sex, CCr, prior cerebrovascular disease, aortic disease, pulse pressure, LV dysfunction, and use of statins (Table 3A), and Model 3 included age, male sex, CCr, prior cerebrovascular disease, and aortic disease (Table 3B). In the Old-Old group, Model 2 included age, male sex, CCr, prior HF, prior cerebrovascular disease, LV dysfunction, and coronary lesions after revascularization (Table 4A), and Model 2 included age, male sex, CCr, and malignancy (Table 4B). Abbreviations as in Tables 1–3.

significant but marginal factor in the Young-Old group (Table 5). The INVEST post hoc analysis demonstrated that, after adjustments with comorbidities, there was no excessive increase in cardiovascular events down to a DBP of 50 mmHg in CAD patients with hypertension.[3] Taken together with the results of the present study, it is possible that low DBP itself may not be the major factor for increasing cardiovascular death in the low DBP patients with CAD. The so-called J-shaped curve phenomenon may be mainly "reverse causality".

The SHEP subanalysis showed that the relative risk for cardiovascular disease became significant for DBP <70 mmHg and started to approach a 2-fold increase in risk for DBP <55 mmHg in on-treatment elderly patients with isolated systolic hypertension.[20] The Syst-Eur subanalysis demonstrated that cardiovascular mortality was not increased in elderly patients with isolated systolic hypertension with or without antihypertensive treatment, at least until DBP reached 55 mmHg, whereas active treatment increased cardiovascular events only in CAD patients with DBP <65 mmHg.[21] Taken together with the present study's findings, BP-lowering therapy appears safe and useful even in elderly patients with isolated systolic hypertension and relatively low DBP, and that myocardial ischemia screening and, if needed, coronary revascularization are important for CAD patients to increase their tolerance to low DBP and to avoid cardiac events.

The details of the causes of cardiovascular death in the low DBP patients of the Young-Old and Old-Old groups remained undetermined in the present study. It was possible that HF might have been a major cause of death because nonfatal MI, nonfatal stroke, and sudden death were not increased in the patient populations (Figures 1,2). Furthermore, aortic disease was a possible cause of death in the Young-Old group because it was a potent independent predictor (Table 3). However, because death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified in this registry, this issue must be interpreted carefully. More specific definitions based on ICD codes would have been preferable on registration.

Study Limitations

The limitations of this study arise from it being a subanalysis of an observational cohort study. First, the CREDO-Kyoto registry cohort-1 did not include follow-up data on BP and medications. Second, the effects of revascularization on cardiac function and hemodynamic parameters were not available in the present study. Next, the institutions participating in this registry were specialized centers for CABG and PCI, so a potential patient selection bias may exist. Finally, a prospective, randomized, controlled trial with well-matched confounding factors is needed to determine whether excessively low DBP is actually a causal risk factor for increasing cardiovascular death in elderly CAD patients.

Conclusions

After adjustments with other independent predictors, DBP <60 mmHg was not a significant predictor of cardiovascular death in Old-Old revascularized CAD patients, whereas DBP <70 mmHg remained a significant but marginal predictor in Young-Old ones. Renal dysfunction, coexisting cardiovascular disease, and poor general condition were the independent predictors for cardiovascular death in elderly revascularized CAD patients with low DBP. The results suggested that low DBP itself is a risk marker, but may not be a major causative factor of cardiovascular death in elderly CAD patients, particularly in the old-old ones. Careful screening and aggressive management of residual myocardial ischemia and other cardiovascular and noncardiovascular comorbidities are needed for the management of elderly CAD patients with extremely low DBP.

Disclosures

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Supplementary Files

Supplementary File 1

Table S1. Cut-off levels of DBP below which nonfatal MI increased in CAD patients after revascularization

Table S2. Cut-off levels of DBP below which nonfatal stroke increased in CAD patients after revascularization

Table S3. Cut-off levels of DBP below which sudden death increased in CAD patients after revascularization

Figure S1. Systolic blood pressure (SBP) (**A**), diastolic blood pressure (DBP) (**B**), and prevalence of systolic/diastolic hypertension (HT) (SBP ≥140 and DBP ≥90 mmHg), isolated systolic HT (SBP ≥140 and DBP <90 mmHg), and isolated diastolic HT (SBP <140 and DBP ≥90 mmHg) in the Young (age ≤64 years), Young-Old (65–74 years), and Old-Old groups (≥75 years) of coronary artery disease patients.

Please find supplementary file(s);
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