Relationships Between Components of Blood Pressure and Cardiovascular Events in Patients with Stable Coronary Artery Disease and Hypertension

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Abstract—Observational studies have shown a J-shaped relationship between diastolic blood pressure (BP) and cardiovascular events in hypertensive patients with coronary artery disease. We investigated whether the increased risk associated with low diastolic BP reflects elevated pulse pressure (PP). In 22 672 hypertensive patients with coronary artery disease from the CLARIFY registry (Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease), followed for a median of 5.0 years, BP was measured annually and averaged. The relationships between PP and diastolic BP, alone or combined, and the primary composite outcome (cardiovascular death or myocardial infarction) were analyzed using multivariable Cox proportional hazards models. Adjusted hazard ratios for the primary outcome were 1.62 (95% confidence interval [CI], 1.40–1.87), 1.00 (ref), 1.07 (95% CI, 0.94–1.21), 1.54 (95% CI, 1.32–1.79), and 2.34 (95% CI, 1.95–2.81) for PP<45, 45 to 54 (reference), 55 to 64, 65 to 74, and ≥75 mm Hg, respectively, and 1.50 (95% CI, 1.31–1.72), 1.00 (reference), and 1.58 (95% CI, 1.42–1.77) for diastolic BPs of <70, 70 to 79 (ref), and ≥80 mm Hg, respectively. In a cross-classification analysis between diastolic BP and PP, the relationship between diastolic BP and the primary outcome remained J-shaped when the analysis was restricted to patients with the lowest-risk PP (45–64 mm Hg), with adjusted hazard ratios of 1.53 (95% CI, 1.27–1.83), 1.00 (ref), and 1.54 (95% CI, 1.34–1.75) in the <70, 70 to 79 (reference), and ≥80 mm Hg subgroups, respectively. The J-shaped relationship between diastolic BP and cardiovascular events in hypertensive patients with coronary artery disease persists in patients within the lowest-risk PP range and is therefore unlikely to be solely the consequence of an increased PP reflecting advanced vascular disease.

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Elevated blood pressure (BP) is a well-established risk factor for cardiovascular events, and lowering elevated BP has been demonstrated to reduce risk.[1,2] However, post hoc analyses of randomized controlled trials[3,4] and observational studies[5,6] have shown that—in hypertensive patients with coronary artery disease (CAD)—the relationship between BP and cardiovascular events is J-shaped, particularly for diastolic BP, with an increased risk of cardiovascular events (except stroke) among patients with diastolic BP <70 mm Hg.

The increased cardiovascular risk observed at low diastolic BP may be a direct consequence of altered myocardial perfusion.[6–8] However, a causal link between low diastolic BP and cardiovascular events has not been demonstrated in randomized controlled trials. Rather, such trials have shown no benefit[9,10] or a decreased risk[11] in the lowest BP groups, although it should be borne in mind that the mean BP in the lowest BP subgroup was never below the inflection point of the J-curve when considering office BP levels, either measured or extrapolated.[12,13]

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Alternatively, the observed association may not be causal, but rather reflect reverse causality, whereby low diastolic BP would be an epiphenomenon of underlying poor health, itself leading to increased morbidity and mortality.[14,15] Although indirect evidence argues against reverse causality being the sole or major explanation for the J-curve,[5,14] irrefutable evidence will require future dedicated randomized interventional trials. Last, the association between low diastolic BP and cardiovascular events may be an epiphenomenon of increased pulse pressure (PP), itself a cardiovascular risk marker,[16–18] which is associated with diminished diastolic BP in patients with stiffened large arteries. Among 2207 patients from a hypertension control program, Madhavan et al[19] reported a J-shaped relation of diastolic BP to myocardial infarction that occurred only among patients with a PP>63 mm Hg. Similarly, Kannel et al[20] showed—in 7798 subjects from the Framingham study and offspring cohort—that the increased risk observed at low diastolic BP was confined to patients with increased systolic BP and, therefore, increased PP, whereas the relationship between diastolic BP and outcome remained linear among patients with systolic BP<140 mm Hg. More recently, Franklin et al[21] observed in 791 individual with a previous cardiovascular event from the Framingham study that a diastolic BP<70 mm Hg was associated with a greater risk than a diastolic BP of 70 to 79 mm Hg only in patients with PP≥68 mm Hg.

The purpose of this study was to explore whether the J-curve observed for diastolic BP is restricted to patients with concomitant high systolic BP or PP, or whether it persists for patients with systolic BP and PP values within the lowest-risk range. We assessed the relationship between PP or diastolic BP and cardiovascular outcomes in a population of CAD patients treated for hypertension from the CLARIFY registry (Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease). We then performed cross-classifications to assess the relationship between diastolic BP and outcomes, stratified by PP or systolic BP subgroup.

Methods

Details of the CLARIFY registry have been reported.[5,22] Briefly, 32 703 outpatients with stable CAD were recruited in 45 countries between November 2009 and June 2010. Exclusion criteria were hospital admission for cardiovascular reasons in the past 3 months, planned revascularization, or any health condition compromising 5-year follow-up, including severe other cardiovascular diseases (eg, advanced heart failure, severe valve disease, or history of valve repair or replacement). Patients received standard clinical care; enrollment did not mandate any specific treatment or procedure.

Data were collected using standardized electronic case report forms at baseline and at every yearly visit for up to 5 years. At each yearly visit, symptoms, clinical examination, results of the main clinical and biological tests, treatment, and clinical outcomes were recorded; office BP was measured in seated subjects after a rest of 5 minutes, using the same arm throughout the study, with no prespecified device.

This analysis was restricted to patients treated for hypertension (Figure S1 in the online-only Data Supplement), defined by treated hypertension on the baseline form and the use of at least 1 antihypertensive drug.

The study was performed in accordance with the Declaration of Helsinki. Local ethical approval was obtained in all countries. All patients gave written informed consent. This study is registered with clarify-registry.com, number ISRCTN43070564.

BP Subgroups

PP was calculated as the difference between systolic BP and diastolic BP. Mean arterial pressure was calculated as diastolic BP+1/3 PP. Analyses were performed using the arithmetic mean of all BP values measured throughout follow-up, from the baseline visit to the visit before an event (the event depending on the outcome), or all available visits if no event occurred.

For the relationship between a single BP component and outcome, patients were categorized into 5 subgroups by 10-mm Hg increments, from <45 to ≥75 mm Hg for PP (with the 45–54-mm Hg subgroup as the reference), and from <60 to ≥90 mm Hg for diastolic BP (with the 70–79-mm Hg subgroup as the reference).

For cross-classification analyses, each BP component was divided in 3 subgroups, defined from the relationship with the primary outcome, using the thresholds below and above which event rates increased compared with the reference group: <70, 70 to 79 (reference), and ≥80 mm Hg for diastolic BP, <45, 45 to 64 (reference), and ≥65 mm Hg for PP, and <120, 120 to 139 (reference), and ≥140 mm Hg for systolic BP. For systolic BP, these thresholds were defined from the previously established relationship between systolic BP and cardiovascular events in this population.[5] In the cross-classification analyses, patients were further categorized into 1 of 9 groups using the combination of the 3-level diastolic BP groupings and the 3-level PP or systolic BP groupings.

Study Outcomes

The primary outcome was the composite of cardiovascular death or myocardial infarction. Secondary outcomes included cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. For patients with multiple events, the time to the first applicable event was considered in each analysis.

Statistical Analyses

Baseline characteristics are summarized according to the average PP categories before a primary outcome. Continuous variables are presented as mean±SD or medians (interquartile ranges), depending on the distribution of the data; categorical data are presented as numbers and percentages. Comparisons between the average PP categories were made using either 1-way ANOVA or the Kruskal–Wallis test for continuous data, depending on the distribution of the data, or the χ^2 test for categorical data.

Cox proportional hazards models, both adjusted and unadjusted, were used to evaluate the relationship between BP categories (either for a single BP component or for combined BP components) and outcomes.

Covariates used for multivariable adjustment were selected a priori as potential confounders and included (model 1) age, sex, geographic region, smoking status, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, diabetes mellitus, low- and high-density lipoprotein cholesterol levels, body mass index, glomerular filtration rate, peripheral artery disease, hospitalization for or symptoms of heart failure, left ventricular ejection fraction, ethnicity, stroke, transient ischemic attack, and baseline medications (aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, calcium channel blockers, diuretics, and other antihypertensive medications).

Analyses performed on PP as a single BP component were also adjusted for mean arterial pressure in a separate model. Analyses performed on diastolic BP as a single BP component were also adjusted for PP in a separate model.

No imputation was performed for missing data. Covariates with a large amount of missing data were categorized, including a category for missing data to minimize the loss of data in the analysis.

The relationship between PP subgroups and all outcomes was further assessed after excluding patients with heart failure, as defined by previous hospitalization for heart failure, symptoms of heart failure (then excluded from covariates), or a left ventricular ejection fraction <45%.

The models were further adjusted by including an interaction term between diastolic BP category and PP category or systolic BP category to determine whether any observed relationship was consistent across PP and systolic BP subgroups, respectively.

In the event of significant interactions with diastolic BP, the relationship of diastolic BP and outcome was further examined in the relevant PP or systolic BP subgroups.

Statistical analyses were performed using SAS (version 9.3). A *P* value <0.05 was used to signify statistical significance using 2-sided testing with no correction for multiple comparisons.

Results

Baseline characteristics of the patients in the total population (22672 patients with CAD and hypertension) and by subgroups of PP are reported in Table 1 and Table S1 (baseline medications). Mean age was 65.2±10.0 years, 17019 (75.1%) were men, and 7591 (33.5%) had diabetes mellitus. Mean systolic BP was 133.7±16.7 mm Hg, mean diastolic BP was 78.2±10.1 mm Hg, and mean PP was 55.4±14.0 mm Hg. Compared with patients with low PP, those with higher PP tended to be older, more likely to be women, have diabetes mellitus, be nonsmokers, less likely to have had a myocardial infarction or percutaneous coronary intervention, had less symptoms of heart failure, and had a higher prevalence of stroke. Baseline characteristics of the patients by subgroups of systolic and diastolic BP have been reported.[5]

Pulse Pressure

After a median (interquartile range) follow-up of 5.0 (4.5–5.1) years, the primary outcome had occurred in 1746 patients (7.7%). Cardiovascular death occurred in 1209 patients (5.3%), myocardial infarction (fatal/nonfatal) in 827 (3.6%), stroke (fatal/nonfatal) in 526 (2.3%), and hospital admission for heart failure in 1306 (5.8%). Event rates and adjusted hazard ratios

Table 1. Demographic and Baseline Characteristics of the Patients, for the Total Population and Each Average On-Treatment PP Subgroup

Parameter	n	Total Population (n=22672)	Average PP Categories					*P* Value
			<45 mm Hg (n=3088)	45–54 mm Hg (n=9013)	55–64 mm Hg (n=6907)	65–74 mm Hg (n=2611)	≥75 mm Hg (n=1053)	
Age, y	22666	65.2±10.0	61.0±10.3	63.4±9.8	66.9±9.4	69.2±8.7	71.5±8.6	<0.0001
Male	22672	17019 (75.1)	2505 (81.1)	6974 (77.4)	5070 (73.4)	1826 (69.9)	644 (61.2)	<0.0001
BMI, kg/m^2	22654	27.7 (25.2–30.9)	27.2 (24.7–30.1)	27.8 (25.4–30.9)	27.8 (25.1–31.1)	27.8 (25.2–31.2)	27.6 (24.8–30.8)	<0.0001
Diabetes mellitus	22670	7591 (33.5)	818 (26.5)	2750 (30.5)	2461 (35.6)	1089 (41.7)	473 (44.9)	<0.0001
Smoking status	22672							<0.0001
Current		2569 (11.3)	478 (15.5)	1100 (12.2)	683 (9.9)	234 (9.0)	74 (7.0)	
Former		10158 (44.8)	1404 (45.5)	4104 (45.5)	3044 (44.1)	1131 (43.3)	475 (45.1)	
Never		9945 (43.9)	1206 (39.1)	3809 (42.3)	3180 (46.0)	1246 (47.7)	504 (47.9)	
PP, mm Hg	22658	55.4±14.0	40.7±7.5	50.3±8.8	59.7±10.2	68.5±12.0	82.3±14.6	…
SBP, mm Hg	22659	133.7±16.7	118.6±11.8	129.3±12.8	137.8±14.2	145.9±16.0	158.1±18.4	…
DBP, mm Hg	22659	78.2±10.1	77.9±9.2	79.0±9.6	78.1±10.2	77.4±11.4	75.8±12.1	…
Heart rate, bpm	22660	68.5±10.6	68.7±10.4	68.6±10.4	68.6±10.7	68.0±11.5	67.0±11.1	<0.0001
Myocardial infarction	22670	13258 (58.5)	2081 (67.4)	5542 (61.5)	3785 (54.8)	1341 (51.4)	509 (48.3)	<0.0001
PCI	22670	12962 (57.2)	1863 (60.3)	5182 (57.5)	3930 (56.9)	1441 (55.2)	546 (51.9)	<0.0001
CABG	22670	5691 (25.1)	695 (22.5)	2073 (23.0)	1804 (26.1)	770 (29.5)	349 (33.1)	<0.0001
TIA	22670	801 (3.5)	86 (2.8)	291 (3.2)	273 (4.0)	110 (4.2)	41 (3.9)	0.0047
Stroke	22670	1089 (4.8)	132 (4.3)	415 (4.6)	341 (4.9)	132 (5.1)	69 (6.6)	0.035
Hospitalization for HF	22670	1211 (5.3)	202 (6.5)	445 (4.9)	343 (5.0)	158 (6.1)	63 (6.0)	0.0019
LVEF, %	15969	56.1±11.0	54.2±12.1	55.9±10.8	56.6±10.6	57.1±10.9	57.8±10.9	<0.0001
HbA1C, %	6173	6.9±1.8	6.7±1.4	6.8±1.7	6.9±1.4	7.0±1.5	7.4±4.2	<0.0001
Creatinine, µmol/L	17165	88 (76–104)	88 (77–103)	88 (76–102)	88 (76–103)	88 (75–106)	90 (76–110)	0.0010
HDL-cholesterol, mmol/L	16054	1.1 (1.0–1.4)	1.1 (0.9–1.3)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.1 (1.0–1.4)	<0.0001
LDL-cholesterol, mmol/L	15257	2.4 (1.9–3.0)	2.3 (1.8–2.9)	2.4 (1.9–3.0)	2.4 (1.9–2.9)	2.3 (1.8–2.8)	2.4 (1.9–3.0)	<0.0001
Fasting triglycerides, mmol/L	16806	1.4 (1.0–2.0)	1.4 (1.0–2.0)	1.5 (1.1–2.0)	1.4 (1.0–1.9)	1.4 (1.0–2.0)	1.4 (1.0–1.9)	0.0018

Values are mean±SD, n (%), or median (IQR). BMI indicates body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PP, pulse pressure; SBP, systolic blood pressure; and TIA, transient ischemic attack.

(HRs) for PP subgroups are indicated in Table 2. The relationship between average PP and crude and adjusted risk of the primary outcome followed a J-shaped curve. A similar J-shaped relationship was found for cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure (Table 2). The increased risk for elevated PP was more pronounced for myocardial infarction than for the other outcomes with progressively increasing HRs as average PP increased. Similar results were found after exclusion of patients with heart failure, except for lost and attenuated associations of elevated PP with stroke and hospitalization for heart failure, respectively (Table 2).

Diastolic BP

As demonstrated previously for cardiovascular death, myocardial infarction, and hospitalization for heart failure, but not for stroke,[5] the relationship between average diastolic BP and the primary composite outcome was J-shaped, even after multiple adjustments for potential confounders. A similar J-shaped pattern was seen after further adjusting for PP (Figure S2).

Diastolic BP Cross-Classified With PP

Diastolic BP, categorized in the 3 subgroups used for cross-classifications, had similar relationships to cardiovascular events as when categorized in 5 subgroups, namely J-shaped for all end points but stroke (Table S2). Event rates and HRs for the 9 BP subgroups defined by cross-classifications between diastolic BP and PP are shown in the Figure 1 (primary outcome) and Table 3 (secondary outcomes). The J-shaped relationship observed between diastolic BP and all end points but stroke remained, with very similar patterns, in patients with a PP within the lowest-risk range (45–64 mm Hg).

Interactions between PP categories and diastolic BP categories were significant for the primary outcome and cardiovascular death, but nonsignificant for myocardial infarction, stroke, and hospitalization for heart failure (Table S3). Analyses by PP subgroup in case of a significant interaction are shown in Table S4. The significant interaction for the primary outcome and cardiovascular death revealed a steeper J-curve, with an even

Table 2. Event Rates and Adjusted Hazard Ratios for PP Subgroups

Parameter	HR (95% CI) for Average PP Subgroups					*P* Value
	<45 mm Hg	45–54 mm Hg	55–64 mm Hg	65–74 mm Hg	≥75 mm Hg	
Cardiovascular death or myocardial infarction (primary composite outcome)						
Event rate, %	9.3	6.0	6.8	10.4	16.3	<0.0001
HR (model 1)	1.62 (1.40–1.87)	1.00	1.07 (0.94–1.21)	1.54 (1.32–1.79)	2.34 (1.95–2.81)	<0.0001
HR (model 2)	1.62 (1.40–1.88)	1.00	1.07 (0.94–1.21)	1.54 (1.31–1.79)	2.33 (1.92–2.83)	<0.0001
Excluding HF	1.63 (1.33–2.00)	1.00	0.99 (0.84–1.17)	1.38 (1.14–1.69)	2.15 (1.70–2.73)	<0.0001
Cardiovascular death						
Event rate, %	7.0	4.0	4.6	7.4	11.7	<0.0001
HR (model 1)	1.80 (1.51–2.13)	1.00	1.02 (0.87–1.19)	1.48 (1.24–1.78)	2.20 (1.77–2.74)	<0.0001
HR (model 2)	1.79 (1.50–2.13)	1.00	1.02 (0.87–1.19)	1.49 (1.24–1.80)	2.23 (1.77–2.80)	<0.0001
Excluding HF	1.90 (1.48–2.44)	1.00	0.94 (0.77–1.16)	1.40 (1.10–1.79)	2.04 (1.52–2.73)	<0.0001
Myocardial infarction						
Event rate, %	3.9	2.9	3.4	4.9	7.8	<0.0001
HR (model 1)	1.39 (1.12–1.73)	1.00	1.25 (1.04–1.50)	1.81 (1.45–2.25)	2.94 (2.25–3.83)	<0.0001
HR (model 2)	1.42 (1.14–1.78)	1.00	1.23 (1.02–1.47)	1.74 (1.39–2.20)	2.79 (2.10–3.69)	<0.0001
Excluding HF	1.41 (1.06–1.88)	1.00	1.18 (0.95–1.48)	1.55 (1.18–2.04)	2.32 (1.65–3.25)	<0.0001
Stroke						
Event rate, %	2.1	1.9	2.2	3.3	4.4	<0.0001
HR (model 1)	1.26 (0.94–1.68)	1.00	1.06 (0.85–1.32)	1.56 (1.20–2.04)	1.98 (1.41–2.80)	0.0001
HR (model 2)	1.39 (1.04–1.86)	1.00	0.98 (0.78–1.23)	1.35 (1.03–1.79)	1.56 (1.09–2.25)	0.0044
Excluding HF	1.55 (1.09–2.21)	1.00	0.78 (0.59–1.03)	1.06 (0.76–1.49)	1.24 (0.81–1.91)	0.0032
Hospitalization for HF						
Event rate, %	7.7	5.3	5.4	6.5	8.6	<0.0001
HR (model 1)	1.47 (1.25–1.73)	1.00	1.17 (1.02–1.35)	1.40 (1.16–1.68)	2.08 (1.63–2.65)	<0.0001
HR (model 2)	1.56 (1.32–1.83)	1.00	1.12 (0.97–1.29)	1.27 (1.05–1.54)	1.82 (1.41–2.35)	<0.0001
Excluding HF	1.51 (1.11–2.06)	1.00	0.98 (0.78–1.25)	0.92 (0.66–1.29)	1.65 (1.13–2.41)	0.0019

Model 1, see Methods. Model 2, additional adjustment for mean arterial pressure. CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and PP, pulse pressure.

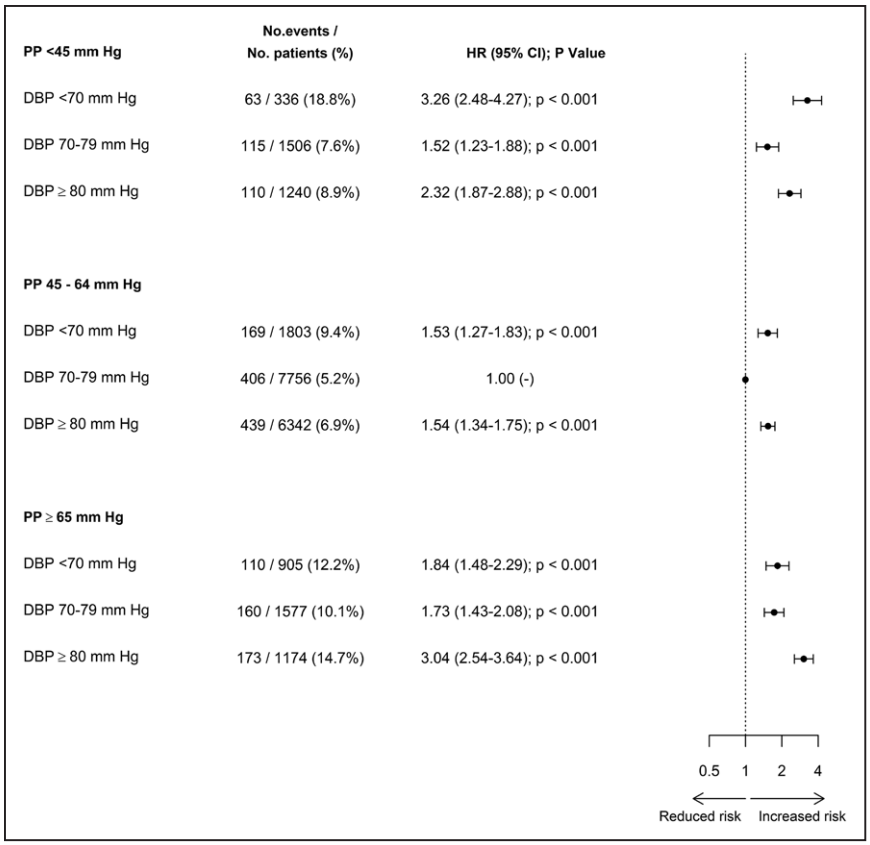

Figure 1. Forest plots of adjusted hazard ratios (HRs) for the primary outcome (cardiovascular death or myocardial infarction) for diastolic blood pressure (DBP) subgroups cross-classified with pulse pressure (PP) subgroups. Analyses are adjusted as defined for model 1. CI indicates confidence interval.

greater risk associated with low diastolic BP (<70 mm Hg) in patients with PP<45 mm Hg. Conversely, in patients with PP≥65 mm Hg, there was no increase in the risk of cardiovascular events in patients with diastolic BP<70 versus 70 to 79 mm Hg. The nonsignificant interaction for other end points showed that the relationship between diastolic BP and cardiovascular events was consistent across PP subgroups. Mean BPs in each subgroup are shown in Table S5.

Diastolic BP Cross-Classified With Systolic BP

Crude and adjusted HRs between BP subgroups, defined by cross-classifications between diastolic BP and systolic BP categories, are indicated in Figure 2 (primary end point) and Table 3 (secondary end points). The J-shaped relationship observed between diastolic BP and cardiovascular events remained when restricting the analysis to patients with systolic BP in the lowest-risk range of 120 to 139 mm Hg. Interaction between diastolic BP and systolic BP was nonsignificant for most end points (Table S3), hence the relationship between diastolic BP and outcome was consistent across systolic BP subgroups. In the case of hospitalization for heart failure, there was a significant interaction between diastolic BP and systolic BP (P=0.0199), and the risk associated with a low diastolic BP increased as systolic BP increased (Table S4). Mean BP values in each subgroup are indicated in Table S5.

Discussion

This large international study evaluated the cardiovascular risk associated with single or combined components of BP in 22 672 patients with CAD treated for hypertension to decipher the underlying mechanisms of the J-shaped relationship observed between diastolic BP and cardiovascular events (except stroke) in this population. Even though elevated PP was strongly associated with all cardiovascular end points, this phenomenon did not account for the increased risk observed at low diastolic BP. Indeed, the J-shaped relationship between diastolic BP and cardiovascular outcomes (primary end point and all secondary end points but stroke) persisted in patients with PP or systolic BP in the lowest-risk range (45–64 and 120–139 mm Hg, respectively).

In this large population of patients with CAD treated for hypertension and followed according to routine clinical practice, elevated PP was associated with an increased risk of all outcomes, even after adjustment for multiple covariates, including mean arterial pressure, confirming previous studies conducted in various populations that have shown that PP is an independent cardiovascular risk marker.[16–18] PP is an indicator of left ventricle ejection volume and velocity and viscoelastic properties of large arteries. Therefore, elevated PP is correlated with vascular aging, both through a weakened Windkessel effect and an increased pulse wave velocity, with an earlier reflection wave increasing systolic BP and reducing diastolic BP. Furthermore, by definition, as PP increases for a given mean arterial pressure, systolic BP—and thus the afterload of the left ventricle—increases, and diastolic BP—and thus myocardial perfusion—decreases, both factors also potentially accounting for the increased risk associated with high PP. However, whether reducing PP reduces cardiovascular risk has not yet been established, unlike the clear beneficial effect of reducing elevated systolic BP.[1,23,24]

In addition to the increased risk associated with elevated PP, we also found an increased risk associated with low PP

Table 3. Cross-Classifications Analysis: Event Rates and Adjusted Hazard Ratios for Secondary Outcomes

		Diastolic BP Subgroups				Diastolic BP Subgroups		
	PP	<70 mm Hg	70–79 mm Hg	≥80 mm Hg	Systolic BP	<70 mm Hg	70–79 mm Hg	≥80 mm Hg
Cardiovascular death								
n/N	<45 mm Hg	50/332	84/1509	81/1230	<120 mm Hg	121/1073	93/1472	13/148
Event rate, %		15.1	5.6	6.6		11.3	6.3	8.8
HR (95% CI)		3.49 (2.56–4.77)	1.64 (1.27–2.10)	2.80 (2.17–3.61)		2.51 (2.02–3.14)	1.77 (1.39–2.26)	4.08 (2.32–7.15)
n/N	45–64 mm Hg	126/1807	278/7805	275/6318	120–139 mm Hg	105/1671	270/7826	218/5101
Event rate, %		7.0	3.6	4.4		6.3	3.5	4.3
HR (95% CI)		1.55 (1.25–1.93)	1.00 (–)	1.52 (1.28–1.81)		1.43 (1.14–1.81)	1.00 (–)	1.59 (1.32–1.91)
n/N	≥65 mm Hg	81/913	113/1581	120/1144	≥140 mm Hg	31/308	112/1597	245/3443
Event rate, %		8.9	7.1	10.5		10.1	7.0	7.1
HR (95% CI)		1.77 (1.37–2.29)	1.67 (1.34–2.09)	3.10 (2.49–3.84)		1.85 (1.26–2.71)	1.72 (1.37–2.14)	2.43 (2.04–2.90)
Myocardial infarction								
n/N	<45 mm Hg	23/338	49/1504	49/1242	<120 mm Hg	61/1075	48/1464	6/149
Event rate, %		6.8	3.3	3.9		5.7	3.3	4.0
HR (95% CI)		2.75 (1.77–4.27)	1.37 (0.99–1.88)	1.91 (1.38–2.64)		2.06 (1.54–2.77)	1.28 (0.93–1.76)	2.13 (0.94–4.83)
n/N	45–64 mm Hg	76/1803	185/7755	234/6341	120–139 mm Hg	74/1665	195/7783	162/5108
Event rate, %		4.2	2.4	3.7		4.4	2.5	3.2
HR (95% CI)		1.61 (1.23–2.12)	1.00 (–)	1.68 (1.38–2.05)		1.62 (1.23–2.14)	1.00 (–)	1.38 (1.12–1.71)
n/N	≥65 mm Hg	49/905	77/1577	84/1174	≥140 mm Hg	13/306	68/1589	199/3500
Event rate, %		5.4	4.9	7.2		4.2	4.3	5.7
HR (95% CI)		2.07 (1.49–2.87)	2.03 (1.55–2.66)	3.46 (2.66–4.49)		1.41 (0.80–2.50)	1.69 (1.28–2.23)	2.60 (2.12–3.18)
Stroke								
n/N	<45 mm Hg	11/339	25/1508	29/1245	<120 mm Hg	26/1076	26/1469	1/147
Event rate, %		3.2	1.7	2.3		2.4	1.8	0.7
HR (95% CI)		2.17 (1.16–4.05)	1.22 (0.79–1.89)	2.10 (1.39–3.18)		1.38 (0.90–2.11)	1.19 (0.78–1.82)	0.67 (0.09–4.83)
n/N	45–64 mm Hg	43/1804	127/7761	157/6327	120–139 mm Hg	46/1669	131/7789	108/5109
Event rate, %		2.4	1.6	2.5		2.8	1.7	2.1
HR (95% CI)		1.32 (0.93–1.87)	1.00 (–)	1.77 (1.39–2.26)		1.42 (1.01–2.01)	1.00 (–)	1.53 (1.17–1.98)
n/N	≥65 mm Hg	31/912	55/1588	47/1155	≥140 mm Hg	13/310	50/1599	124/3471
Event rate, %		3.4	3.5	4.1		4.2	3.1	3.6
HR (95% CI)		1.66 (1.11–2.49)	1.93 (1.40–2.66)	2.82 (2.01–3.95)		1.80 (1.01–3.22)	1.74 (1.25–2.42)	2.47 (1.92–3.18)
Hospitalization for heart failure								
n/N	<45 mm Hg	28/299	79/1444	121/1200	<120 mm Hg	84/1016	87/1408	16/135
Event rate, %		9.4	5.5	10.1		8.3	6.2	11.9
HR (95% CI)		2.07 (1.39–3.07)	1.40 (1.09–1.81)	2.52 (2.02–3.14)		2.12 (1.65–2.72)	1.47 (1.15–1.88)	4.67 (2.80–7.79)
n/N	45–64 mm Hg	109/1754	274/7576	444/6105	120–139 mm Hg	86/1618	265/7590	302/4915
Event rate, %		6.2	3.6	7.3		5.3	3.5	6.1
HR (95% CI)		1.82 (1.45–2.29)	1.00 (–)	1.66 (1.42–1.94)		1.68 (1.31–2.15)	1.00 (–)	1.43 (1.21–1.70)
n/N	≥65 mm Hg	55/874	77/1539	118/1120	≥140 mm Hg	22/293	78/1561	365/3375
Event rate, %		6.3	5.0	10.5		7.5	5.0	10.8
HR (95% CI)		1.89 (1.40–2.55)	1.41 (1.09–1.83)	2.63 (2.11–3.28)		2.38 (1.53–3.71)	1.45 (1.12–1.87)	2.60 (2.21–3.07)

Covariates at those indicated for model 1. BP indicates blood pressure; CI, confidence interval; HR, hazard ratio; N, number of patients; and PP, pulse pressure.

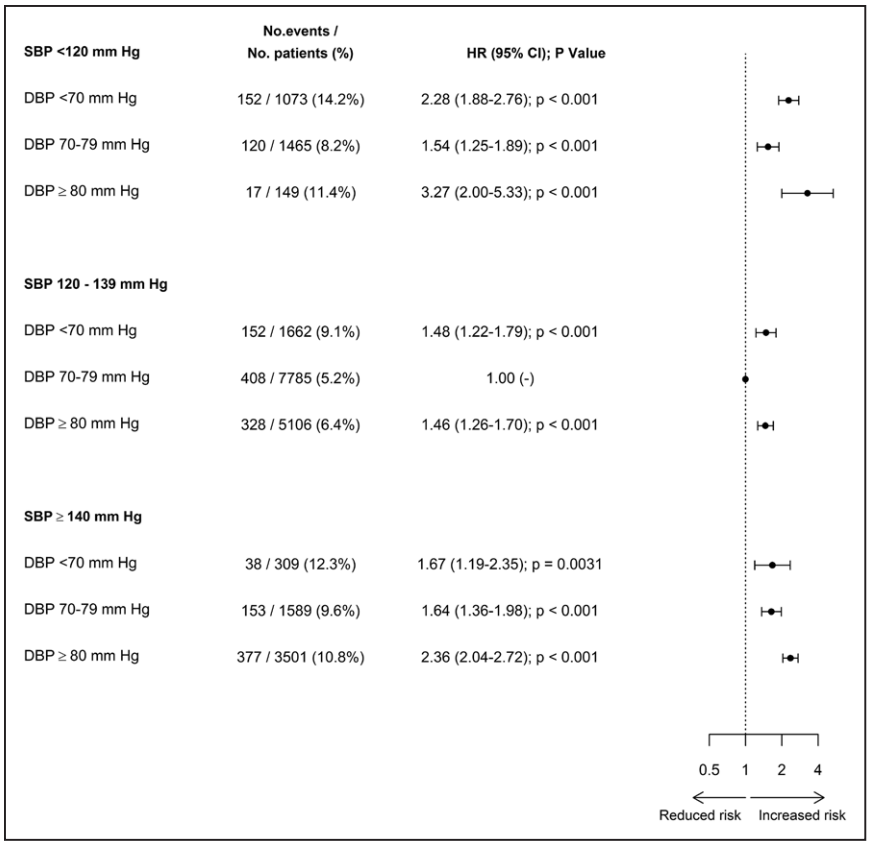

Figure 2. Forest plots of adjusted hazard ratios (HRs) for the primary outcome (cardiovascular death or myocardial infarction) for diastolic blood pressure (DBP) subgroups cross-classified with systolic blood pressure (SBP) subgroups. Analyses are adjusted as defined for model 1. CI indicates confidence interval.

(<45 mm Hg). Such a J-shaped pattern for the link between PP and the rate of cardiovascular events had not been shown in all previous studies.[16,25] However, in a post hoc analysis of the INVEST trial,[18] which included 22 576 CAD patients with hypertension, the relationship between PP and cardiovascular death and myocardial infarction was J-shaped, with an increased risk below a nadir value of 54 mm Hg (95% confidence interval, 42–60 mm Hg), in line with our results. In addition, in one of the largest studies examining the risk associated with PP, conducted in the REACH registry (45 087 high-risk subjects), we recently showed that not only was elevated PP associated with multiple adverse cardiovascular outcomes, but patients in the first quartile of PP (<50 mm Hg) also displayed an increased risk of cardiovascular death.[17] Reverse causality, associated with low stroke volume,[26] may at least in part explain this phenomenon. However, patients with severe aortic stenosis were excluded from the study, this association persisted after multiple adjustments for confounding factors and in a sensitivity analysis excluding patients with heart failure. Alternatively, the increased risk observed for low PP, which was highest in the lower end of the BP spectrum, may be driven by the possibly additive risks of low diastolic BP (compromising myocardial perfusion) combined with low mean arterial pressure (compromising perfusion of all other organs). Because the relationship between PP and the primary outcome was J-shaped in our study population, we divided PP in 3 subgroups for cross-classifications, the middle subgroup being that associated with the lowest risk (45–65 mm Hg).

The increased risk associated with elevated PP has led many authors to hypothesize that the J-shaped relation to cardiovascular risk associated with diastolic BP largely reflects increased PP, an indicator of advanced vascular disease and stiffened large arteries.[16,27–29] However, our results do not confirm previous studies, which had suggested that the increased risk associated with low diastolic BP was restricted to patients with increased PP[19,21] or increased systolic BP.[20] Importantly, these studies were conducted in much smaller cohorts, and did not specifically include patients with CAD. We showed that, even in patients within the lowest-risk range of PP or systolic BP, the J-shaped relationship between diastolic BP and cardiovascular events remained, which strongly argues against increased PP being the sole explanation for the increased risk observed at low diastolic BP. Similarly, the J-curve relationship between diastolic BP and the primary outcome persisted after adjustment for PP, as shown previously in 10 001 patients with CAD enrolled in the TNT trial (Treating to New Targets).[4] In line with our results, in a cohort of 331 frail elderly patients, Protogerou et al[30] had found that a diastolic BP ≤60 mm Hg was associated with increased mortality during a 2-year follow-up, independently of large artery stiffness as measured by pulse wave analysis.

Not only was the J-shaped relationship between diastolic BP and cardiovascular events not restricted to patients with increased PP, it was actually attenuated as PP increased, at least for the primary outcome and cardiovascular death, for which the interaction between diastolic BP and PP was significant. The increased risk observed at low values of diastolic BP was highest when accompanied by a low PP, as discussed above. Conversely, in patients with elevated PP (≥65 mm Hg), the risk was higher than in patients with intermediate levels of PP, but there was no further increase in the risk when diastolic

BP was <70 mm Hg. A likely explanation for that is that in this subgroup (PP≥65 mm Hg and diastolic BP<70 mm Hg), although the lower diastolic BP is expected to be deleterious, this may be compensated by the lower systolic BP accompanying these lower diastolic BP values (138 mm Hg in the lowest diastolic BP subgroup versus 147 mm Hg in the 70–79-mm Hg subgroup), itself clearly beneficial.

The main limitation of our study is that it is an observational registry, and we cannot therefore draw conclusions on whether associations between single or combined components of BP and cardiovascular risk are causal or would be reversed by interventions to diminish PP or increase low diastolic BP. Our results suggest that low myocardial perfusion may be a more likely explanation for the J-curve than increased vascular aging associated with high PP and low diastolic BP, but do not demonstrate that it is the sole or major mechanism, nor rule out some reverse causality. Assumptions based on observational studies are the basis for future randomized trials to define optimal BP targets. Among other limitations of our study, our results were obtained in hypertensive patients with stable CAD free from other severe conditions, and cannot be extrapolated to healthier hypertensive subjects, or to elderly frail patients. Similarly, these data should not be extrapolated to nonhypertensive patients with CAD, who are commonly treated with BP-lowering drugs and in whom the potential deleterious effects of low BP remain to be studied. Finally, the CLARIFY registry reflects routine clinical practice, and although our results may have wider external validity than randomized trials, measurements of BP were less standardized and outcome identification possibly less accurate than in randomized trials.

Perspectives

Even though elevated PP is associated with increased cardiovascular risk and is closely intertwined with decreased diastolic pressure, it does not seem to be the major determinant of the increased risk associated with low diastolic BP in this large cohort of patients with CAD. A compromised myocardial perfusion associated with low diastolic BP in patients with CAD seems to be a more plausible explanation, although reverse causation cannot be ruled out.

Our data, although observational, suggest caution when lowering diastolic BP below 70 mm Hg, and even more so 60 mm Hg, in patients with CAD treated for hypertension. However, only randomized trials will provide irrefutable evidence for a causal link between low diastolic BP and adverse cardiovascular events. BP target trials comparing levels of achieved BP, especially levels of diastolic BP in patients with CAD, are needed to define optimal BP targets in this population.

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Novelty and Significance

What Is New?

- In this large population of patients with coronary artery disease and treated hypertension, we show for the first time that the J-shaped relationship between diastolic blood pressure (BP) and cardiovascular events persists in patients with the lowest-risk pulse pressure.

What Is Relevant?

- The increased risk observed at low diastolic BP is not an epiphenomenon of increased pulse pressure.
- Although reverse causality cannot be ruled out by our observational study, the alternative hypothesis of a compromised myocardial perfusion associated with low diastolic BP seems to be a likely explanation for the J-curve of diastolic BP.

Summary

In 22 672 hypertensive patients from the CLARIFY registry (Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease), the J-shaped relationship between diastolic BP and the primary outcome (cardiovascular death or myocardial infarction) remained in patients within the lowest-risk pulse pressure range (45–65 mm Hg), with adjusted hazard ratios of 1.53, 1.00, and 1.54 in the <70, 70 to 79 (reference), and ≥80 mm Hg diastolic BP subgroups, respectively.