JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 22, 2019

Impact of Pre-Procedural Blood Pressure on Long-Term Outcomes Following Percutaneous Coronary Intervention

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on behalf of the Melbourne Interventional Group Investigators

ABSTRACT

BACKGROUND High systolic blood pressure (SBP) increases cardiac afterload, whereas low diastolic blood pressure (DBP) may lead to impaired coronary perfusion. Thus, wide pulse pressure (high systolic, low diastolic [HSLD]) may contribute to myocardial ischemia and also be a predictor of adverse cardiovascular events.

OBJECTIVES The purpose of this study was to determine the relationship between pre-procedural blood pressure and long-term outcome following percutaneous coronary intervention (PCI).

METHODS The study included 10,876 consecutive patients between August 2009 and December 2016 from the Melbourne Interventional Group registry undergoing PCI with pre-procedural blood pressure recorded. Patients with ST-segment elevation myocardial infarction, cardiogenic shock, and out-of-hospital cardiac arrest were excluded. Patients were divided into 4 groups according to SBP (high ≥120 mm Hg, low <120 mm Hg) and DBP (high >70 mm Hg, low ≤70 mm Hg).

RESULTS Mean pulse pressure was 60 ± 21 mm Hg. Patients with HSLD were older and more frequently women, with higher rates of hypercholesterolemia, renal impairment, diabetes, and multivessel and left main disease (all $p \leq 0.0001$). There was no difference in 30-day major adverse cardiac events, but at 12 months the HSLD group had a greater incidence of myocardial infarction ($p = 0.018$) and stroke ($p = 0.013$). Long-term mortality was highest for HSLD (7.9%) and lowest for low systolic, high diastolic (narrow pulse pressure) at 2.1% ($p = 0.0002$). Cox regression analysis demonstrated significantly lower long-term mortality in the low systolic, high diastolic cohort (hazard ratio: 0.50; 99% confidence interval: 0.25 to 0.98; $p = 0.04$).

CONCLUSIONS Pulse pressure at the time of index PCI is associated with long-term outcomes following PCI. A wide pulse pressure may serve as a surrogate marker for risk following PCI and represents a potential target for future therapies. (J Am Coll Cardiol 2019;73:2846–55) © 2019 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.03.493

Hypertension is a well-established and powerful risk factor for cardiovascular disease (1–4). Accordingly, treatment of hypertension is a priority in the management of coronary artery disease (CAD) (5,6). Historically, the emphasis has been on targeting systolic blood pressure (SBP), as there was a presumed positive linear correlation between increasing SBP and risk of adverse cardiovascular outcomes (7–9). The recent SPRINT (Systolic Blood Pressure Intervention Trial) study provided compelling support for aggressive treatment of SBP (10) in high-risk nondiabetic patients, demonstrating more favorable outcomes with a target SBP <120 mm Hg.

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However, it has become increasingly well recognized that aggressively lowering diastolic blood pressure (DBP) can lead to a paradoxical increase in adverse outcomes, particularly in the presence of CAD (11–13). A subanalysis of the Framingham study (14) demonstrated a J-curve between DBP and risk of adverse cardiac events, with an increased risk of adverse events either side of target range, and subsequent studies have confirmed that this effect appears to be independent of pharmacotherapy and structural function (14–17).

Coronary perfusion occurs predominantly during cardiac diastole; therefore, aggressive reduction of DBP may compromise cardiac perfusion and worsen ischemia in patients with CAD (17,18). The detrimental impact of systolic hypertension on cardiac function and cardiovascular risk has been well described, and elevated SBP also increases afterload and myocardial energy requirements (19). As such, the combination of a high SBP and low DBP, that is, a wide pulse pressure, may amplify the individual detrimental effects of systolic hypertension and diastolic hypotension. Pulse pressure, the calculated difference between SBP and DBP, reflects cardiac contractility and arterial stiffness (20). Elevated pulse pressure is associated with an increased risk of adverse cardiac events (21,22) and has been found to be a superior independent predictor of risk than its individual components (23,24).

In this context, we aimed to examine the effect of pre-procedural blood pressure (BP) on outcomes in the setting of percutaneous coronary intervention (PCI), with the hypothesis that a wide pulse pressure may predict poor outcomes following PCI.

METHODS

We reviewed 10,876 consecutive PCI procedures from August 2009 to December 2016 with a pre-procedural BP recorded. The patients were prospectively enrolled in the Melbourne Interventional Group (MIG) registry.

The MIG registry, which has been previously described in detail (25), is a collaboration of interventional cardiologists practicing at 6 Australian tertiary referral hospitals in the state of Victoria. The registry collates patient data from all PCI procedures and includes follow-up at 30 days and at 12 months (26). Periodically, linkage is made with the Australian National Death Index, which records all deaths in Australia, for the purposes of long-term follow-up. Baseline, clinical, and procedural characteristics are recorded on standardized case-report forms. The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics from the Department of Epidemiology and Preventive Medicine at Monash University (Melbourne, Australia). An audit of a number of verifiable fields from 5% of randomly selected procedures at each institution is undertaken periodically (27). At the most recent audit, data accuracy was 98%, which compares favorably to other large registries (28). Approval was gained from each individual hospital's ethics committee prior to commencement of the registry. "Opt-out" informed consent was obtained in all patients (26).

STUDY DEFINITIONS. Based on a recent study by McEvoy et al. (13) reporting myocardial damage and adverse events with low DBP, we defined high SBP as ≥120 mm Hg and low SBP as <120 mm Hg. Based on recent reports (3,13,29,30), low DBP was defined as <70 mm Hg, and high as ≥70 mm Hg. Patients were then divided into 4 categories based on the classification of their SBP and DBP, i.e., high systolic, low diastolic blood pressure (HSLD), low systolic, low diastolic blood pressure (LSLD), high systolic, high diastolic blood pressure (HSHD), and low systolic, high diastolic blood pressure (LSHD). Patients presenting with ST-segment elevation myocardial infarction (MI), cardiogenic shock, and/or

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
DBP = diastolic blood pressure
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
SBP = systolic blood pressure

served as Guest Associate Editor for this paper. A full list of the Melbourne Interventional Group Investigators can be found in the Online Appendix.

Manuscript received January 7, 2019; revised manuscript received March 6, 2019, accepted March 7, 2019.

TABLE 1 Baseline Characteristics

	LSHD	HSHD	LSLD	HSLD	p Value
Frequency	869 (8.0)	4,158 (38.2)	3,006 (27.6)	2,843 (26.2)	–
Systolic BP, mm Hg	111 ± 6	147 ± 20	104 ± 10	138 ± 16	–
Diastolic BP, mm Hg	77 ± 5	83 ± 9	59 ± 8	62 ± 7	–
Pulse pressure, mm Hg	34 ± 8	64 ± 19	45 ± 11	77 ± 17	–
Age, yrs	57.5 ± 11	63.9 ± 11.3	63.9 ± 11.7	70.2 ± 10.3	0.0001
Female	91 (10.5)	983 (23.7)	562 (18.7)	940 (33.1)	0.0001
Current smoker	262 (30.5)	940 (23.0)	697 (23.5)	430 (15.4)	0.0001
Hypertension	539 (62.0)	3,193 (76.8)	1,990 (66.2)	2,283 (80.3)	0.0001
Hypercholesterolemia	600 (69.0)	2,983 (71.8)	600 (69.0)	2,130 (75.0)	0.002
eGFR, ml/min/1.73 m^2					
≥60	734 (86.4)	3,229 (79.2)	2,370 (81)	1,950 (70.3)	
30–59	109 (12.8)	755 (18.5)	487 (16.6)	692 (25)	
<30	7 (0.8)	93 (2.3)	70 (2.4)	132 (4.8)	0.0001
Diabetes	212 (24.4)	1,154 (27.8)	815 (27.1)	999 (35.1)	0.0001
Left ventricular ejection fraction					
>46%	393 (52.1)	1,783 (51.2)	1,257 (48.0)	1,177 (50.0)	
36%–45%	71 (9.4)	325 (9.3)	342 (13.1)	233 (9.9)	
<36%	291 (38.5)	1,376 (39.5)	1,020 (39.0)	945 (40.1)	0.0001
Family history of CAD	368 (44.6)	1,611 (41.0)	1,040 (36.1)	838 (30.7)	0.0001
Prior MI	254 (29.3)	1,134 (27.3)	1,019 (33.9)	1,034 (36.4)	0.0001
Prior CABG	46 (5.3)	379 (9.1)	296 (9.9)	418 (14.7)	0.0001
Heart failure	27 (3.1)	174 (4.2)	185 (6.1)	163 (5.7)	0.0001
Peripheral vascular disease	27 (3.1)	220 (5.3)	191 (6.4)	296 (10.4)	0.0001
Stroke	30 (3.5)	230 (5.5)	175 (5.8)	256 (9.0)	0.0001

Values are n (%) or mean ± SD.

BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; HSHD = high systolic high diastolic blood pressure; HSLD = high systolic low diastolic blood pressure; LSHD = low systolic high diastolic blood pressure; LSLD = low systolic low diastolic blood pressure; MI = myocardial infarction.

out-of-hospital cardiac arrest were excluded from the analysis cohort.

Baseline characteristics, including patient demographics, comorbidities, and procedural details, were recorded at the time of the index PCI. Indication for PCI was classified as stable angina, unstable angina, or non-ST-segment elevation MI. The vascular access approach, stent selection, antithrombotic therapy, and interventional strategy were at the individual operator's discretion.

In-hospital complications were recorded at the time of discharge or death. The 30-day and 12-month follow-up was conducted by telephone, and patient medical records were reviewed to verify events. All cardiac events were documented including death (all-cause mortality; cardiac mortality), MI, target lesion revascularization (TLR), target vessel revascularization (TVR), and the composite of major adverse cardiac events (MACE) (death, MI, or target vessel revascularization). MI was defined as: 1) an increase in creatine kinase or creatine kinase-MB ≥3× the upper limit of normal; and/or 2) significant ST-segment change, development of new Q waves in 2 or more contiguous electrocardiographic leads, or new left branch bundle block pattern. Major bleeding was defined by a decrease in hemoglobin of 3.0 g/dl and/or requiring blood transfusion. Causes of major bleeding were recorded as retroperitoneal, access site complications, gastrointestinal, and "others," which included bleeding at all other sites. Acute renal failure was defined by an increase of serum creatinine to >0.20 mmol/l (2.27 mg/dl, or 2× the baseline creatinine level) or new need for dialysis. Stroke was defined by the sudden onset of persistent loss of neurological function caused by an ischemic or hemorrhagic event during or after PCI. Cardiogenic shock was defined by hypotension (systolic blood pressure <90 mm Hg for ≥30 min or needing supportive measures), evidence of end-organ hypoperfusion or a cardiac index <2.2 l/min/m^2, and a pulmonary capillary wedge pressure ≥15 mm Hg. Stent thrombosis was defined according to the Academic Research Consortium definitions of definite or probable (26). Only early (0 to 30 days) stent thrombosis was included in this analysis.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD and compared among BP

TABLE 2 Presentation Characteristics

	LSHD	HSHD	LSLD	HSLD	p Value
Presentation					
Atypical angina	79 (8.3)	355 (7.6)	288 (9.6)	252 (8.8)	0.0001
Stable angina	259 (29.8)	1,500 (36.1)	1,075 (35.8)	1,246 (43.8)	
Unstable angina	97 (11.2)	497 (12.0)	338 (11.3)	324 (11.4)	
NSTEMI	434 (49.9)	1,806 (43.4)	1,303 (43.4)	1,021 (35.9)	
Atrial fibrillation	37 (4.4)	198 (4.9)	123 (4.3)	143 (5.2)	0.34
NYHA functional class					
I	487 (63.8)	2,132 (60.2)	1,828 (67.4)	1,649 (64.6)	0.0001
II	132 (17.3)	625 (17.7)	508 (18.7)	535 (21.0)	
III–IV	144 (18.9)	782 (22.1)	375 (13.8)	367 (14.4)	
Heart rate, beats/min	71 ± 13	71 ± 13	68 ± 13	66 ± 12	0.0001

Values are n (%) or mean ± SD.

NSTEMI = non-ST-segment elevation myocardial infarction; NYHA = New York Heart Association; other abbreviations as in Table 1.

categories using Kruskal-Wallis equality-of-populations rank test. Categorical variables are expressed as number (percentage) and compared using Pearson's chi-square test or Fisher exact test as appropriate. The analyses of the primary outcomes and other composites of death and adverse cardiovascular events were performed using Kaplan-Meier survival estimates, with the log-rank test for the comparison of groups. Cox proportional hazards modeling was used to identify hazard ratios (HRs) and 95% confidence intervals (CIs) of: 1) independent predictors of 30-day MACE on the whole cohort; and 2) independent predictors of mortality hazard on 5,818 patients who had linkage with the National Death Index on July 30, 2014. The variables included in the multivariable analysis model were blood pressure classification, previous hypertension, age, sex, diabetes, dyslipidemia, current smoking, estimated glomerular filtration rate category, previous MI, previous PCI, previous coronary artery bypass graft (CABG), previous congestive heart failure (CHF), peripheral vascular disease, chronic lung disease, previous cerebrovascular disease, rheumatoid arthritis, obstructive sleep apnea, presence of CHF <2 weeks prior to procedure, heart rate, femoral artery access, left ventricular ejection fraction category, disease extent, left main disease, left main coronary artery lesion, left anterior descending lesion, circumflex lesion, right coronary artery lesion, bypass graft lesion, chronic total occlusion, and drug-eluting stent use.

Statistical analysis was performed using Stata/MP version 14.2 for Windows (College Station, Texas). All p values <0.05 were considered to represent statistical significance.

RESULTS

The cohort's mean SBP was 130 ± 24 mm Hg and the mean DBP was 70 ± 13 mm Hg. Mean pulse pressure was 60 ± 21 mm Hg.

BASELINE DATA. The baseline demographics of each group are summarized in Table 1. The most frequent blood pressure combination was HSHD (38.2%; n = 4,158) and the least frequent was LSHD (8%; n = 869). There were 3,006 patients (27.6%) with LSLD and 2,843 (26.2%) with HSLD. The mean pulse pressure for HSLD was 77 ± 17 mm Hg, 64 ± 19 mm Hg for HSHD, 45 ± 11 mm Hg for LSLD, and 34 ± 8 mm Hg for LSHD. Patients with HSLD (wide pulse pressure) were older, with a mean age of 70.2 ± 10.3 years (p < 0.0001), compared with LSLD (69.9 ± 11.7 years), HSHD (63.9 ± 11.3 years), and LSHD (narrow pulse pressure; 57.5 ± 11.0 years). Patients with HSLD were also more frequently female (33%; n = 940; p < 0.001), and more frequently experienced hypertension, hypercholesterolemia, and diabetes. Patients

TABLE 3 Angiographic Characteristics

	LSHD	HSHD	LSLD	HSLD	p Value
Access					
Radial or brachial	420 (48.3)	1,410 (33.9)	1,079 (35.9)	631 (22.2)	0.0001
Femoral	449 (51.7)	2,747 (66.1)	1,927 (64.1)	2,212 (77.8)	
Multivessel disease	511 (58.8)	2,331 (56.1)	1,869 (62.2)	1,843 (64.8)	0.0001
Left main disease	20 (3.9)	128 (5.5)	117 (6.3)	185 (10.0)	0.0001
Chronic total occlusion	53 (5.0)	224 (4.6)	169 (4.7)	148 (4.4)	0.81
Drug-eluting stent	603 (69.4)	2,595 (62.4)	2,017 (67.1)	1,918 (67.5)	0.0001

Values are n (%).

LVEF = left ventricular ejection fracture; other abbreviations as in Table 1.

TABLE 4 30-Day Outcomes

	LSHD	HSHD	LSLD	HSLD	p Value
Mortality	5 (0.6)	15 (0.4)	19 (0.6)	17 (0.6)	0.37
Cardiac death	2	9	9	9	0.84
Myocardial infarction	7 (0.8)	64 (1.5)	53 (1.8)	51 (1.8)	0.19
Target vessel revascularization	17 (2.0)	4,158 (2.0)	42 (1.4)	37 (1.3)	0.06
MACE	25 (2.9)	135 (3.3)	96 (3.2)	88 (3.1)	0.95
Stroke	3 (0.4)	9 (0.2)	7 (0.2)	10 (0.4)	0.68

Values are n (%) or n.
MACE = major adverse cardiovascular events; other abbreviations as in Table 1.

with HSLD were more likely to have prior vascular disease, with a greater frequency of previous MI, coronary artery bypass graft surgery, peripheral vascular disease, and stroke. At presentation, patients with HSLD had the lowest resting heart rate, whereas patients with LSHD had the highest resting heart rate (66.1 ± 11.8 beats/min vs. 71.3 ± 13.1 beats/min; p = 0.0001), as shown in Table 2. In terms of angiographic characteristics, HSLD patients had more complex CAD, with a greater number of patients presenting with multivessel and left main disease (Table 3).

OUTCOMES. Outcomes at 30 days are summarized in Table 4. There was no significant difference between rates of mortality (including cardiac death), MI, TVR, MACE, or stroke between blood pressure groups. Blood pressure was not an independent predictor of MACE at 30 days on multivariate analysis.

TABLE 5 Medication Use at 30 Days

	LSHD	HSHD	LSLD	HSLD	p Value
ACE inhibitor/ARB	632 (75.5)	3,076 (77.2)	2,131 (73.8)	2,078 (76.2)	0.014
Beta-blocker	661 (79.4)	3,074 (77.4)	2,228 (77.4)	2,017 (74.0)	0.001
Calcium-channel blocker	120 (14.4)	906 (22.8)	493 (17.1)	769 (28.3)	0.0001
Mineralocorticoid antagonists	33 (4.0)	112 (2.8)	163 (5.7)	90 (3.3)	0.0001
Nitrate	70 (8.4)	502 (12.6)	315 (10.9)	353 (13.0)	0.001
Lipid therapy					
Statin	788 (94.2)	3,734 (93.8)	2,716 (94.1)	2,552 (93.8)	0.95
Fibrate	23 (2.8)	103 (2.6)	77 (2.7)	66 (2.4)	0.93
Ezetimibe	43 (5.2)	271 (6.8)	195 (6.8)	220 (8.1)	0.02
Anticoagulant therapy					
Warfarin	41 (4.9)	199 (5.0)	155 (5.4)	153 (5.6)	0.68
DOAC	10 (1.4)	49 (1.6)	37 (1.6)	36 (1.7)	0.94
Antiplatelet					
Aspirin	824 (98.0)	3,905 (97.6)	2,829 (97.7)	2,664 (97.3)	0.63
Clopidogrel	466 (55.4)	2,654 (66.5)	1,854 (64.1)	2,036 (74.4)	0.0001
Prasugrel	79 (9.4)	302 (7.6)	216 (7.5)	112 (4.1)	0.0001
Ticagrelor	266 (37.7)	905 (28.9)	737 (31.8)	492 (23.7)	0.0001

Values are n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; DOAC = direct oral anticoagulant; other abbreviations as in Table 1.

Antihypertensive use at 30 days is summarized in Table 5. Of note, calcium-channel blocker (CCB) use was most common in HSLD (28.3% vs. LSLD 17.1%, HSHD 22.8%, and LSHD 14.4%; p = 0.0001). Overall, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and beta-blocker use was high in all blood pressure groups, with reported adherence >70% for both medications.

At 12 months post-procedure, patients with HSLD had a higher incidence of MI (5.9% [n = 121] vs. LSLD 4.7%, HSHD 4.9%, and LSHD 2.9%; p = 0.018) and stroke (1.2%; n = 24; p = 0.013). There was no difference in rate of cardiac death (p = 0.34), all-cause mortality (HSLD 3.4% [n = 69] vs. LSLD 3.1%, HSHD 2.5%, and LSLD 1.7%; p = 0.08), TVR (p = 0.32), or MACE (p = 0.32), as demonstrated in Table 6.

Long-term mortality data were available for 5,818 patients, and Kaplan-Meier estimates for survival are shown in Figure 1. The median follow-up period was 903 days (interquartile range: 547 to 1,310 days). Patients with HSLD had the highest National Death Index-linked mortality rates (7.9%; n = 126) compared with LSLD (6.6%; n = 104), HSHD (5.2%; n = 115), and LSHD (2.1%; n = 9, p = 0.0002). Cox regression analysis did not show that HSLD (wide pulse pressure) was an independent predictor of mortality hazard, but LSHD (narrow pulse pressure) predicted lower hazard when compared with the reference category of LSLD (HR: 0.50; 95% CI: 0.25 to 98.2; p = 0.04).

DISCUSSION

Our study has demonstrated that the combination of high SBP and low DBP (wide pulse pressure) prior to PCI is associated with higher burden of chronic cardiac risk factors, reflecting higher baseline risk and potentially less arterial compliance (Central Illustration). This cohort of patients also had higher long-term mortality and major adverse cardiac outcomes. In contrast, patients with high DBP in combination with low SBP (narrow pulse pressure) had lower long-term mortality, and this was an independent predictor of lower long-term mortality.

Our study is one of the first to examine the influence of pulse pressure in the setting of PCI and provides insight into potential targets for therapy in this context (31,32). The cohort with HSLD demonstrated a significantly higher burden of cardiovascular risk factors such as older age, diabetes, previous CAD, and hypercholesterolemia. Age and diabetes have been previously linked to wide pulse pressure and likely reflect older, stiffened pathological arteries (33). Chronic age-related hypertension tends to result in an

increase in systolic BP and no change or reduction in DBP, and thus a wider pulse pressure (34). Arterial stiffness and pulse wave velocity (a surrogate marker) have been demonstrated as independent predictors of adverse outcomes (35-39). The detrimental impact of reduced coronary supply in diastolic hypotension appears to be amplified by the increased myocardial requirements in systolic hypertension (19).

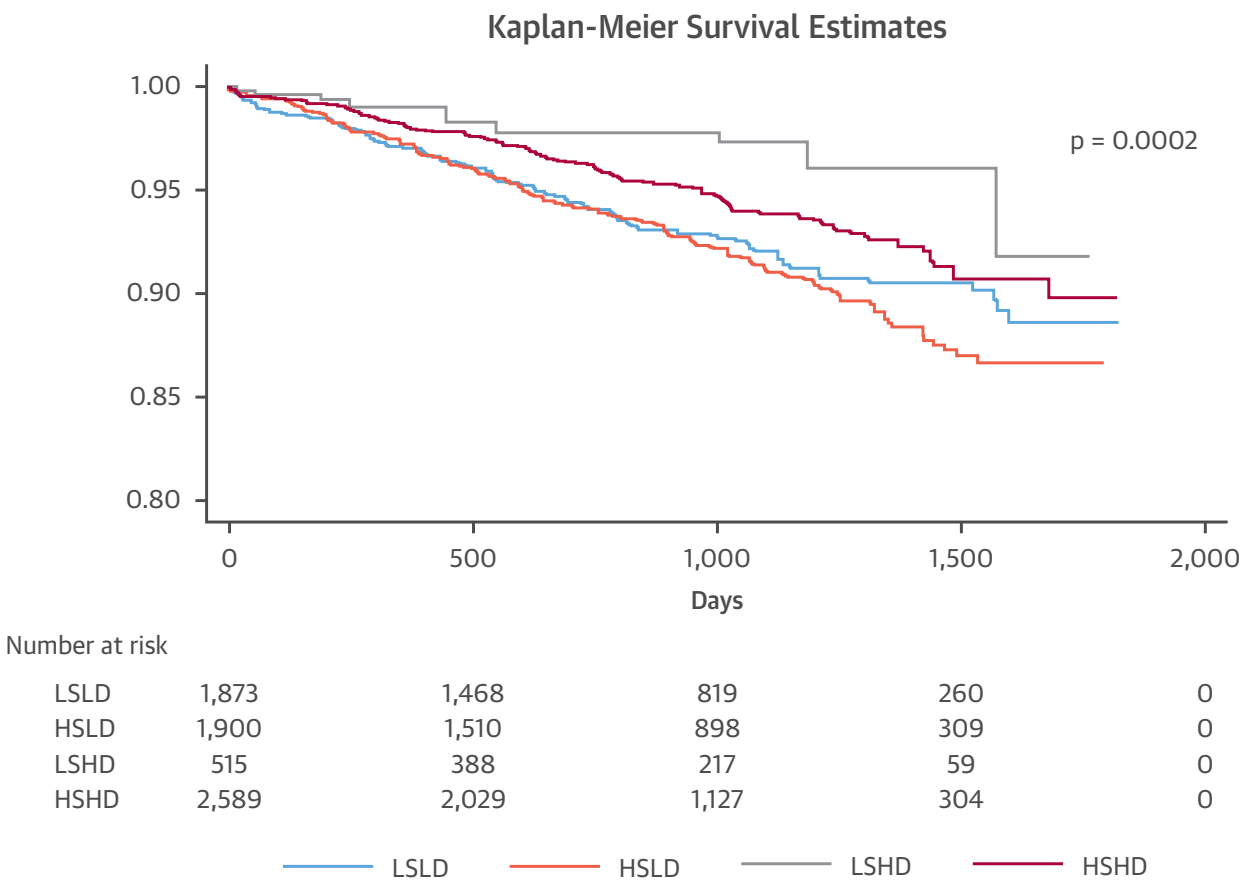
Mortality was significantly higher in patients with HSLD, followed by patients with LSLD. Recent published data confirms the poor prognostic value of a low DBP. McEvoy et al. (13), in a substudy of the ARIC (Atherosclerosis Risk In Communities) cohort, assessed the independent association of diastolic hypotension with subclinical myocardial ischemia by observing long-term troponin elevation in patients treated for hypertension. Lowering DBP to <70 mm Hg was associated with higher troponin elevation, incident ischemic heart disease (HR: 1.5; 95% CI: 1.2 to 1.9; p = 0.01), heart failure, and mortality. This outcome was more marked when DBP <60 mm Hg and associated with SBP >120 mm Hg.

TABLE 6 12-Month Outcomes

	LSHD	HSHD	LSLD	HSLD	p Value
Mortality	10 (1.7)	73 (2.5)	66 (3.1)	69 (3.4)	0.08
Cardiac death	4	21	24	30	0.34
Myocardial infarction	17 (2.9)	143 (4.9)	99 (4.7)	121 (5.9)	0.018
Target vessel revascularization	44 (7.5)	189 (6.5)	118 (5.6)	126 (6.2)	0.32
MACE	63 (10.7)	337 (11.6)	228 (10.7)	254 (12.5)	0.32
Stroke	4 (0.7)	15 (0.5)	9 (0.4)	24 (1.2)	0.013

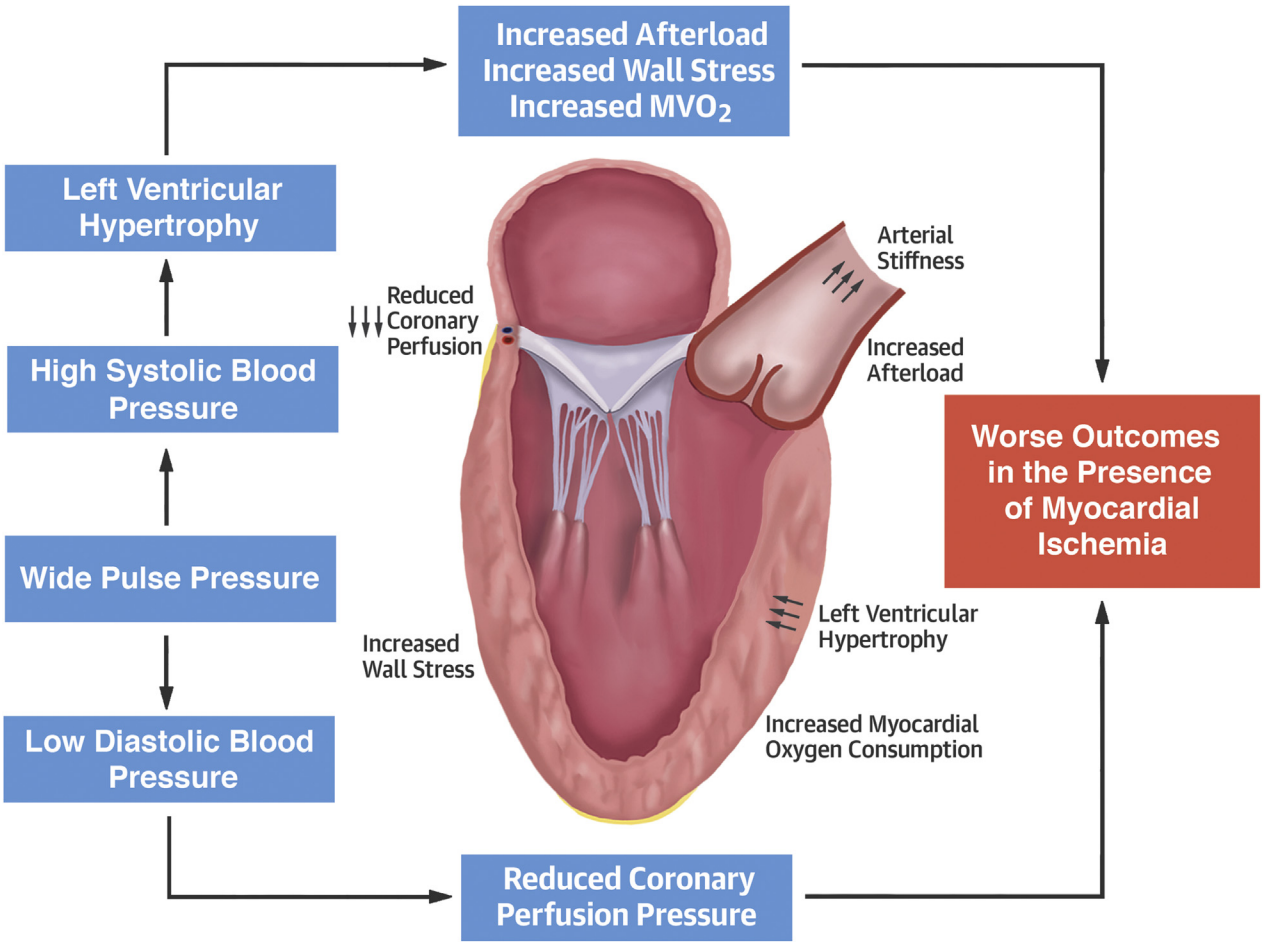
Values are n (%) or n.
Abbreviations as in Tables 1 and 4.

FIGURE 1 Kaplan-Meier Long-Term Mortality



Long-term mortality of the cohort according to the combinations of systolic and diastolic blood pressure, including the numbers at risk. It shows that low systolic associated with high diastolic (LSHD) blood pressure predicts lower mortality, whereas high systolic associated with low diastolic (HSLD) blood pressure is associated with worse survival. The analyses of the primary outcomes and other composites of death and adverse cardiovascular events were performed with the use of Kaplan-Meier survival estimates, with the log-rank test for the comparison of groups. HSHD = high systolic high diastolic; LSLD = low systolic low diastolic.

CENTRAL ILLUSTRATION **Pulse Pressure and Long-Term Outcomes Post-Percutaneous Coronary Intervention**



Warren, J. et al. J Am Coll Cardiol. 2019;73(22):2846–55.

Pathophysiological changes associated with a wide pulse pressure. High systolic blood pressure results in left ventricular hypertrophy, resulting in increased afterload, wall stress, and myocardial oxygen consumption. In addition, low diastolic blood pressure results in reduced coronary perfusion pressure. The combination of the 2 pathophysiological consequences, that is, a wide pulse pressure, leads to worse outcomes in the presence of myocardial ischemia. MVO_2 = myocardial oxygen consumption.

The HOT (Hypertension Optimal Treatment) trial, which examined 18,790 patients with hypertension, observed a 22% increase in rates of MI with a DBP <80 mm Hg compared with DBP 85 mm Hg (3). Subsequently, the INVEST (International Verapamil-Trandolapril) study showed a 2-fold increase in all-cause mortality and MI with DBP <70 mm Hg, which doubled in patients with DBP <60 mm Hg (30). Patients who had been revascularized tolerated lower DBP better than those not undergoing a procedure. The CLARIFY (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease) study, which examined 22,672 patients with stable CAD, found that a J-curve existed for both SBP and DBP. The nadir of the diastolic J-curve was between 70 and 80 mm Hg (29). Most recently, the CLARIFY investigators found that the diastolic J-curve in hypertensive patients with CAD exists independently of pulse pressure, suggesting that the effect is not explained by arterial stiffness alone (40).

Our study suggests that a narrow pulse pressure independently predicts lower long-term mortality. Wide pulse pressure has previously been described as a predictor of adverse outcomes in the setting of CAD (4,14,22,33,41,42), and pulse pressure has been demonstrated to be a better predictor than SBP, DBP, and mean arterial pressure (21,33). Vaccarino et al. (33) found that a 10-mm Hg increase in pulse pressure

is associated with a 12% increase in risk of CAD in the elderly, and it was a stronger predictor than both mean arterial pressure and SBP alone (33).

As coronary perfusion occurs during diastole, a reduction in DBP may impede coronary flow and amplify ischemia, particularly in arteries with pre-existing obstruction (41). The presence of coronary stenoses results in poor flow reserve and renders the myocardium vulnerable to ischemia (43). Coronary perfusion is autoregulated such that a constant perfusion pressure is maintained over a wide range of blood pressures (44). This intrinsic mechanism is disrupted in the presence of coronary disease, and therefore, a drop in pressure can result in heightened ischemia distal to stenosis (45). Patients with chronic hypertension operate at a higher perfusion threshold (45), and a reduction of BP in these patients may result in hypoperfusion and ischemia (44,46–48). In a study examining patients with ambulatory BP and electrocardiographic monitoring, ischemic events were temporally associated with diastolic rather than systolic hypotension (49).

The ideal blood pressure target prior to PCI is undefined. The recent SPRINT trial was prematurely ceased due to the benefits of controlling hypertensive patients' SBP to <120 mm Hg rather than <140 mm Hg, supporting the aim for a low systolic BP. The composite endpoint of an acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes was 25% less likely in those with a target blood pressure of <120 mm Hg (10). Similarly, our study suggests that SBP <120 mm Hg in combination with DBP >70 mm Hg prior to PCI is associated with lower long-term mortality. However, both CLARIFY and a joint analysis of 30,937 high-risk patients with CAD by Böhm et al. (50) suggest that there is a significant increase in adverse events with a SBP below 120 mm Hg, potentially due to poor perfusion leading to an increased risk of ischemic events.

There are little data directly comparing the effects of antihypertensive therapies on pulse pressure and outcomes following PCI. Indeed, there are no agents that target SBP in isolation, which may be the preferential form of treatment in this setting. However, examining the pharmacological action of antihypertensive agents gives insight into potential advantages of various agents (17). Antihypertensive agents that reduce heart rate, such as centrally acting CCBs and beta-blockers, prolong diastole and therefore potentially extend coronary perfusion time. However, in the absence of heart failure, evidence for the survival benefit of using beta-blockers in the setting of MI is limited (51). In addition, central CCBs also improve arterial compliance through their vasodilatory effects and, therefore, preferentially target systolic blood pressure (52). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, as well as CCBs, reduce left ventricular hypertrophy and hypertensive vascular disease more than beta-blockers (53,54), making them potentially preferable agents in certain patient groups. Interestingly, the HSLD cohort had the highest use of CCBs 30 days post-PCI, suggesting that their practitioners may have recognized these benefits in this group. Further research is required in this domain.

STUDY LIMITATIONS. Despite the fact that all data in our registry are collected prospectively, our study was limited by its retrospective design, as well as the relatively short-term follow-up. Furthermore, a single pre-procedural blood pressure only provides a snapshot into hemodynamics and may not reflect the patient's usual blood pressure. Indeed, there may be an element of "white-coat" hypertension that we are unable to control for. However, the clear differentiation between our blood pressure cohorts in mortality with long-term follow-up suggests that pre-PCI blood pressure may be a useful prognostic indicator.

CONCLUSIONS

The present study emphasizes the adverse effect of a wide pulse pressure prior to PCI, and has shown that a narrow pulse pressure independently predicts lower long-term mortality. A pre-PCI wide pulse pressure could potentially serve as a marker of risk, in its reflection of chronic disease burden, as well as a potential target for future therapies (55).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with coronary artery disease, pulse pressure measured prior to undergoing PCI is a predictor of long-term prognosis; the combination of narrow pulse pressure and low SBP is associated with better outcomes.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine whether the relationship between pulse pressure and longer-term outcomes in patients with ischemic heart disease is due to arterial noncompliance, reduced diastolic myocardial perfusion pressure, or other factors.

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KEY WORDS blood pressure, coronary artery disease, outcomes, percutaneous coronary intervention, pulse pressure

APPENDIX For a full list of the Melbourne Interventional Group Investigators, please see the online version of this paper.