Pulse Pressure and Risk for Cardiovascular Events in Patients With Atherothrombosis

From the REACH Registry

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ABSTRACT

BACKGROUND Pulse pressure (PP) provides valuable prognostic information in specific populations, but few studies have assessed its value on cardiovascular outcomes in a broad, worldwide population.

OBJECTIVES The aim of this study was to determine whether PP is associated with major adverse cardiovascular outcomes, independently of mean arterial pressure.

METHODS Participants from the international REACH (Reduction of Atherothrombosis for Continued Health) registry, which evaluates subjects with clinical atherothrombotic disease or risk factors for its development, were examined. Those with incomplete 4-year follow-up or PP data (final n = 45,087) were excluded. Univariate and multivariate regression analyses were performed to determine the association between PP and cardiovascular outcomes, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, all myocardial infarction, all stroke, cardiovascular hospitalization, and a combined outcome. PP was analyzed as a continuous and categorical (i.e., by quartile) variable.

RESULTS The mean age of the cohort was 68 ± 10 years, 35% were women, and 81% were treated for hypertension. The mean blood pressure was $138 \pm 19/79 \pm 11$ mm Hg, rendering a mean PP of 49 ± 16 mm Hg. On univariate analysis, increasing PP quartile was associated with worse outcomes ($p < 0.05$ for all comparisons). After adjusting for sex, age, current smoking status, history of hypercholesterolemia, history of diabetes, aspirin use, statin use, blood pressure medication use, and mean arterial pressure, PP quartile was still associated with all outcomes except all stroke and cardiovascular death ($p < 0.05$ for all comparisons). Analysis of PP as a continuous variable yielded similar results.

CONCLUSIONS In an international cohort of high-risk subjects, PP, a readily available hemodynamic parameter, is associated with multiple adverse cardiovascular outcomes and provides prognostic utility beyond that of mean arterial pressure. (J Am Coll Cardiol 2016;67:392–403) © 2016 by the American College of Cardiology Foundation.

Pulsatile components of blood pressure capture elements of cardiac risk beyond that captured by steady components (1-3). The former, often measured as pulse pressure (PP), is recognized as a potent risk factor for cardiovascular disease, including myocardial infarction (MI), stroke, and cardiovascular mortality (4). According to the Windkessel model of arterial blood pressure, PP can be thought simply as a reflection of both stroke volume and arterial wall compliance. Although left ventricular ejection contributes, high PP typically reflects decreased arterial compliance, particularly in older patients. Hypertension, diabetes, atherosclerosis, and many more conditions alter the cellular matrix of the wall, reducing wall elasticity, and thus their relationship to elevation in PP becomes clear.

Several studies have examined the relationship in specific populations between PP and adverse cardiovascular outcomes, with the preponderance of evidence favoring an association (4-11). However, there are few data regarding the predictive value of PP for cardiovascular outcomes in a large, international cohort. In addition, peripheral PP, although clinically more accessible than central PP, may not be the most accurate reflection of left ventricular stress and coronary perfusion (10). Thus, understanding whether peripheral PP is clinically useful warrants further study. Finally, although a significant proportion, though certainly not all (12,13), of the PP data have been generated from hypertensive clinical trials with restricted patient populations, less is known about its relationship to a broad array of subjects in an outpatient setting. We therefore sought to examine the relationship between PP and adverse cardiovascular events using data from the REACH (Reduction of Atherothrombosis for Continued Health) registry.

METHODS

STUDY POPULATION. We studied participants from the REACH registry, an international, longitudinal study of atherothrombosis. Details regarding the methodology of the study have been previously reported (14-17). In brief, REACH enrolled stable outpatients ≥45 years of age with either established atherothrombotic disease (coronary artery disease, cerebrovascular disease, or peripheral artery disease) or with ≥3 risk factors for atherothrombosis. Subjects were recruited during a 7-month period between December 2003 and June 2004. Because of regulatory requirements, enrollment in Japan was delayed and occurred between August 2004 and December 2004. Final data collection occurred until April 2009. Exclusion criteria for the present study were lack of either a complete set of blood pressure measurements or 4 years of follow-up data. Complete follow-up of the initial cohort could not be completed because of withdrawal of some of the study sites. All REACH study participants gave written informed consent, and each study site's local Institutional Review Board approved the REACH study.

CLINICAL CHARACTERISTICS AND OUTCOME VARIABLES. Baseline height, weight, and seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained. Blood pressure was measured using a brachial mercury sphygmomanometer. PP was defined as the difference between the SBP and DBP. A quality control check with the number of blood pressure readings ending in zero was performed (18) and showed that 58% of SBP readings and 60% of DBP readings ended in zero (20% expected). Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. Medical history and medications were established using

techniques previously documented (14). In particular, diabetes was defined as any history of diabetes or current diabetes (diagnosed by at least 2 fasting blood glucose measures >7 mmol/l or >126 mg/dl), treated or not. Hypercholesterolemia was defined as treatment with lipid-lowering therapy. Hypertension was defined as past or current treatment with antihypertensive agents. The primary outcome of the study was a combined outcome of cardiovascular death (including fatal MI and fatal stroke), nonfatal MI, nonfatal stroke, and cardiovascular hospitalization. Secondary outcomes included each of the individual outcomes used to formulate the primary outcome in addition to fatal and nonfatal MI as well as fatal and nonfatal stroke. Reasons for cardiovascular hospitalization included atherothrombotic events, such as transient ischemic attack, unstable angina, and other ischemic arterial events. Further elaboration of the definitions of these outcomes is provided elsewhere (14,16).

STATISTICAL ANALYSIS. Clinical characteristics are displayed by PP quartile, for descriptive purposes. Continuous data are presented as mean ± SD. Categorical variables are presented as counts and percentages. Cox proportional hazard models were constructed to determine the relationship of PP (per 10 mm Hg increase) with all outcomes. Cutoff ranges for each of the PP quartiles were defined as follows: quartile 1, ≤50 mm Hg; quartile 2, 50 <PP ≤60 mm Hg; quartile 3, 60 <PP ≤70 mm Hg; and quartile 4, >70 mm Hg. **Figure 1** displays the raw relationship between PP quartiles and cardiovascular outcomes. Given the nonlinear relationship observed in a few of the analyses, adjusted Cox models for each outcome with PP introduced as restricted cubic splines were performed using knots at PP = 40, 60, and 80 mm Hg (**Figure 2**) (19).

Covariates included in multivariate models were selected on the basis of clinical relevance as well as association with PP in previous studies. Model 1 covariates included sex, age, current smoker status, history of hyperlipidemia, history of diabetes mellitus, aspirin use, and statin use. Model 2 further adjusted for history of atherothrombosis (defined as history of MI, stroke, or peripheral artery disease). Model 3 additionally adjusted for medications known to influence PP, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blocker, calcium-channel blockers, and diuretic agents. Finally, model 4 additionally adjusted for mean arterial pressure (defined as: $[2 \times DBP + SBP] / 3$) to determine whether PP adds clinically useful information beyond these parameters (20).

On sensitivity analyses, we analyzed the results only including: 1) women, for whom PP data are limited in the published research; 2) subjects >60 years of age, for whom the relationship with PP is typically stronger (4); 3) subjects without established atherothrombotic disease; 4) subjects with SBP >140 mm Hg (vs. ≤140 mm Hg); and 5) subjects treated for hypertension versus those not treated for hypertension, given the reduction of PP with antihypertensive treatment (21).

All primary analyses were repeated using SBP and DBP as the predictor variables instead of PP. A 2-sided p value ≤0.05 was considered to indicate statistical significance. Analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS.
Descriptive characteristics of the REACH study sample are displayed in **Table 1**. Among an eligible 67,888 participants, more than two-thirds (n = 45,087) met the inclusion criteria and were analyzed in the present study. The vast majority of exclusions were due to incomplete 4-year follow-up data (n = 22,661). The mean age of the cohort was 68 ± 10 years, and 35% were women. Subjects from 29 countries were represented. Comorbidities were common, including hypertension (81%), hypercholesterolemia (70%), coronary artery disease (58%), and diabetes mellitus (44%); 82% had established atherothrombotic disease. Long-term medication use reflected standard therapies used for the comorbidities detailed in **Table 1**. Blood pressure was relatively well controlled (mean 138 ± 19/79 ± 11 mm Hg; mean PP 49 ± 16 mm Hg) and obesity was common (mean BMI 28 ± 5 kg/m², 28% obese [BMI >30 kg/m²]). Increasing PP was associated with increasing age, BMI, and female sex. There was a significant difference in comorbidity burden profile in the lower and higher PP quartiles. Higher PP quartiles were more likely to have hypertension, peripheral arterial disease, and diabetes (p < 0.01 for all comparisons). Lower PP quartiles were associated with increasing prevalence of congestive heart failure, coronary artery disease, smoking, hypercholesterolemia, and atrial fibrillation (p < 0.05 for all comparisons). Medication difference likewise reflected the disparity in comorbidity burden (i.e., higher antiplatelet agent, nitrate or antianginal agent, statin, and beta-blocker use with lower PP quartiles; p < 0.01 for all comparisons). Online Table 1 shows the distribution of PP by SBP tiers (<140, 140 ≤PP <160, and ≥160 mm Hg). Of note, 93% of subjects in PP quartile 4 had SBP ≥140 mm Hg.

FIGURE 1 Pulse Pressure Quartiles and Cardiovascular Outcomes
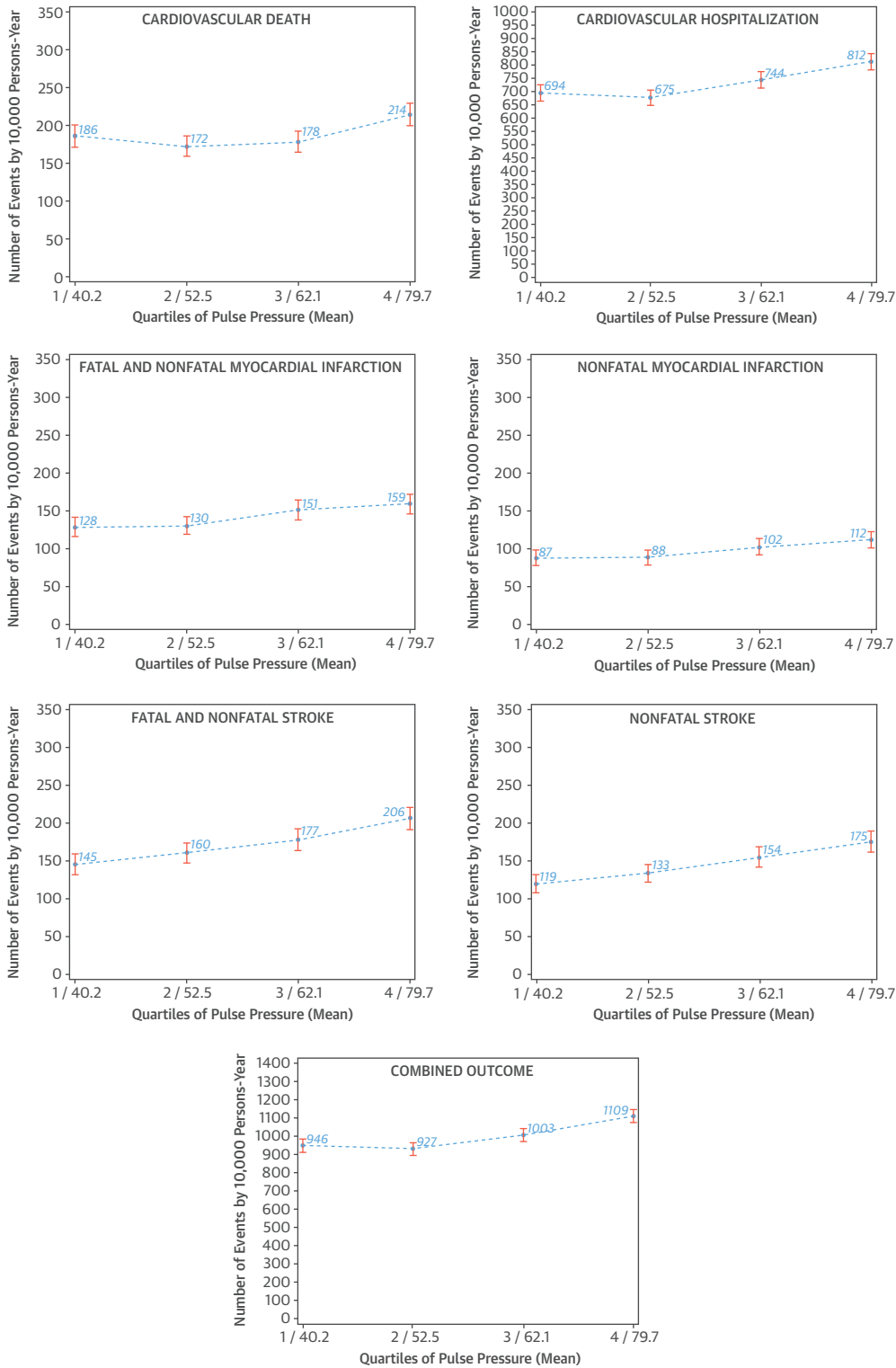
Unadjusted relationship between pulse pressure quartiles and outcomes (p < 0.01 for trend of all outcomes). Mean pulse pressure (millimeters of mercury) is labeled on the x-axis for each pulse pressure quartile.

FIGURE 2 Continuous Relationship Between Pulse Pressure and Cardiovascular Outcomes
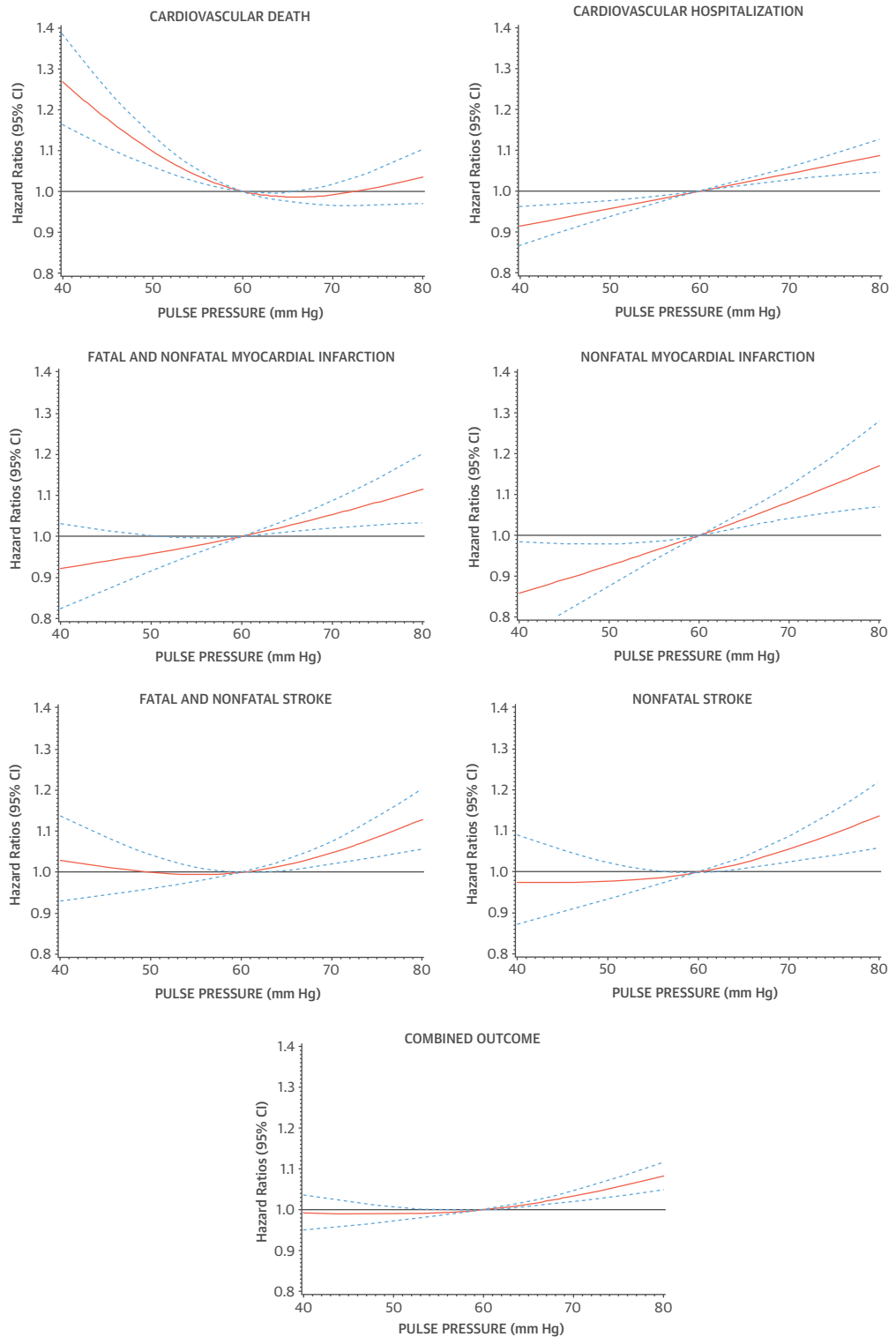
Pulse pressure as a continuous variable is nonlinearly associated with cardiovascular death, fatal and nonfatal stroke, and the combined outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or cardiovascular hospitalization (p < 0.05 for nonlinearity). However, pulse pressure is linearly associated with nonfatal myocardial infarction, fatal and nonfatal myocardial infarction, nonfatal stroke, and cardiovascular hospitalization (p = 0.95, p = 0.70, p = 0.14, and p = 0.84 for nonlinearity, respectively). CI = confidence interval.

TABLE 1 Clinical Characteristics of the Study Sample

	All Cohort (N = 45,087)	Quartiles of PP (mm Hg)			
		First Quartile (PP ≤50 mm Hg) (n = 10,153)	Second Quartile (50 <PP ≤60 mm Hg) (n = 11,842)	Third Quartile (60 <PP ≤70 mm Hg) (n = 11,061)	Fourth Quartile (PP >70 mm Hg) (n = 12,031)
Age, yrs	68.41 ± 9.97	65.29 ± 10.35	67.71 ± 9.98	69.24 ± 9.64	70.99 ± 9.11
BMI, kg/m^2	27.86 ± 5.46	27.67 ± 5.46	27.88 ± 5.39	27.89 ± 5.42	28.01 ± 5.58
Diastolic blood pressure, mm Hg	78.64 ± 11.03	78.12 ± 10.05	78.75 ± 10.21	79.15 ± 11.18	78.52 ± 12.38
Systolic blood pressure, mm Hg	137.98 ± 19.22	118.34 ± 11.35	131.22 ± 10.48	141.24 ± 11.37	158.23 ± 16.1
Pulse pressure, mm Hg	49.34 ± 15.91	40.22 ± 5.92	52.47 ± 2.93	62.09 ± 2.77	79.71 ± 11.29
Male	29,167 (64.71)	7,232 (71.27)	8,026 (67.79)	7,018 (63.48)	6,891 (57.28)
Region					
North America	15,602 (34.60)	4,151 (40.88)	4,173 (35.24)	3,416 (30.88)	3,862 (32.10)
Latin America	1,373 (3.05)	399 (3.93)	334 (2.82)	266 (2.40)	374 (3.11)
Western Europe	14,542 (32.25)	2,481 (24.44)	3,624 (30.60)	4,138 (37.41)	4,299 (35.73)
Eastern Europe	4,523 (10.03)	1,002 (9.87)	1,232 (10.40)	1,141 (10.32)	1,148 (9.54)
Middle East	464 (1.03)	103 (1.01)	106 (0.90)	95 (0.86)	160 (1.33)
Asia	3,510 (7.78)	950 (9.36)	962 (8.12)	737 (6.66)	861 (7.16)
Japan	5,073 (11.25)	1,067 (10.51)	1,411 (11.92)	1,268 (11.46)	1,327 (11.03)
Medical history					
Congestive heart failure	6,070 (13.65)	1,555 (15.50)	1,539 (13.13)	1,389 (12.74)	1,587 (13.44)
History of hypertension	36,649 (81.29)	7,131 (70.24)	9,184 (77.57)	9,249 (83.63)	11,085 (92.14)
Peripheral artery disease	5,841 (12.95)	1,046 (10.30)	1,327 (11.21)	1,498 (13.54)	1,970 (16.37)
Coronary artery disease	26,318 (58.37)	6,812 (67.09)	7,255 (61.26)	6,255 (56.55)	5,996 (49.84)
Current smoker	6,821 (15.61)	1,674 (16.96)	1,787 (15.54)	1,705 (15.95)	1,655 (14.21)
Hypercholesterolemia	31,685 (70.34)	7,371 (72.64)	8,456 (71.47)	7,695 (69.66)	8,163 (67.93)
Diabetes	19,492 (43.50)	3,779 (37.43)	4,882 (41.45)	4,876 (44.38)	5,955 (49.86)
Atrial fibrillation/flutter	4,571 (10.30)	1,093 (10.94)	1,183 (10.11)	1,117 (10.24)	1,178 (9.98)
Baseline medication					
Angiotensin-converting enzyme inhibitors	20,345 (45.35)	4,515 (44.61)	5,147 (43.61)	4,961 (45.05)	5,722 (47.96)
Angiotensin II receptor antagonists	10,117 (22.57)	1,872 (18.52)	2,389 (20.25)	2,566 (23.33)	3,290 (27.60)
Beta-blockers	21,280 (47.39)	5,235 (51.71)	5,681 (48.08)	4,963 (45.06)	5,401 (45.19)
Calcium-channel blockers	15,742 (35.07)	2,625 (25.97)	3,813 (32.27)	4,097 (37.21)	5,207 (43.58)
Diuretic agents	18,019 (40.09)	3,590 (35.44)	4,290 (36.32)	4,475 (40.56)	5,664 (47.34)
Hypoglycemic agents	17,813 (39.52)	3,414 (33.63)	4,430 (37.42)	4,480 (40.52)	5,489 (45.64)
Acetylsalicylic acid	30,260 (67.22)	7,206 (71.10)	8,105 (68.52)	7,278 (65.92)	7,671 (63.86)
Nitrates/other antiangina agents	10,980 (24.75)	2,575 (25.75)	2,966 (25.41)	2,690 (24.74)	2,749 (23.28)
Other antihypertensive agents	4,038 (9.03)	649 (6.43)	885 (7.51)	1,039 (9.46)	1,465 (12.33)
Statins	30,683 (68.12)	7,331 (72.28)	8,222 (69.45)	7,394 (66.92)	7,736 (64.39)
Antiplatelet agents	35,690 (79.20)	8,288 (81.69)	9,489 (80.16)	8,716 (78.84)	9,197 (76.49)

Values are mean ± SD or n (%). p value for all comparisons <0.01, with the exception of atrial fibrillation/flutter (p = 0.04).

BMI = body mass index; PP = pulse pressure.

ASSOCIATION OF PP WITH ADVERSE CARDIOVASCULAR EVENTS.

Figure 1 displays the relationship of PP quartiles to all outcomes, including cardiovascular death, nonfatal MI, fatal and nonfatal MI, nonfatal stroke, fatal and nonfatal stroke, cardiovascular hospitalization, and the combined outcome (p < 0.01 for trend). Given the J-shaped relationship between PP and some of these outcomes, cubic splines modeling was performed (**Figure 2**). Cardiovascular death, fatal and nonfatal stroke, and the combined outcome showed nonlinear relationships (p < 0.05) with PP, whereas nonfatal MI, fatal and nonfatal MI, nonfatal stroke, and cardiovascular hospitalization did not

(p = 0.95, p = 0.70, p = 0.14, and p = 0.84, respectively). Exclusion of participants with congestive heart failure linearly transformed the relationship for the combined outcome (p = 0.14) but not for cardiovascular death (p = 0.01).

Table 2 shows event rates and unadjusted and multivariate-adjusted hazard ratios that occurred over a 4-year follow-up period by PP quartile. Approximately 30% experienced at least 1 of the outcomes over this period, with the majority of events attributed to cardiovascular hospitalization, reflecting a high-risk cohort. On univariate analysis, the fourth quartile of PP, and sometimes the third quartile, was

TABLE 2   Association of Pulse Pressure With Adverse Cardiovascular Events on Unadjusted and Multivariate-Adjusted Analyses

Outcome	Event Rate, n/N (%)	Unadjusted			Multivariate Adjusted*		
		HR	95% CI	p Value	HR	95% CI	p Value
CV death							
Quartile 1	586/10,153 (6.95)	–	–	–	–	–	–
Quartile 2	637/11,842 (6.58)	0.9	0.8-1.0	0.19	0.8	0.7-0.9	<0.01
Quartile 3	611/11,061 (6.63)	0.9	0.8-1.0	0.47	0.7	0.6-0.8	<0.01
Quartile 4	796/12,031 (8.09)	1.1	1.0-1.2	<0.01	0.8	0.7-0.9	<0.01
Nonfatal MI							
Quartile 1	271/10,153 (3.23)	–	–	–	–	–	–
Quartile 2	321/11,842 (3.4)	1.0	0.8-1.1	0.90	1.0	0.8-1.2	0.47
Quartile 3	345/11,061 (3.81)	1.1	1.0-1.3	0.05	1.2	1.0-1.4	0.01
Quartile 4	408/12,031 (4.14)	1.2	1.0-1.4	<0.01	1.3	1.1-1.5	<0.01
Fatal and nonfatal MI							
Quartile 1	399/11,068 (4.73)	–	–	–	–	–	–
Quartile 2	474/11,407 (4.98)	1.0	0.8-1.1	0.84	1.0	0.9-1.1	0.60
Quartile 3	508/12,821 (5.52)	1.1	1.1-1.3	0.01	1.1	0.9-1.3	0.05
Quartile 4	580/9,791 (5.86)	1.2	1.0-1.4	<0.01	1.1	1.0-1.3	0.03
Nonfatal stroke							
Quartile 1	368/10,153 (4.46)	–	–	–	–	–	–
Quartile 2	480/11,842 (4.89)	1.1	0.9-1.2	0.11	1.0	0.8-1.1	0.91
Quartile 3	517/11,061 (5.77)	1.2	1.1-1.4	<.01	1.1	0.9-1.2	0.12
Quartile 4	632/12,031 (6.33)	1.4	1.2-1.6	<.01	1.2	1.0-1.3	<0.01
Fatal and nonfatal stroke							
Quartile 1	448/10,153 (5.36)	–	–	–	–	–	–
Quartile 2	577/11,842 (5.86)	1.1	0.9-1.2	0.12	0.9	0.8-1.1	0.82
Quartile 3	592/11,061 (6.57)	1.2	1.0-1.3	<0.01	1.0	0.9-1.1	0.64
Quartile 4	743/12,031 (7.4)	4	1.2-1.5	<0.01	1.1	0.9-1.2	0.05
CV hospitalization							
Quartile 1	1,929/10,153 (21.54)	–	–	–	–	–	–
Quartile 2	2,203/11,842 (21.16)	0.9	0.9-1.0	0.37	1.0	0.9-1.0	0.63
Quartile 3	2,231/11,061 (22.92)	1.0	1.0-1.1	0.03	1.1	1.0-1.1	<0.01
Quartile 4	2,611/12,031 (24.63)	1.1	1.0-1.2	<.01	1.1	1.1-1.2	<0.01
CV death/MI/stroke/hospitalization							
Quartile 1	2,619/10,153 (29.27)	–	–	–	–	–	–
Quartile 2	3,008/11,842 (28.81)	0.9	0.9-1.0	0.40	0.9	0.9-1.0	0.53
Quartile 3	2,993/11,061 (30.6)	1.0	1.0-1.1	0.04	1.0	0.9-1.0	0.25
Quartile 4	3,548/12,031 (33.4)	1.1	1.1-1.2	<.01	1.1	1.0-1.1	<0.01

*Multivariate model adjusted for sex; age; current smoking status; history of hypercholesterolemia, diabetes, or atherothrombosis; and aspirin, statin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, calcium-channel blocker, or diuretic agent use.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

associated with increasing risk for all individual as well as combined adverse cardiovascular events. On multivariate analysis, the fourth quartile of PP showed a significant increase in the risk for all outcomes except fatal and nonfatal stroke (p value nonsignificant) but also for cardiovascular death, for which the relationship was inverted and higher PP quartile was protective (p <0.05). Given the discrepancy in comorbidity profile, further adjustment for coronary artery disease and congestive heart failure was performed, which abolished this trend for cardiovascular death (p = 0.14 for PP quartile 4).

Figure 3 demonstrates the strength of these associations per 10 mm Hg increase in PP, including both univariate and multivariate models. On univariate analysis, increasing PP was associated with worse outcomes (p < 0.01 for all outcomes). After adjustment for several potential confounding factors (model 1; covariates: sex, age, current smoking status, history of hypercholesterolemia, history of diabetes, aspirin use, and statin use), PP was still associated with all outcomes, except cardiovascular death. Additional adjustments in models 2 (covariates: history of stroke, MI, and peripheral arterial disease) and 3 (covariates: use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, calcium-channel blocker, or diuretic agent) yielded similar results.

FIGURE 3 Forest Plot of Pulse Pressure and Cardiovascular Outcomes Using Univariate and Multivariate Analysis

	Hazard Ratios	
	HR 95% CI	P Value
CV Death		
Univariate model	1.03 [1.01 - 1.06]	<.01
Multivariate (1) model	0.96 [0.94 - 0.98]	<.01
Multivariate (2) model	0.97 [0.95 - 1.00]	0.03
Multivariate (3) model	0.97 [0.94 - 0.99]	0.01
Multivariate (4) model	0.98 [0.95 - 1.01]	.16
Nonfatal MI		
Univariate model	1.07 [1.04 - 1.11]	<.01
Multivariate (1) model	1.07 [1.03 - 1.10]	<.01
Multivariate (2) model	1.09 [1.05 - 1.13]	<.01
Multivariate (3) model	1.08 [1.04 - 1.12]	<.01
Multivariate (4) model	1.08 [1.04 - 1.12]	<.01
Fatal and Nonfatal MI		
Univariate model	1.07 [1.04 - 1.10]	<.01
Multivariate (1) model	1.05 [1.02 - 1.08]	<.01
Multivariate (2) model	1.06 [1.03 - 1.09]	<.01
Multivariate (3) model	1.05 [1.02 - 1.08]	<.01
Multivariate (4) model	1.05 [1.02 - 1.09]	<.01
Nonfatal Stroke		
Univariate model	1.09 [1.06 - 1.12]	<.01
Multivariate (1) model	1.05 [1.02 - 1.08]	<.01
Multivariate (2) model	1.05 [1.02 - 1.08]	<.01
Multivariate (3) model	1.05 [1.02 - 1.08]	<.01
Multivariate (4) model	1.01 [0.98 - 1.04]	64
Fatal and Nonfatal Stroke		
Univariate model	1.09 [1.06 - 1.12]	<.01
Multivariate (1) model	1.04 [1.01 - 1.07]	<.01
Multivariate (2) model	1.04 [1.01 - 1.07]	<.01
Multivariate (3) model	1.04 [1.01 - 1.07]	<.01
Multivariate (4) model	1.00 [0.97 - 1.03]	.91
CV Hospitalization		
Univariate model	1.04 [1.02 - 1.05]	<.01
Multivariate (1) model	1.05 [1.03 - 1.06]	<.01
Multivariate (2) model	1.05 [1.04 - 1.07]	<.01
Multivariate (3) model	1.04 [1.03 - 1.06]	<.01
Multivariate (4) model	1.03 [1.02 - 1.05]	<.01
CV Death/MI/Stroke/Hospitalization		
Univariate model	1.04 [1.03 - 1.05]	<.01
Multivariate (1) model	1.03 [1.02 - 1.05]	<.01
Multivariate (2) model	1.03 [1.02 - 1.05]	<.01
Multivariate (3) model	1.03 [1.02 - 1.04]	<.01
Multivariate (4) model	1.02 [1.01 - 1.03]	<.01

Forest plots showing the relationship between pulse pressure, per 10 mm Hg increase, with several cardiovascular (CV) outcomes on univariate and multivariate analysis. Refer to the "Methods" section for a complete listing of covariates included for analysis. CI = confidence interval; MI = myocardial infarction.
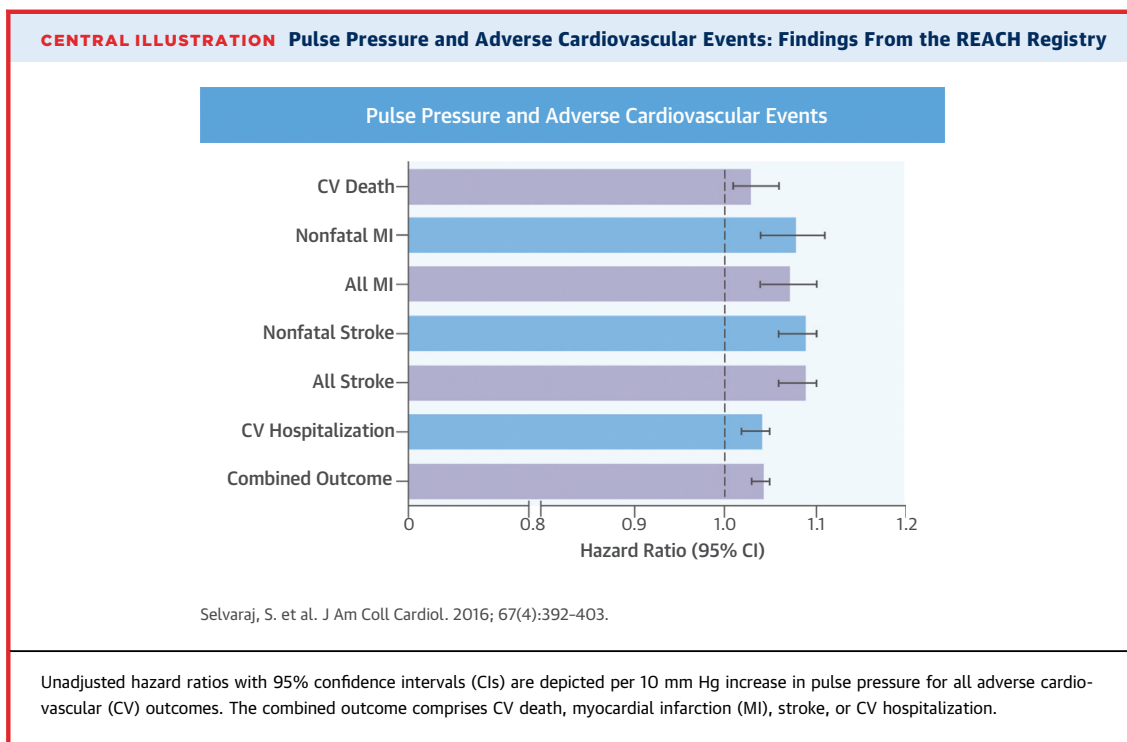
To determine whether PP adds prognostic information over mean arterial pressure, model 4 was performed (Figure 3). After additionally adjusting for mean arterial pressure, the relationships between PP and adverse events persisted for nonfatal MI, fatal and nonfatal MI, cardiovascular hospitalization, and the combined outcome (p < 0.01).

SUBGROUP ANALYSES. Sensitivity analyses were conducted in several subgroups, and these results are displayed as forest plots in Online Figures 1 to 7. When comparing estimates derived from model 4, the relationship between PP and adverse events varied by subgroup. In women, the only association that was significant was observed between PP and nonfatal MI

(p < 0.01). For participants greater than 60 years of age, associations were observed with nonfatal MI (p < 0.01), fatal and nonfatal MI (p < 0.01), and cardiovascular hospitalization (p = 0.02). For participants without established atherothrombotic disease, several statistically significant associations were found, including increasing risk with increasing PP for the following outcomes: nonfatal stroke, fatal and nonfatal stroke, cardiovascular hospitalization, and the combined outcome (p < 0.01 for all comparisons).

When stratifying by SBP levels using 140 mm Hg as the cutoff, the relationships between PP and nonfatal MI as well as the combined outcome were significant in hypertensive patients (p ≤ 0.05 for both

CENTRAL ILLUSTRATION   Pulse Pressure and Adverse Cardiovascular Events: Findings From the REACH Registry

Pulse Pressure and Adverse Cardiovascular Events

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Unadjusted hazard ratios with 95% confidence intervals (CIs) are depicted per 10 mm Hg increase in pulse pressure for all adverse cardiovascular (CV) outcomes. The combined outcome comprises CV death, myocardial infarction (MI), stroke, or CV hospitalization.

comparisons). In nonhypertensive patients, increasing PP was associated with higher risk for nonfatal MI and cardiovascular hospitalization but was protective against all stroke and cardiovascular death (p < 0.05 for all comparisons). Finally, when stratifying by antihypertensive treatment, increasing PP was associated with higher risk for cardiovascular hospitalization, all MI, and the combined outcome. However, in the untreated group, higher PP was associated with lower risk for nonfatal stroke and all stroke (p < 0.01 for all comparisons).

ASSOCIATION OF SBP AND DBP WITH ADVERSE CARDIOVASCULAR EVENTS. Data regarding the relationship between both SBP and DBP and adverse outcomes are presented in the Online Appendix. Similar to PP, increase in SBP quartile (particularly the fourth quartile) was associated with worsened outcomes in multivariate analysis (Online Table 2) (p < 0.05 for all comparisons except fatal and nonfatal MI). The complex relationship with cardiovascular death was similarly observed with SBP as was observed with PP (19). Similar adjustment for presence of coronary artery disease and congestive heart failure weakened, but did not abolish, the relationship (p = 0.04). The fourth quartile of DBP was associated with increasing risk for nonfatal stroke, fatal and nonfatal stroke, cardiovascular hospitalization, and the composite outcome (Online Table 3) (p ≤ 0.01 for all comparisons). However, quartile 2

was protective against nonfatal MI, fatal and nonfatal MI, cardiovascular hospitalization, and the combined outcome. In addition, all quartiles aside from the referent quartile were protective against cardiovascular death. Adjustment of all quartiles for coronary artery disease and congestive heart failure eliminated the relationship with cardiovascular death (p = 0.06).

DISCUSSION

In a large, international registry of >45,000 participants with established or at high risk for arterial disease, we found that higher PP conferred an increased risk for multiple adverse cardiovascular events (Central Illustration). The adverse relationships persisted between PP and several adverse outcomes, notably the combined outcome of cardiovascular death, cardiovascular hospitalization, nonfatal MI, and nonfatal stroke, after controlling for several potential confounding risk factors, including mean arterial pressure. Our study is among the largest international studies of PP and adds further support to the prognostic utility of PP. In addition, the REACH registry offers a contemporary analysis of the relationship between PP and adverse cardiovascular events, which is important given the change in patterns of cardiovascular disease in the past few decades (22).

Furthermore, given the large population and significant number of events, we were able to perform multiple sensitivity analyses to define more precisely the relationship between PP and adverse events in several subgroups. Of note, strong relationships were observed in participants without established atherothrombotic disease, suggesting that despite being lower risk, PP still has strong prognostic value. In participants older than 60 years of age, PP was associated with nonfatal MI and cardiovascular hospitalization. As shown previously, PP is particularly useful in older patients, because SBP and DBP tend to diverge after age 55 (23). Therefore, the resultant PP widening becomes a more accurate assessment of vascular bed compliance and cardiovascular risk.

The degree of SBP, we found, was also important. In hypertensive patients, there were significant increases in nonfatal MI and the combined outcome. However, in nonhypertensive subjects, this relationship with cardiovascular outcomes was mixed. Increasing PP was associated with higher risk for nonfatal MI and cardiovascular hospitalization; however, it was also protective against fatal and nonfatal stroke and, as a result, cardiovascular death, likely secondary to the resultant relationship between stroke and low DBP with widening PP (24). Two studies from the Framingham cohort found that PP independently predicted cardiovascular disease but that elevated SBP was an important modifying risk factor in the relationship (25,26). Finally, antihypertensive treatment also influences the relationship between PP and adverse events. For patients on treatment for hypertension, there was an increased risk for cardiovascular hospitalization, all MI, and the combined endpoint. For patients not on treatment for hypertension, increasing PP was protective again against nonfatal stroke and all stroke, which is again likely secondary to lower stroke risk with lower DBP.

It is important to note that these adverse relationships observed in the entire study population were most prominent with the fourth quartile of PP (corresponding to a PP of >70 mm Hg) and sometimes with the third quartile. The vast majority of patients in the fourth quartile of PP were hypertensive (SBP ≥140 mm Hg), while nearly one-half were very hypertensive (SBP ≥160 mm Hg). Thus, it is particularly notable that this quartile of PP continued to have significant associations with numerous adverse events even after adjusting for mean blood pressure. In addition, some of these relationships were J shaped (including cardiovascular death, all stroke, and the combined outcome). Thus, high PP states likely reflect adverse hemodynamic status, whereas low PP is not necessarily reassuring, because the latter may

indicate poor perfusion states. This hypothesis was further explored by removing patients with heart failure, which linearly transformed the relationship for the combined outcome, suggesting that low PP may be most problematic in this group and likely reflects low stroke volume (27).

Despite several studies on the topic, there is still some debate as to whether PP adds to cardiovascular risk stratification. The Framingham Heart Study showed in a cohort of nearly 2,000 participants that neither SBP nor DBP was superior to PP in predicting coronary events (4). However, this cohort was initially free of coronary heart disease and not taking antihypertensive medications. Conversely, in MRFIT (Multiple Risk Factor Intervention Trial), PP was, interestingly, found to be inferior to SBP and DBP in cardiovascular risk assessment in male patients free of diabetes mellitus and MI (11). The cohort analyzed in the present study was at higher risk than these other cohorts, with a predominantly hypertensive population and many with established atherothrombosis. Our findings of the additive utility of PP are consistent with other studies in higher risk populations (19,20).

The pathophysiologic correlates of elevated PP are complex. Increasing PP causes increased cyclic stretch on vascular structures. These changes in intramural tension catalyze numerous pathways, including atherosclerotic remodeling, facilitate proinflammatory cell migration, and increase oxidant production (1). Although increasing PP clearly accelerates atherothrombosis, the reverse is also true, whereby plaque formation increases vascular stiffness, and thereby PP, creating a vicious cycle. Previous study of peripheral PP has yielded inconsistent results in relation to adverse cardiovascular events. The large sample size of the present study provided enough power to detect a relationship. The relative risks for adverse events calculated here are comparable with those observed in previous studies (20,28).

We also examined the relationship between both SBP and DBP and adverse cardiovascular events. PP and SBP followed similar trends, as changes in PP quartiles largely reflect changes in SBP. In addition, there were J-shaped relationships between DBP and a few outcomes, including the combined outcome, which is consistent with a large, previous study in patients with atherothrombosis, in whom low blood pressure may not be ideal (19,29). Low diastolic pressure may be poorly tolerated because this may reflect reduced coronary filling, which predominantly occurs during diastole. Conversely, low DBP may reflect "reverse causality," wherein low pressure is a symptom of the disease, not a cause, and therefore may

represent a sicker population (30). Furthermore, PP continued to show a more linear relationship with stroke, as seen previously (19,31). The discrepant relationships between SBP and DBP and adverse cardiovascular events stress the importance of calculating PP. However, our findings are not meant to support the isolated use of PP. As also demonstrated in the Framingham Heart Study, the combined use of both static (i.e., SBP or mean arterial pressure) and dynamic (i.e., PP) measurements best captures cardiovascular risk (32).

Current guidelines for the management of hypertension have focused on SBP and DBP (33). PP has previously been identified as providing prognostic value even beyond the previous iteration of the Joint National Committee classification for hypertension (3). In addition, normal mean arterial pressure can still signify increased cardiovascular risk in the setting of high PP (34). Because PP is easily calculated from blood pressure, its clinical utility is high. Reduction in PP may serve as a therapeutic target; however, future research is necessary to delineate its role more precisely.

STUDY LIMITATIONS. Our results should be interpreted in the context of several limitations. First, central PP may provide physiologically more relevant information than peripheral measurements, because proximal measurements capture effects perceived by the heart as well as the coronary and carotid arteries. However, obtaining these data requires special devices not amenable to routine clinical practice; in addition, a recent meta-analysis showed that central PP does not offer a significant increase in predictive ability over peripheral PP (28).

Second, heart rate was not collected and therefore could not be adjusted for on multivariate analysis.

Third, REACH studied high-risk subjects with clinical atherothrombotic disease or multiple risk factors for atherothrombosis. Therefore, our results may not be generalizable to healthier cohorts. However, we performed subgroup analysis in subjects without established atherothrombosis, and many adverse relationships were still observed.

Fourth, REACH did not identify subjects with severe aortic stenosis, which could explain the relationship between low PP and increased cardiovascular

mortality even after excluding patients with heart failure.

Fifth, the REACH registry does not provide ambulatory blood pressure measurements, which have been shown to improve cardiovascular risk stratification (35).

Sixth, our study demonstrated digit preference bias, reflected by the higher than expected number of blood pressure readings ending in zero, which has been observed in numerous previous studies (36-38). It is not clear if this affected our results, but it does underscore the need for better training in the measurement of blood pressure in clinical practice.

CONCLUSIONS

In a large study of high-risk subjects with risk factors for, or established, atherothrombosis, PP adds valuable information in cardiovascular risk stratification to standard risk factors, including mean arterial pressure. These results are particularly relevant because the population reflects many modern clinical practices, given the large burden of atherothrombotic disease studied here. PP, which is readily available in the office setting, can help risk stratify high-risk patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PP, which can arise as a consequence of arterial stiffness in patients with atherosclerosis, is a marker of cardiovascular disease burden and identifies patients at risk for ischemic events irrespective of age, sex, SBP, antihypertensive therapy, or previous atherothrombotic events.

TRANSLATIONAL OUTLOOK: Future studies should assess the outcomes of therapies that specifically target long-term reduction of arterial PP.

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