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Visit-to-Visit Blood Pressure Variability, Coronary Atheroma Progression, and Clinical Outcomes

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IMPORTANCE Visit-to-visit blood pressure variability (BPV) is associated with cardiovascular events, but mechanisms and therapeutic implications underlying this association are not well understood.

OBJECTIVE To examine the association of intraindividual BPV, coronary atheroma progression, and clinical outcomes using serial intravascular ultrasonography.

DESIGN, SETTING, AND PARTICIPANTS Post hoc patient-level analysis of 7 randomized clinical trials conducted from 2004 to 2016 involving 3912 patients in multicenter, international, clinic-based primary and tertiary care centers. Adult patients with coronary artery disease who underwent serial intravascular ultrasonography in the setting of a range of medical therapies were included. Data were analyzed between November 2017 and March 2019.

EXPOSURES Visit-to-visit BPV measured using intraindividual standard deviation over 3, 6, 12, 18, and 24 months.

MAIN OUTCOMES AND MEASURES Percent atheroma volume (PAV) progression and major adverse cardiovascular events (defined as death, myocardial infarction, stroke, urgent revascularization for acute coronary syndrome, and hospitalization for unstable angina).

RESULTS Of 3912 patients, the mean (SD) age was 58 (9) years, 1093 (28%) were women, and 3633 (93%) were white . Continuous change in PAV was significantly associated with systolic BPV (β, .049; 95% CI, 0.021-0.078; P = .001), diastolic BPV (β, .031; 95% CI, 0.002-0.059; P = .03), and pulse pressure variability (β, .036; 95% CI, 0.006-0.067; P = .02), without a signal for differential effect greater than or less than a mean BP of 140/90 mm Hg. The PAV progression as a binary outcome was significantly associated with systolic BPV (odds ratio, 1.09; 95% CI, 1.01-1.17; P = .02) but not diastolic BPV (odds ratio, 1.04; 95% CI, 0.97-1.11; P = .30) or pulse pressure variability (odds ratio, 1.03; 95% CI, 0.96-1.10; P = .47). Survival curves revealed a significant stepwise association between cumulative major adverse cardiovascular events and increasing quartiles of systolic BPV (Kaplan-Meier estimates for quartiles 1-4: 6.1% vs 8.5% vs 10.1% vs 12.0%, respectively; log-rank P <.001). These distinct stepwise associations were not seen with diastolic BPV or pulse pressure variability.

CONCLUSIONS AND RELEVANCE Greater BPV, particularly systolic BPV, is significantly associated with coronary atheroma progression and adverse clinical outcomes. These data suggest maintaining stable blood pressure levels may be important to further improve outcomes in patients with coronary disease.

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Supplemental content

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Higher visit-to-visit blood pressure variability (BPV) is a predictor of cardiovascular events and all-cause mortality, findings demonstrated across multiple cohorts over the last 20 years.[1] Despite the established prognostic importance of BPV, little is known about underlying mechanisms or therapeutic implications of this phenomenon. Blood pressure variability has been associated with measures of arterial stiffness and endothelial dysfunction, but whether BPV is directly associated with coronary atheroma progression-regression remains less well explored.

Intravascular ultrasonography (IVUS) provides precise and reproducible volumetric measurements of coronary atheroma.[2] Serial IVUS permits the examination of the association of intraindividual BPV with coronary atheroma progression. We tested the hypothesis that intraindividual systolic BPV, diastolic BPV, and pulse pressure variability are associated with coronary atheroma progression-regression and clinical outcomes.

Key Points

Question Is blood pressure variability associated with coronary atheroma progression and adverse clinical outcomes in patients with coronary artery disease?

Findings In this post hoc analysis of 7 randomized clinical trials including patients who underwent serial intravascular ultrasonography, greater blood pressure variability was significantly associated with coronary atheroma progression and major adverse cardiovascular events.

Meaning These findings suggest greater blood pressure variability is associated with a proatherosclerotic process, and maintaining stable blood pressure levels may improve cardiovascular outcomes in patients with coronary artery disease.

Methods

Study Population

This analysis included all participants across 7 randomized clinical trials assessing the effect of medical therapies on serial changes in coronary atheroma burden using IVUS. Each trial protocol included at least 4 blood pressure (BP) measurements, therefore allowing for variability assessment. Included in this analysis were trials assessing intensive lipid lowering with statins (Reversal of Atherosclerosis With Aggressive Lipid Lowering [REVERSAL]),[3] antihypertensive therapies (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study [AQUARIUS][4] and Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation [NORMALISE]),[5] the antiatherosclerotic efficacy of acyl-coenzyme A:cholesteryl ester transfer protein inhibition (ACAT Intravascular Atherosclerosis Treatment Evaluation [ACTIVATE]),[6] cholesteryl ester transfer protein inhibition (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation [ILLUSTRATE]),[7] endocannibanoid receptor antagonism (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabont-The Intravascular Ultrasound Study [STRADIVARIUS]),[8] and proprotein convertase sbtilisin kexin type inhibitors (Effect of Evolucumab on Progression of Coronary Disease in Statin-Treated Patients [GLAGOV]).[9] All trials were conducted with written informed consent from study participants and approved by the institutional review board of each participating institution. Institutional review board approval was not obtained for this post hoc analysis because no direct patient identifying information was used in this data set.

Blood Pressure Measurement and Drug Adherence

Trials included in this analysis were not conducted to specifically assess BP; rather, the primary focus was to assess differences in coronary atheroma progression using IVUS in response to a variety of antiatherosclerotic compounds, some of which affected BP. All trials were conducted by the Cleveland Clinic Coordinating Center for Clinical Research, and protocols were rigorously designed and implemented by trained academic investigators. Blood pressure measurements were obtained in a standardized fashion by trained research personnel using a manual cuff and stethoscope. Timing and position of BP measurements varied between trials; details are outlined in eTable 3 in the Supplement. Detailed pill counts of concomitant medications were not a routine part of the serial IVUS trials included in this analysis; therefore, a granular assessment of objective medication compliance is not possible. However, self-reported study drug compliance was assessed and charted. Study drug compliance was determined by dividing the percentage of time each participant took the study drug by the duration of the study. Across studies, median study drug compliance was 95.1 (interquartile range, 92.7-97.5). Furthermore, across studies, expected changes in lipid and various metabolic parameters in response to therapies being tested support the likelihood of globally high rates of medication adherence.

Variability Assessment

Blood pressure variability was assessed across 3-month, 6-month, 12-month, 18-month, and 24-month measures. Visit-to-visit variability was defined as variability in systolic BP, diastolic BP, and pulse pressure between visits. For patients with missing BP values at any specific visit, available values at other times were used to calculate variability. A sensitivity analysis was conducted using multiple imputation for missing values. Variability was measured in 2 ways: (1) standard deviation (SD) of BP values and (2) coefficient of variation (CV) calculated as (SD/mean) × 100 for each individual patient.[10]

Acquisition and Analysis of Serial IVUS Images

The acquisition and serial analysis of IVUS images in each of these trials has been previously described in detail.[3] Briefly, target vessels for imaging were selected if they contained no luminal stenosis of greater than 50% angiographic severity within a segment of at least 30-mm length. Imaging was performed within the same coronary artery at baseline and at study completion, which ranged from 18 to 24 months. Imaging in all trials was screened by the Atherosclerosis Imaging Core Laboratory of Cleveland Clinic Coordinating Center for Clinical Research. Patients meeting prespecified requirements for

image quality were eligible for randomization. An anatomically matched segment was defined 2 times on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. Leading edges of the lumen and external elastic membrane were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges. The accuracy and reproducibility of this method have been reported previously.[11] The percent atheroma volume (PAV) was determined by calculating the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the segment of interest as follows:

$$PAV = \frac{\sum(EEM_{area} - Lumen_{area})}{\sum EEM_{area}} \times 100$$

Statistical Analysis

Continuous variables are reported as mean and SD. Categorical variables are reported as frequency and percent. A paired *t* test was used to test whether the mean change in BP from baseline was different from zero. While adjusting for trial and baseline PAV, a mixed model was used to test whether the least-squares mean annualized change in PAV from baseline was different from zero. Spearman correlation was used to assess the association between BPV and different follow-up blood pressure measures; ρ with 95% confidence intervals are reported.

Multivariable mixed models were constructed to assess the association of BPV with annualized change in PAV (ΔPAV). To compare regression coefficients across models, continuous data were first standardized to have a mean of zero and an SD of 1, and then the models were run on this standardized data. Variables adjusted for in each model included age; sex; race/ethnicity; body mass index (calculated as weight in kilograms divided by height in meters squared); diabetes; history of cardiovascular event (myocardial infarction, stroke, or coronary artery bypass grafting); respective baseline and mean follow-up BP measure; region; concomitant statin use; concomitant antihypertensive medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, β-blockers, and diuretics); baseline PAV; baseline, mean, and maximum follow-up BP; study drug discontinuation; and clinical trial. Covariates were selected based on prior knowledge as potentially relevant clinically meaningful factors with an association between the exposure and outcomes. β Coefficients with 95% confidence intervals are reported. Similarly, logistic regression models were constructed to assess the association of BPV with any plaque progression. The same standardization and adjustments were made in these models as those previously mentioned. Odds ratio (OR) with 95% CI are reported. Sensitivity analyses were also performed in an effort to account for missing data. Missing values were imputed using multiple imputation procedures. These imputed data were then standardized as before and the models were rerun.

Kaplan-Meier curves illustrate the first incidence of major adverse cardiovascular event (MACE; defined as death, myocardial infarction, stroke, urgent revascularization for acute coronary syndrome, and/or hospitalization for unstable angina) stratified by quartiles of the SD of each BP measure. The data for the curves are censored at 24 months. Kaplan-Meier estimates of cumulative incidence of MACE are reported by quartile on each plot with tests of trend reported. Patients who received torcetrapib in ILLUSTRATE were excluded from the MACE sensitivity analysis owing to torcetrapib's toxic effect.[12]

All tests were 2-tailed, with a .05 significance level. Analyses were done using SAS, version 9.4 (SAS Institute, Inc). Figures were made using R, version 3.0.1 (R Foundation for Statistical Computing) and SigmaPlot, version 11.0 (Systat Software Inc).

Results

Table 1 describes baseline demographics, clinical characteristics, and medication use of the pooled study population (n = 3912) stratified by quartile of SD of BPV. Overall, mean (SD) age was 58 (9) years, 1093 of 3912 were women (28%), 1002 of 3912 had diabetes mellitus (26%), and the mean (SD) body mass index was 30.9 (5.9). On-trial medication rates of statins, aspirin, β-blockers, and angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use were 3727 of 3912 (95%), 3591 of 3912 (92%), 3009 of 3912 (77%), 2678 of 3912 (68%), respectively. Baseline characteristics stratified by quartile of SD of BPV for diastolic BP and pulse pressure are presented in eTable 1 in the Supplement.

Baseline and follow-up for BP measurements and plaque volume are presented in eTable 2 in the Supplement. In the overall population, the mean (SD) achieved levels of systolic BP, diastolic BP, and pulse pressure were 129.2 (12.2) mm Hg, 76.8 (7.0) mm Hg, and 52.4 (10.2) mm Hg, respectively. Overall, there was no significant change in mean (SD) PAV from baseline (37.8% [9.0%]) until follow-up (38.0% [9.1%]); $P = .08$. Associations between BPV and mean, minimum, and maximum follow-up BP are presented in eTable 3 in the Supplement, demonstrating high association among all measurements. Trial characteristics as well as the mean intraindividual SD of each BP variable stratified by clinical trial are presented in eTable 4 in the Supplement.

Table 2 describes the association of annualized change in PAV with systolic BPV, diastolic BPV, and pulse pressure variability using SD. The SD of systolic BPV measurements was significantly associated with PAV progression (β systolic BPV, .096; 95% CI, 0.026-0.166; $P = .007$). The association was not statistically significant for diastolic BPV (β, .003; 95% CI, −0.056 to 0.062; $P = .92$) or pulse pressure variability (β, .072; 95% CI, −0.005 to 0.149; $P = .07$). These results were consistent when CV was used as a measure of variability, presented in eTable 5 in the Supplement.

Trial participants with missing BP values (only 1, 2, or 3 BP measurements) were not included in the primary analysis. A sensitivity analysis using multiple imputation for missing BP values was performed and presented in eTable 6 in the Supplement. Overall, there was not a major change in results.

Figure 1 illustrates the association of the binary outcome of PAV progression vs no progression (defined as ΔPAV >0 or

Table 1. Patient Characteristics by Quartiles of SD of Systolic Blood Pressure (N = 3912; 978 per Quartile)

Characteristic	Quartile of SD of Systolic Blood Pressure, No. (%)				Test of Trend *P* Value
	1	2	3	4	
Systolic BP SD, mean (SD), mm Hg	4.4 (1.2)	7.6 (0.8)	10.8 (1.1)	17.3 (4.4)	NA
Demographics					
Age, mean (SD), y	57 (9)	58 (9)	58 (9)	60 (9)	<.001
Female	226 (23)	267 (27)	279 (29)	321 (33)	<.001
White	916 (94)	898 (92)	925 (95)	894 (91)	.28
BMI, mean (SD)	30.2 (5.5)	30.8 (5.6)	31.2 (6.0)	31.4 (6.2)	<.001
Current smoker	241 (25)	228 (23)	222 (23)	233 (24)	.60
Medical history					
Hypertension	721 (74)	734 (75)	767 (78)	826 (85)	<.001
Diabetes	206 (21)	251 (26)	262 (27)	283 (29)	<.001
Hyperlipidemia	724 (74)	733 (75)	764 (78)	798 (82)	<.001
Congestive heart failure	48 (5)	44 (5)	42 (4)	66 (7)	.09
MI	312 (32)	299 (31)	300 (31)	303 (31)	.69
CABG	16 (2)	28 (3)	32 (3)	26 (3)	.13
PCI	412 (42)	414 (42)	423 (43)	447 (46)	.10
CVA	25 (3)	21 (2)	30 (3)	46 (5)	.003
PVD	26 (3)	43 (4)	48 (5)	64 (7)	<.001
Medication use during trial					
Aspirin	898 (92)	905 (93)	883 (90)	905 (93)	.98
β-Blockers	721 (74)	750 (77)	767 (78)	771 (79)	.005
ACE inhibitors	508 (52)	521 (53)	534 (55)	572 (59)	.003
Angiotensin-receptor blockers	165 (17)	179 (18)	192 (20)	265 (27)	<.001
Calcium channel blockers	302 (31)	353 (36)	341 (35)	398 (41)	<.001
Diuretics	286 (29)	329 (34)	319 (33)	452 (46)	<.001
Statins	941 (96)	927 (95)	932 (95)	927 (95)	.21

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CABG, coronary artery bypass graft; CVA, cerebral vascular accident; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention, PVD, peripheral vascular disease.

ΔPAV <0) with BPV. The SD of systolic BPV was significantly associated with PAV progression (OR, 1.09; 95% CI, 1.02-1.17; *P* = .02) when maximum BP is not in the model but lost significance when maximum follow-up BP was included (OR, 1.17; 95% CI, 0.98-1.39; *P* = .09). There was no significant association with PAV progression and diastolic BPV (OR, 1.00; 95% CI, 0.87-1.15; *P* = .98) or pulse pressure variability (OR, 1.13; 95% CI, 0.94-1.36; *P* = .20).

Figure 2 illustrates Kaplan-Meier curves assessing MACE among patients stratified across quartiles of BP measurement SD. At 24 months, there were significant stepwise associations between cumulative MACE and increasing quartiles of systolic BPV (Kaplan-Meier estimates for quartiles 1 to 4, 6.1% vs 8.5% vs 10.1% vs 12.0%, respectively; *P* value for trend <.001). Generally, there was increasing incidence of MACE with increasing diastolic BPV; however, there was not a distinct continuous trend across consecutive quartiles (8.0% vs 6.0% vs 11.9% vs 10.9%; *P* = .005). Results were similar for the quartiles of pulse pressure variability, with the general trend of increasing incidence of MACE approaching significance, but again, not with a distinct continuous trend across consecutive quartiles (7.6% vs 7.6% vs 11.7% vs 10.4%; *P* = .07). Kaplan-Meier estimates of MACE stratified by quartiles using CV are presented in eTable 7 in the Supplement; similar results are observed.

Discussion

In this post hoc patient-level analysis of 7 clinical trials using serial coronary IVUS, we demonstrate that greater visit-to-visit BPV is significantly associated with coronary atheroma progression and adverse clinical outcomes. Our results confirm prior work outlining BPV to be a predictor of cardiovascular events and further extend these findings to indicate that BPV, in particular systolic BPV, manifests as a proatherosclerotic process. This analysis thus demonstrates an association linking BPV and cardiovascular events and suggests maintaining BP stability may be important to further improve cardiovascular outcomes in patients with coronary artery disease.

Several analyses during the last 2 decades across multiple cohorts have demonstrated that higher visit-to-visit BPV is associated with cardiovascular events.[1,13] However, mechanisms and therapeutic implications of this phenomenon remain unclear. Higher BPV has been associated with measures of arterial stiffness and endothelial dysfunction, suggesting that alterations in vascular function may contribute to greater BPV.[14-16] Smaller studies evaluating the association of BPV and measures of atherosclerosis have yielded discrepant results. Analysis of the PREVENT trial[17] demonstrated BPV to be associated with change in carotid intima-media thickness, find-

ings not evident in a similar analysis of the European Lacidipine Study on Atherosclerosis.[18] Further, a small analysis showed no association with BPV and coronary atheroma volume, leading to speculation regarding differential hemodynamic effects across vascular beds.[17] This analysis is substantially larger than prior studies, represents a range of studies coordinated by the same academic group with consistent image-based inclusion-exclusion criteria, and all were analyzed in the same core laboratory spanning more than a decade of expertise.

Table 2. Standardized Association of BP Variability with Annualized Change in PAV[a]

BP Category[b]	SD and ΔPAV Standardized β (95% CI)	*P* Value
Systolic BP		
Overall population	0.096 (0.026 to 0.166)	.007
Mean follow-up[c,d]		
BP <140/90 mm Hg	0.123 (0.042 to 0.203)	.003
SBP >140 mm Hg or DBP >90 mm Hg	0.023 (−0.117 to 0.162)	.75
Diastolic BP		
Overall population	0.003 (−0.056 to 0.062)	.92
Mean follow-up[c,d]		
BP <140/90 mm Hg	0.009 (−0.057 to 0.074)	.80
SBP >140 mm Hg or DBP >90 mm Hg	0.002 (−0.131 to 0.134)	.98
Pulse pressure		
Overall population	0.072 (−0.005 to 0.149)	.07
Mean follow-up[c,d]		
BP <140/90 mm Hg	0.106 (0.017 to 0.194)	.02
SBP >140 mm Hg or DBP >90 mm Hg	−0.042 (−0.194 to 0.110)	.59

Abbreviations: BP, blood pressure; CV, coefficient of variation; PAV, percent atheroma volume; SBP, systolic blood pressure.

[a] All models are adjusted for age; sex; race/ethnicity; body mass index; diabetes; history of cardiovascular event (myocardial infarction, stroke, or coronary artery bypass grafting); respective baseline, mean, and maximum follow-up BP measure; region; concomitant statin use; concomitant antihypertensive medications (angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, β-blockers, calcium channel blockers, and diuretics); baseline PAV; baseline and mean follow-up low-density lipoprotein cholesterol; study drug discontinuation; and trial.

[b] Overall population: N = 3830.

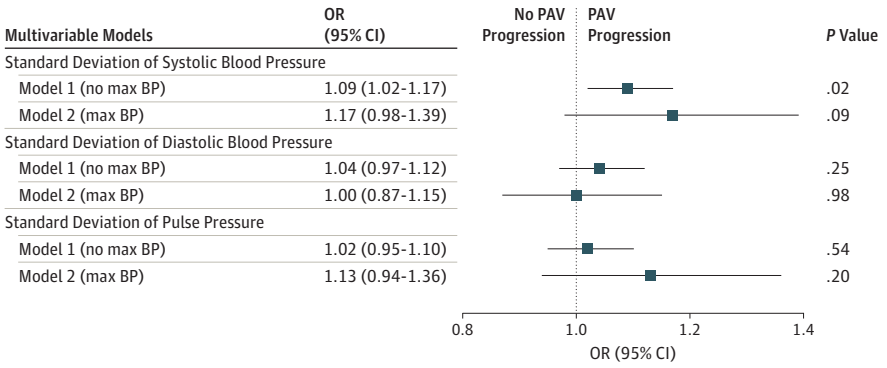
[c] Mean follow-up BP <140/90 mm Hg: n = 3106.

[d] Mean follow-up SBP >140 mm Hg or DBP >90 mm Hg: n = 724.

These data more definitively establish the association between higher BPV, particularly systolic BPV, and coronary atheroma progression. The stronger association with systolic BPV may be linked to the relatively older age of participants included in this analysis. Systolic BP, as compared with diastolic BP or pulse pressure, is known to have more prognostic importance with increasing age.[19] It is important to note the high association with BPV and maximum BP, minimum BP, and mean BP. While there exists an independent association between BPV and coronary atheroma progression, it is possible that variability per se may not be the underlying fundamental mechanism; rather, it may be associated with some other BP-related cause. It is interesting that BPV is most strongly associated with maximum BP and that the association between BPV and ΔPAV as a binary outcome loses significance when adjusting for maximum BP. This observation may suggest the adverse associations with BPV are more attributed to periodic spikes in BP, as compared with the pure up-and-down oscillation of measurements. While it is difficult to disentangle the interaction, our primary analysis evaluating ΔPAV as a continuous outcome represents the most granular assessment and suggests that variability remains significant for systolic BP even when adjusting for maximum BP.

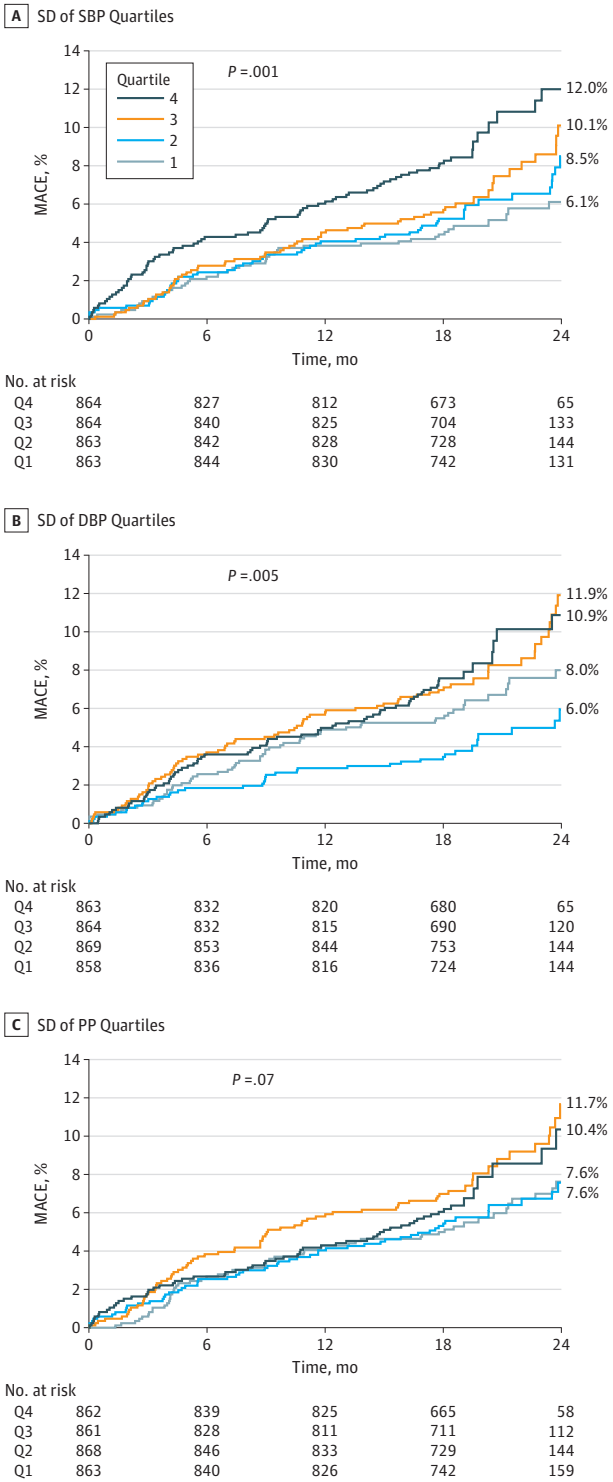
Additionally, further research is needed to evaluate the association between atheroma progression and BPV. Atheroma progression in the coronary arteries and/or other vascular beds may be the inciting event leading to higher BPV via underlying pathobiologic mechanisms influenced by ischemia or baroreflexes. Another proposed mechanism implicates increased oscillatory shear

Figure 1. Standardized Association of Variability With Coronary Atheroma Progression



Models 1 and 2 without and with maximum blood pressure (BP) included, respectively. All models are adjusted for age; sex; race/ethnicity; body mass index; diabetes; history of cardiovascular event (myocardial infarction, stroke, or coronary artery bypass grafting); respective baseline and mean follow-up blood pressure measure; region; concomitant statin use; concomitant antihypertensive medications (angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, β-blockers, calcium channel blockers, and diuretics); baseline percent atheroma volume (PAV); baseline and mean follow-up BP; study drug discontinuation, and trial. Max indicates maximum; OR, odds ratio.

Figure 2. Major Adverse Cardiovascular Events (MACE) Among Patients Stratified Across Quartiles of Blood Pressure (BP) Variability



MACE is defined as death, myocardial infarction, stroke, urgent revascularization for acute coronary syndrome, and hospitalization for unstable angina. DBP indicates diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

stress, a result of higher BPV, promoting atheroma progression.[17] Regardless, these findings establish a significant association between higher BPV and a proatherosclerotic process, rather than a broader homeostatic imbalance, in mediating the association between BPV and CVD events.

It is important to note that this analysis includes patients with stable coronary artery disease, most of whom had hypertension (78%) and well-controlled systolic BP (mean [SD] follow-up systolic BP, 129.2 [12.2] mm Hg). The association between atheroma progression and visit-to-visit BPV was significant among those with mean systolic BP of less than 140/90 mm Hg. These findings suggest that BPV is a phenomenon that may portend risk even among those with well-controlled BP. Patients with hypertension with controlled BP are known to have excessive cardiovascular risk compared with normotensive patients.[20,21] Moreover, recent work has demonstrated that BPV, but not mean BP, is associated with CVD events,[22] and that most CVD events in the modern era occur in individuals with BP less than 140/90 mm Hg.[23] This analysis suggests that visit-to-visit BPV may be an important determinant of outcomes among high-risk patients with hypertension, even when BP is well controlled, thus highlighting the concept of achieving BP stability as well as a numerical target for optimal risk reduction.

Results of this analysis may have implications when considering treating patients at risk for cardiovascular events. While higher BPV is associated with increased risk of CVD events, clinicians are without direction regarding its treatment: should high BPV prompt further diagnostic workup or medication adjustment?[24] Coronary atheroma progression is a process that is significantly associated with incident CVD events.[25] Medications, such as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), curb coronary atheroma progression and induce its regression,[26] and these findings suggest this may be a potential therapeutic intervention to lower CVD risk among those with higher BPV. Furthermore, there is renewed interest for renal denervation for BP management, with improved ablation techniques and more rigid trial design.[27] The effect of renal denervation vs medication alone on BPV may be an important determinant of outcomes. Further studies are required to evaluate therapeutic implications of BPV.

Limitations

Several caveats of this analysis warrant further consideration. This analysis is limited to patients enrolled in clinical trials with established coronary artery disease with an indication for coronary angiography, and thus may not be applicable to those without documented atherosclerotic heart disease. Despite a rigorous statistical approach and relatively uniform inclusion/exclusion criteria in each trial, unmeasured confounding biasing the results cannot be excluded. Methods of BP measurement were not consistent across trials; however, measurement was consistent within each trial, therefore introducing less measurement effect on intraindividual BPV. Trials included in this analysis were not designed to study the effect of BPV and MACE; therefore, it is important to note that the Kaplan-Meier curves in this

analysis represent an association, not prediction or causation, and should be viewed as hypothesis generating. On the other hand, these data are unique in analyzing BPV across multiple clinical trials using appropriate statistical means to account for both confounders and the range of trialed therapies included in this analysis. Detailed pill counts were not a routine part of the serial IVUS trials included in this analysis; however, compliance rates were shown to be systematically greater than 90% across these trials, thereby minimizing the issue of medication noncompliance. Further, it has been shown that medication adherence likely only accounts for a small percentage of BPV.[13]

Conclusions

In conclusion, in patients with coronary artery disease receiving established medical therapies, greater visit-to-visit BPV, particularly systolic BPV, was significantly associated with coronary atheroma progression and adverse clinical outcomes. These observations establish a mechanistic link underlying a body of literature demonstrating an association between BPV and CVD risk and suggest maintaining stable BP levels may be important to further improve outcomes in patients with coronary disease.

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Acquisition, analysis, or interpretation of data: Clark, Nicholls, St. John, Elshazly, Ahmed, Nissen, Puri.
Drafting of the manuscript: Clark, Puri.
Critical revision of the manuscript for important intellectual content: All authors.
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