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SPECIAL FOCUS ISSUE: BLOOD PRESSURE

Low Diastolic Blood Pressure Is Associated With Angina in Patients With Chronic Coronary Artery Disease

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ABSTRACT

BACKGROUND In patients with coronary artery disease (CAD), low diastolic blood pressure (DBP) is associated with increased risk of myocardial infarction, but its association with angina is unknown.

OBJECTIVES The goal of this study was to examine the association of low DBP and angina in patients with CAD.

METHODS The study assessed the frequency of angina (measured by using the Seattle Angina Questionnaire–Angina Frequency score) according to DBP in patients with known CAD from 25 U.S. cardiology clinics. Hierarchical logistic regression was used to test the association between DBP and angina, with a spline term for DBP to assess nonlinearity.

RESULTS Among 1,259 outpatients with CAD, 411 (33%) reported angina in the prior month, with higher rates in the lowest DBP quartile (40 to 64 mm Hg: 37%). In the unadjusted model, DBP was associated with angina with a J-shaped relationship ($p = 0.017$, p for nonlinearity $= 0.027$), with a progressive increase in odds of angina as DBP decreased below ~70 to 80 mm Hg. This association remained significant after sequential adjustment for demographic characteristics ($p = 0.002$), comorbidities ($p = 0.002$), heart rate ($p = 0.002$), systolic blood pressure ($p = 0.046$), and antihypertensive antianginal medications ($p = 0.045$).

CONCLUSIONS In patients with chronic CAD, there seemed to be an association between lower DBP and increased odds of angina. If validated, these findings suggest that clinicians should consider less aggressive blood pressure control in patients with CAD and angina. (J Am Coll Cardiol 2018;72:1227–32) © 2018 by the American College of Cardiology Foundation.

Treatment of hypertension (HTN) through reduction in blood pressure (BP) is a cornerstone for the prevention of cardiovascular events in patients with and without established coronary artery disease (CAD) (1). However, the optimal BP range for patients is unclear, as aggressively reducing BP has the potential risks of symptomatic hypotension, worsening kidney function (2), and an increased risk for cardiovascular events (3). The association of BP with outcomes has generally

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ABBREVIATIONS AND ACRONYMS

AF = angina frequency
BP = blood pressure
CAD = coronary artery disease
DBP = diastolic blood pressure
HTN = hypertension
SAQ = Seattle Angina Questionnaire
SBP = systolic blood pressure

been observed to have a J-shaped relationship, although there has been much discussion about where the nadir of the J-point lies (4). Although much of this research has focused on systolic BP (SBP), studies have also shown that aggressively treating diastolic BP (DBP) is associated with an increased risk of myocardial infarction and cardiovascular death (5).

Despite the extensive literature associating low DBP with cardiac events, there is limited information on its association with angina. Because coronary perfusion occurs during diastole, where the perfusion pressure is the difference between DBP and end-diastolic left ventricular pressure, we hypothesized that excessive reduction in DBP could lead to inadequate coronary perfusion and a greater prevalence of angina in patients with stable CAD (6). This clinical question is particularly relevant, as many antianginal medications may also lower DBP, and the present analysis could provide guidance on the optimal level of BP control among patients with symptomatic CAD. We therefore used a multicenter registry of outpatients with CAD to describe the association of DBP with the presence of angina.

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METHODS

STUDY POPULATION AND PROCEDURES. The APPEAR (Angina Prevalence and Provider Evaluation of Angina Relief) study was a cross-sectional, observational trial designed to quantify and assess angina and quality of life in outpatients with chronic CAD. Consecutive patients with a diagnosis of CAD (defined as stable angina, prior myocardial infarction, or prior coronary revascularization) were enrolled from 25 U.S. cardiology outpatient practices between April 2013 and July 2015. Eligible patients included those ≥18 years of age who had ≥1 prior office visit to the practice. Patients who had dementia, were unable to speak or read English, or were unable or unwilling to participate were excluded. Trained site coordinators recorded patient demographic characteristics, comorbidities, medications (before and after the clinic visit), and vital signs via chart review at the time of the office visit. Each site obtained institutional research board approval for the study, and all patients provided written informed consent.

ASSESSMENT OF ANGINA. Before meeting their clinician, patients completed the Seattle Angina Questionnaire (SAQ), a reliable and valid, 19-item, self-administered, disease-specific health status questionnaire with a 4-week recall period that measures clinically relevant dimensions of health in patients with CAD (7,8). The primary outcome for this study was the Angina Frequency (SAQ-AF) scale, which correlates well with daily angina diaries and is associated with mortality, hospitalizations for acute coronary syndromes, and health care costs in patients with chronic CAD (9–11). Scores range from 0 to 100, with higher scores indicating less angina, and were dichotomized into any angina (SAQ-AF score <100) versus no angina (SAQ-AF score = 100) over the past 4 weeks, congruent with previous research (12).

Because there are no established categories of risk for DBP, we first divided the cohort into quartiles of DBP. Demographic, socioeconomic, and clinical characteristics were then compared across the DBP quartiles by using analysis of variance for continuous variables and chi-square tests for categorical variables. A hierarchical, logistic regression model was constructed to examine the association of DBP with the odds of angina, first unadjusted and then sequentially adjusted for factors that could confound the association of DBP with angina. These factors included the following: 1) sociodemographic variables (age, sex, race, insurance status, education history, and avoidance of care due to cost); 2) comorbidities (body mass index, HTN, diabetes, history of stroke or transient ischemic attack, history of myocardial infarction, and chronic kidney disease; 3) heart rate; and 4) antihypertensive antianginal medications (calcium-channel blockers and beta-blockers). Restricted cubic spline terms were included for all continuous variables. For the primary predictor DBP, the number of knots was chosen based on fit statistics and visual inspection of the smoothness of the resulting curve. The overall association of DBP with angina was evaluated by a k – 1 degree of freedom F-test jointly testing all associated model terms. A DBP of 80 mm Hg was used as the reference. Site was included in all models as a random effect to account for patient clustering within sites.

The inclusion of beta-blockers and calcium-channel blockers in the model is complex, as these medications both reduce angina (e.g., through coronary vasodilation, reducing myocardial demand) and DBP (thereby potentially blunting the antianginal effects). As such, we were overadjusting by adjusting for these medications, but we believed that their inclusion in the model was important to reduce confounding. Because ranolazine does not affect DBP and long-acting nitrates affect DBP slightly on a chronic

basis, we did not adjust for these medications. Finally, despite a strong correlation between SBP and DBP (r = 0.5), a model was constructed that additionally adjusted for SBP. This approach was used because high SPB has been associated with increased myocardial wall stress (13), which can also contribute to angina.

All analyses were conducted by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina), and p values <0.05 were considered statistically significant.

RESULTS

STUDY COHORT. APPEAR included 1,259 outpatients with CAD who were evaluated by 155 cardiologists from 25 sites located in 19 U.S. states. The mean age of the analytic cohort was 71.1 years, 68.5% were male, 89.7% were white, and 10.1% were current smokers (Table 1). A history of myocardial infarction was noted in 38.3%, coronary stenting in 56.7%, and bypass graft surgery in 37.5%; 32.7% of patients reported at least 1 episode of angina in the prior month. A diagnosis of HTN was documented in 79.7% of patients, and patients were taking an average of 1.3 ± 0.8 antihypertensive medications. Mean SBP was 127.9 ± 17.1 mm Hg, and mean DBP was 72.3 ± 10.2 mm Hg, with a median of 72 mm Hg (interquartile range: 65 to 80 mm Hg; range: 40 to 108 mm Hg). Patients with lower DBP values were more likely to be older, have chronic kidney disease, and have lower body mass indices. Use of diuretics, long-acting nitrates, and ranolazine was higher in patients with lower DBP values.

TABLE 1 Patient Characteristics According to Quartile of Diastolic Blood Pressure

	Q1: 40-64 (n = 309)	Q2: 65-71 (n = 316)	Q3: 72-79 (n = 278)	Q4: 80-108 (n = 356)	p Value
Age, yrs	75.0 ± 10.5	72.2 ± 10.1	70.6 ± 11.1	67.3 ± 11.0	<0.001
Female	35.3	31.0	34.9	26.1	0.030
Race					0.084
White	87.1	91.1	91.7	89.0	
Black	3.6	3.8	3.6	5.9	
Other	9.4	5.1	4.7	5.1	
Avoid care due to cost	4.9	6.3	6.9	6.2	0.770
High school education	32.6	36.1	37.1	35.0	0.684
Heart rate, beats/min	68.1 ± 11.7	69.5 ± 11.7	73.2 ± 56.9	70.0 ± 11.1	0.182
Systolic BP, mm Hg	117.7 ± 16.3	124.4 ± 14.6	128.8 ± 13.2	139.1 ± 16.0	<0.001
Heart failure	23.0	18.7	17.7	14.6	0.049
Current smoker	6.6	9.6	12.1	12.0	0.077
Hypertension	77.0	80.1	79.8	81.7	0.509
Diabetes	35.9	39.9	33.9	32.3	0.207
History of stroke/TIA	7.4	7.6	7.9	7.6	0.996
History of MI	34.0	35.4	45.1	39.3	0.027
Chronic kidney disease	17.8	14.2	9.0	9.0	<0.001
Body mass index, kg/m^2	29.6 ± 6.5	30.5 ± 6.4	30.6 ± 6.5	31.3 ± 6.2	0.008
Calcium-channel blocker	26.9	26.9	21.6	27.5	0.320
Beta-blocker	77.3	81.0	82.7	76.4	0.166
ACE inhibitor	35.3	40.2	38.8	37.4	0.623
ARB	27.2	20.9	23.7	26.1	0.259
Diuretic	51.1	42.7	36.3	34.6	<0.001
Nitrate	58.6	52.5	52.5	46.9	0.028
Ranolazine	7.4	6.0	7.9	2.8	0.023
Any angina in past month	37.0	33.7	29.9	30.3	0.198
SAQ-Angina Frequency	90.0 ± 17.5	91.1 ± 15.1	92.6 ± 15.3	92.4 ± 15.3	0.143

Values are mean ± SD or %. Continuous variables were compared by using analysis of variance; categorical variables were compared by using chi-square tests.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CAD = coronary artery disease; MI = myocardial infarction; SAQ = Seattle Angina Questionnaire; TIA = transient ischemic attack.

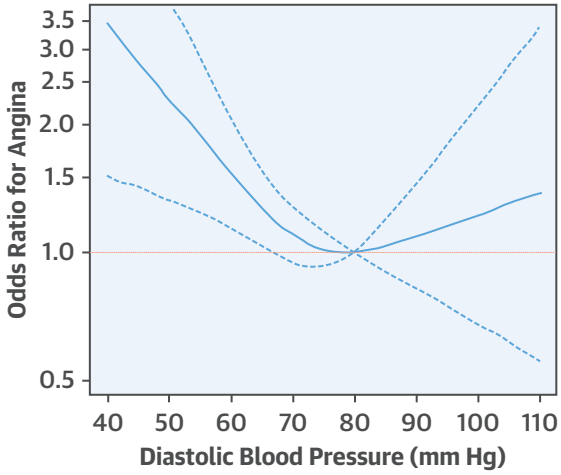
ASSOCIATION OF DBP WITH ANGINA. DBP was 71.6 ± 10.8 mm Hg for those with any angina and 72.7 ± 9.8 mm Hg for those without angina (p = 0.074). In unadjusted analysis, 37.0% of patients in the lowest DBP quartile reported having at least 1 episode of angina in the prior month, compared with 33.7%, 29.9%, and 30.3% of patients in quartiles 2, 3, and 4, respectively.

Mean SAQ-AF scores were similar across DBP quartiles (Table 1). In the unadjusted logistic regression model, DBP was significantly associated with angina (p = 0.017) with a J-shaped relationship (p for nonlinearity = 0.027) (Central Illustration). For example, compared with a patient having a DBP of 80 mm Hg, a patient with a DBP of 60 mm Hg had 1.37 greater odds of angina (95% confidence interval: 1.06 to 1.77). This association remained significant after sequential adjustment for demographic characteristics (p = 0.002), comorbidities (p = 0.002), heart rate (p = 0.002), and antihypertensive antianginal medications (p = 0.002). Finally, after additionally adjusting for SBP, the association of DBP with angina remained significant (p = 0.045). Online Table 1 displays the multivariable adjusted odds of angina according to DBP level.

DISCUSSION

Although aggressive BP control is a cornerstone of cardiovascular risk reduction, excessive reduction of DBP could reduce coronary perfusion pressure and be associated with worse outcomes. Adding to previous analyses showing an association between very low DBP and increased risk of myocardial infarction and cardiovascular death (3,5), we observed a J-shaped relationship between DBP and angina, with the nadir between ~70 and 80 mm Hg. This association persisted after adjusting for patient demographic characteristics, comorbidities, SBP, and medications, thereby underscoring the need for caution when

CENTRAL ILLUSTRATION **Unadjusted Association Between Odds of Angina and Diastolic Blood Pressure Levels**



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Dotted lines represent the 95% confidence interval.

aggressively lowering BP in patients with CAD and angina.

Our findings extend previous knowledge regarding the potential risks of excessive BP reduction and are particularly relevant in light of the new HTN guidelines recommending aggressive BP lowering for cardiovascular risk reduction (14,15). These guidelines were driven to a large degree from the results of SPRINT (Systolic Blood Pressure Intervention Trial), which reported improved mortality with aggressive SBP treatment to a goal of <120 mm Hg (2). These findings were in contrast with those seen in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, in which intensive BP control was not associated with a significant reduction in cardiovascular events compared with the standard BP goal in patients with diabetes and HTN (16). Importantly, the mean DBP in the intensive BP arm of ACCORD was 64 mm Hg versus 69 mm Hg in SPRINT, which could partially account for the seemingly discordant findings between trials.

Treatment-induced diastolic hypotension, which is more common in older patients and those with diabetes, has been associated with an increased risk of adverse cardiovascular events in both observational studies (3,5) and in post hoc analyses of BP-lowering trials (4,17). It is for this reason that guidelines recommend caution in reducing DBP to <60 mm Hg in patients with CAD (1,18). By describing an increased prevalence of angina in patients with a DBP value <~70 to 80 mm Hg, our study identifies an additional potential concern for aggressive DBP lowering and can provide a therapeutic option (de-intensifying BP control) for patients with angina and low DBP.

The present study suggests that in patients with low DBP and CAD, alternative medications for angina, such as ranolazine, ivabradine, or isosorbide (although this does affect BP acutely but likely less long-term effect), may be more beneficial; head-to-head trials of antianginal medications in patients with low DBP would be needed, however, to definitively support such a strategy. Alternatively, patients with low DBP may benefit more from revascularization or other nonpharmacological antianginal treatment (e.g., enhanced external counterpulsation, coronary sinus–reducing device), as opposed to further titration of beta-blockers or calcium-channel blockers.

STUDY LIMITATIONS. First and foremost, the cross-sectional design of our study means that we cannot establish the direction of causality in the association between low DBP and angina risk. This is evident as patients who have more angina are treated more aggressively with beta-blockers and calcium-channel blockers for their angina, which also lowers DBP. Although we reported minimal attenuation in the association of DBP with angina after adjustment for these medications, we were unable to examine doses

of medications or to monitor patients longitudinally to better understand this association. Future studies are needed to better disentangle this potential source of confounding. Second, the interplay between DBP, SBP, coronary perfusion pressure, coronary flow, and myocardial wall stress is complex and cannot be fully analyzed in a cross-sectional study. For example, we cannot account for the effect of coronary autoregulation in our analysis, nor can we account for the effect of myocardial wall stress, which is a determinant of coronary perfusion pressure. In addition, high SBP values can increase myocardial wall stress, which may precipitate angina. All of these factors impede our ability to make firm conclusions based on our results. Third, because APPEAR was an observational cohort study, office BP measurement was not standardized across participating sites, and, as such, we may be underestimating or overestimating the association of low DBP with angina. However, we believe that the real-world nature of the present study signifies an important strength and supports the generalizability of our study, as this approach represented BP assessment in routine clinical practice. Fourth, SAQ-AF integrates angina experienced over a 4-week period, whereas DBP was measured once. It is unclear how results may differ if BP is averaged during the same period as the recall frame of the SAQ. Finally, the overall burden of angina in the study cohort was moderate, which limited our ability to assess the relationship between DBP and angina burden. This study instead explored the association of DBP and the prevalence of angina.

CONCLUSIONS

In this multicenter, cross-sectional analysis of patients with stable CAD, we found that very low DBP was associated with an increased odds of angina. With recent guidelines promoting an aggressive BP-lowering paradigm, it will become increasingly important to individualize treatment strategies to minimize adverse events and maximize benefits. Prospective studies are needed to further examine the relationship between DBP and angina and to help guide management of patients with CAD and low DBP.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Low DBP may precipitate or worsen angina pectoris in patients with CAD, and clinicians should consider reducing antihypertensive medications in patients with CAD and low DBP who have angina.

TRANSLATIONAL OUTLOOK: Further research is required to define the minimum DBP for patients with CAD and angina.

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KEY WORDS angina, coronary artery disease, diastolic blood pressure

APPENDIX For a supplemental table, please see the online version of this paper.