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ORIGINAL ARTICLE

Low diastolic blood pressure is associated with a high atherosclerotic burden in patients with obstructive coronary artery disease

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Abstract

Background: *The optimal blood pressure (BP) treatment target is still being debated, specifically diastolic BP (DBP) in patients with obstructive coronary artery disease (CAD); a DBP which is too low could compromise myocardial perfusion and is associated with adverse outcomes.*

Methods: *This study examined the relationship between DBP levels and the severity and atherosclerotic burden of CAD in 231 consecutive stable patients with evidence of obstructive CAD as detected by elective coronary angiography. The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Score and SYNTAX Score II were used to quantify the atherosclerotic burden.*

Results: *The patients were male (71%), median age 62, interquartile range [IQR] of 57 to 67, and 84% had hypertension. The median DBP was 71.0 mmHg (IQR: 61 to 80) and the median SYNTAX Score was 16.0 (IQR 9.0–23.0). DBP levels were inversely correlated with SYNTAX Score ($r = -0.61$) and SYNTAX Score II ($r = -0.73$). Adjusting for traditional risk factors, unprotected left main CAD, systolic BP, renal function, and medications, DBP levels remained independently inversely associated with a higher tertile of SYNTAX Score (adjusted odds ratio [OR] 0.89; 95% confidence interval [CI] 0.85–0.92, $p < 0.001$) and SYNTAX Score II (adjusted OR 0.75; 95% CI 0.69–0.80, $p < 0.001$). The frequency of high atherosclerotic burden identified by the presence of intermediate or high SYNTAX Score and SYNTAX Score II was significantly higher among patients with a DBP < 60 mmHg.*

Conclusions: *Low DBP levels are independently associated with high SYNTAX Score and SYNTAX Score II in stable patients with obstructive CAD.* (Cardiol J 2018; 25, 3: 345–352)

Key words: hypertension, diastolic blood pressure, coronary artery disease, J-curve phenomenon, SYNTAX Score, atherosclerosis

Introduction

The prevalence of hypertension, a common risk of cardiovascular disease (CVD), has been increasing and remains the leading cause of CVD and death worldwide [1, 2]. Lowering blood pressure (BP) reduces the risk of CVD and death [3], but the optimal BP target has been extensively debated [4, 5]. Recently, a SPRINT (Systolic Blood pressure Intervention Trial) [6] showed that intensive systolic BP (SBP) ≤ 120 mmHg among high-risk patients was associated with a reduction in the

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primary outcomes (stroke, myocardial infarction [MI], non-MI acute coronary syndrome, heart failure and cardiovascular [CV] death), and all-cause deaths. There is a potential concern, however, that intensive BP reduction is particularly related to CV events due to a J-curve phenomenon [7]. Because SBP reduction also lowers diastolic BP (DBP) and coronary blood flow during diastole; therefore, low DBP might compromise coronary perfusion pressure and result in associated myocardial ischemia and damage, especially in patients with obstructive coronary artery disease (CAD) [8, 9].

Recently, exciting new data reported by McEvoy et al. [10] showed that low DBP, particularly among patients with DBP < 60 mmHg had a higher prevalence of subclinical myocardial damage (quantified by high-sensitivity cardiac troponin T [hs--cTnT]) and was associated with CAD incidents and mortality. Furthermore, results from a recent study have shown that patients with hypertension and stable CAD and DBP < 70 mmHg were associated with an increased risk of CV events [11], which supports the existence of the J-curve phenomenon. Therefore, the relationship between a drop in DBP and myocardial damage and adverse CV outcomes may be associated with severity or complexity of diseased coronary vessels. A relationship, however, between DBP level and detailed characterization and quantification of the atherosclerotic burden has not been investigated.

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trials have shown that SYNTAX Score is an anatomical angiographic scoring system used to determine the complexity and burden of atherosclerotic CAD [12, 13]. The SYNTAX Score has been shown to predict major adverse cardiac events (MACE) and long term prognostic risk among patients with stable CAD who underwent coronary revascularization by coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) [14, 15]. The lack of clinical variables and purely anatomical focus of consideration, however, are major limitations of the SYNTAX Score. Subsequently, the SYNTAX Score II was recently developed. This consists of a combination of two anatomical (anatomical SYNTAX Scores and unprotected left main CAD) and 6 clinical variables (age, creatinine clearance, left ventricular ejection fraction [LVEF], sex, chronic obstructive pulmonary disease, and peripheral artery disease). The SYNTAX Score II has shown better long-term (4-year) mortality predictions between CABG and PCI than the original anatomical SYNTAX Score [16]. As such, both the SYNTAX Score and SYNTAX Score II may provide insight into understanding whether a lower DBP level, is associated with myocardial damage and adverse CV outcomes.

In this prospective cross-sectional study, the relationship between DBP and severity and burden of coronary artery atherosclerotic lesions quantified by SYNTAX Score and SYNTAX Score II was sought.

Methods

Study population

This single-center cross-sectional study was approved by the Khon Kaen University Ethics Committee in Human Research (HE510414) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed, written consent. Adult subjects (aged ≥ 20 years) with signs or symptoms of CAD who underwent elective, non-urgent coronary angiography in the absence of emergency conditions were included at the Queen Sirikit Heart Center of the Northeast, Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand between 2008 and 2012. Patients who had experienced acute coronary syndrome or revascularization procedures within 30 days prior to enrollment, or CABG, or PCI, had a LVEF < 40% and patients who had no evidence of significant CAD were specifically excluded (total exclusion: 168 patients) (Fig. 1). Therefore, a total of 231 consecutive patients were included in this study.

Angiographic analysis

Images of diagnostic coronary angiograms were obtained with the Xcelera cardiology image management system (Philips, Netherlands) and each coronary lesion with evidence of significant stenosis in vessels of 1.5 mm or more were scored. Significant CAD was defined by diameter stenosis of 50% or more in at least one epicardial coronary artery based on the American College of Cardiology Foundation and American Heart Association guidelines [17, 18]. The SYNTAX Score and SYNTAX Score II were calculated for each patient using a computer program consisting of sequential and interactive self-guided questions according to the SYNTAX Score calculator version 2.28, and divided into tertiles, according to the STNTAX trial, which were defined as low (0–22), intermediate (23–32), and high (≥ 33) SYNTAX Score. The SYNTAX Score II was stratified according to tertiles of SYNTAX Score II for PCI as previously

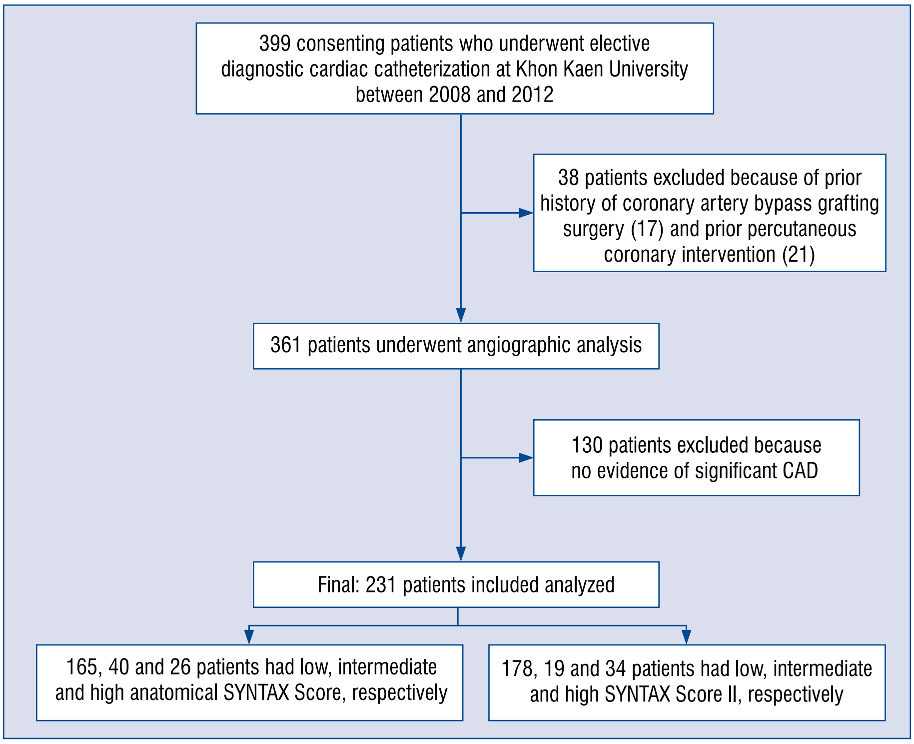

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram; CAD — coronary artery disease.

described [19]. All angiograms were reviewed by the board-certified interventional cardiologist who was blinded to DBP and variable clinical data.

Laboratory testing and BP measurement

After informed consent was obtained from all patients, blood samples were collected after 12-h overnight fasting before catheterization procedures, and was sent for analysis within 3 h of collection. Analysis of routine biochemical markers were performed on samples using the Hitachi 917 automatic analyzer (Roche Diagnostics, Basel, Switzerland). An estimated glomerular filtration rate (eGFR [mL/min/1.73 m^2]) was calculated using the Modification of Diet in Renal Disease equation.

Blood pressure was measured in the left arm after the patient was resting supine for 15 min in a quiet room in an inpatient care unit, using a digital automatic sphygmomanometer (DINAMAP CARESCAPE V100, GE Medical Systems, WI, USA). Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, a history of hypertension or the use of antihypertensive medications.

Statistical analysis

Descriptive statistics were used to calculate baseline characteristics of all eligible patients. Patients were divided into three groups according to the SYNTAX Score as low, intermediate, and high. Studied variables of all three groups were compared by one-way analysis of variance or the Kruskal-Wallis test or χ^2 or Fisher Exact test where appropriate. Spearman correlation analysis was used to examine the associations between DBP and SYNTAX Score, and SYNTAX Score II. An ordinal logistic regression analysis was adjusted for traditional risk factors (including age, sex, body mass index [BMI], hypertension, diabetes mellitus, smoking, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides), SBP, eGFR, LVEF and medications (statins, angiotensin converting enzyme inhibitors [ACEI] or angiotensin receptor blocker [ARB], aspirin, and beta-blocker) were employed to examine the relationship of DBP and the higher SYNTAX Score and SYNTAX Score II. All analyses were performed used STATA version10.1 (STATA Corp., College Station, Tx, USA). A $p < 0.05$ was considered statistically significant.

Results

The baseline characteristics of this study are provided in Table 1. Overall, the median age of the patients involved in this study was 62 years; 70%

Table 1. Baseline characteristics of study patients.

Variables	SYNTAX Score				P
	Total (n = 231)	Low (0–22, n = 165)	Intermediate (23–32, n = 40)	High (≥ 33, n = 26)	
Age [year]	62 (57–67)	62 (56–67)	63 (58–67)	63 (58–71)	0.42
Men	69.3%	69.7%	67.5%	69.2%	0.96
Body mass index [kg/m^2]	24.49 (22.6–26.7)	24.4 (22.5–26.9)	24.7 (22.5–26.5)	24.7 (23.3–26.2)	0.95
Systolic BP [mmHg]	129 (120–142)	130 (120–144)	129 (119.5–143)	124 (116–130)	0.09
Diastolic BP [mmHg]	71.0 (61–80)	74 (67–82)	61.5 (55–69.5)	58.5 (55–64)	< 0.001
Left ventricular ejection fraction	55% (45–62)	53% (46–60)	55% (50–60)	56% (52–64)	0.11
Diabetes mellitus	27.0%	29.4%	27.3%	15.5%	0.22
Hypertension	84.4%	80%	82.5%	80.8%	0.77
Current smoker	42.4%	43.6%	50%	23.1%	0.08
Unprotected left main CAD	22.1%	12.7%	45%	46.2%	< 0.01
LDL-C [mg/dL]	96.5 (72.5–124)	93 (71.5–117.5)	113 (77–141)	86 (70–132)	0.056
HDL-C [mg/dL]	39 (31–45)	37 (31–44)	39 (31–46)	40.5 (28–48)	0.85
Triglyceride [mg/dL]	162.5 (117–226)	158 (118.5–220)	178.5 (121–265)	161.5 (88–240)	0.53
eGFR [mL/min/1.73 m^2]	71.5 (55–92)	71.8 (53.8–93.3)	72.8 (57.7–89)	70.4 (59–85.4)	0.92
Medication:					
Aspirin	94.4%	97.5%	97.5%	84.6%	0.06
ACEI or ARB	28.8%	29.5%	25%	30.8%	0.83
Statin	76.9%	77.4%	80%	69.2%	0.57
Beta-blocker	55.9%	55.8%	55%	57.7%	0.97

ACEI or ARB — angiotensin-converting enzyme inhibitors or angiotensin receptor blocker; BP — blood pressure; CAD — coronary artery disease; eGFR — estimated glomerular filtration rate; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol

were men, 27% had diabetes, 84% had hypertension, and the median BMI was 24.5 kg/m^2. The median DBP was 71.0 mmHg (interquartile range [IQR] 61–80 mmHg), median SBP was 129.0 mmHg (IQR 120–142 mmHg) and the median LVEF was 55% (45–62). The medians of the SYNTAX Score were 16.0 (IQR 9.0–23.0), and 165 (71%), 40 (17%) and 26 (12%) patients had low (0–22), intermediate (23–32), and high (≥ 33) SYNTAX Score. The medians of the SYNTAX Score II were 13.0 (IQR 10.0–19.0) and 178 (77%), 19 (8%) and 34 (15%) patients had low (≤ 21), intermediate (> 21 and ≤ 28), and high (> 28) SYNTAX Score II. Patients with a higher SYNTAX Score were more likely to have an unprotected left main CAD and tended to have a decreased SBP. Histories of smoking, sex, age, BMI, diabetes and hypertension were similar across SYNTAX Score tertiles. DBP was significantly lower with an increased SYNTAX Score (Fig. 2A) and SYNTAX Score II tertiles (Fig. 2B).

Associations between DBP and SYNTAX Score and SYNTAX Score II

Diastolic BP levels were strongly inversely correlated with both SYNTAX Score and SYNTAX Score II (Spearman correlation; $r = -0.61$, and -0.73, both $p < 0.0001$). Following ordinal logistic regression analysis adjusting for traditional risk factors (including age, sex, BMI, hypertension, diabetes mellitus, smoking, LDL-C, HDL-C, and triglycerides), SBP, eGFR, LVEF and medications including statins, ACEI or ARB, aspirin, and beta-blockers, DBP levels remained independently inversely associated with a higher tertile of SYNTAX Score (adjusted odds ratio [OR] 0.89; 95% confidence interval [CI] 0.85–0.92, $p < 0.001$) and SYNTAX Score II (adjusted OR 0.75; 95% CI 0.69–0.80, $p < 0.001$) (Table 2).

DBP and high atherosclerotic burden

High atherosclerotic burdens were identified by the presence of intermediate or high SYNTAX

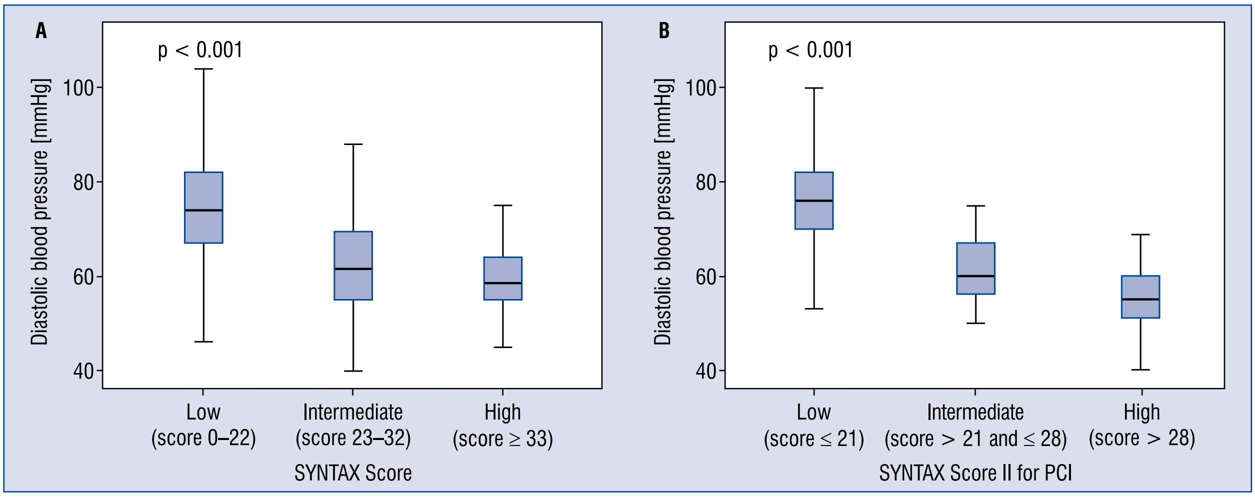

Figure 2. Relationship between diastolic blood pressure and measure of atherosclerotic burden. Lower diastolic blood pressure (BP) levels were associated with an increased SYNTAX Score (Anatomical) (**A**), SYNTAX Score II (**B**); PCI — percutaneous coronary intervention.

Table 2. Lower diastolic blood pressure is associated with increased likelihood of higher SYNTAX Score and SYNTAX Score II.

Variable	SYNTAX Score		SYNTAX Score II	
	OR (95% CI)	P	OR (95% CI)	P
Unadjusted	0.88 (0.87–0.93)	< 0.001	0.79 (0.75–0.83)	< 0.001
Adjusted	0.89 (0.85–0.92)	< 0.001	0.75 (0.69–0.80)	< 0.001

Adjusted for age, sex, body mass index, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, hypertension, systolic blood pressure, smoking, estimated glomerular filtration rate, left ventricular ejection fraction and medications (statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, aspirin, and beta-blocker); CI — confidence interval; OR — odds ratio

Score and SYNTAX Score II scores. The frequency of high atherosclerotic burden was significantly increased with decreasing DBP, for SYNTAX Scores of 69%, 36%, 16% and 3% in DBP < 60, 60–69, 70–79, and ≥ 80 mmHg; p<0.0001 for all (Fig. 3A) and SYNTAX Score II levels of 67%, 30.4%, 5.8% and 1.7% in DBP < 60, 60–69, 70–79, and ≥ 80 mmHg; p < 0.0001 for all (Fig. 3B).

Discussion

This study demonstrates the strongly significant inverse association between DBP levels and coronary artery atherosclerotic burden quantified by the SYNTAX Score and SYNTAX Score II in stable patients with obstructive CAD. Furthermore, lower DBP levels were found to serve as an independent predictor of higher SYNTAX Score and SYNTAX Score II, even after adjustment for traditional risk factors, i.e. unprotected left main CAD, SBP, eGFR, and medications. Additionally, the frequency of high atherosclerotic burden identified by the presence of an intermediate or high SYNTAX Score and SYNTAX Score II was significantly increased with a decreasing of DBP. Taken together, the present findings further demonstrates that the low DBP levels are associated with a greater atherosclerotic burden.

Randomized data regarding the optimal BP target are still being debated, in particular, the most recent data from SPRINT showed that more-intensive is better than less-intensive antihypertensive treatment [6]. There is a potential concern, however, for a J-curve phenomenon that is related to adverse cardiac events, especially regarding DBP in CAD patients [7, 8]. Low DBP has previously been shown to possibly promote myocardial ischemia and subclinical myocardial damage [10]. Moreover, specifically in patients with stable CAD and with hypertension, a low DBP (< 70 mm Hg) was associ-

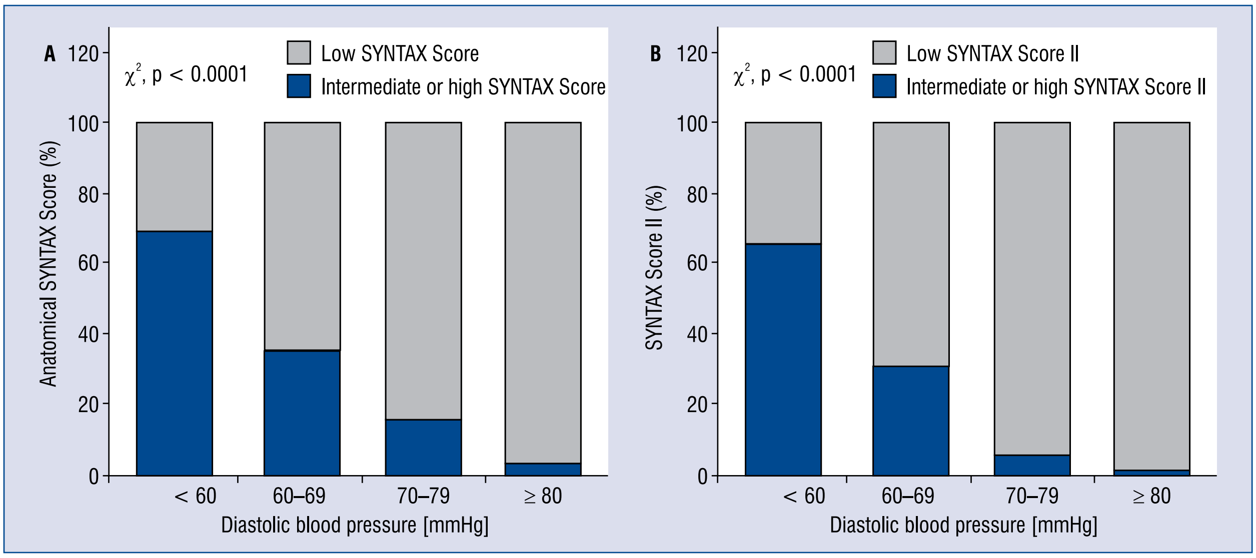

Figure 3. Diastolic blood pressure and atherosclerotic burden. The frequency of high atherosclerotic burden according to (**A**) SYNTAX Score and (**B**) SYNTAX Score II when compared to the diastolic blood pressure level.

ated with adverse CV outcomes [11]. The present study extends these findings by demonstrating a strongly independent association between low DBP and high atherosclerotic burden. Thus, the results are consistent that intensive reduction in DBP would be expected to decrease coronary perfusion pressure that would be associated with subclinical myocardial damage, which may be mechanistically linked with the development of high severity of an atherosclerotic burden of coronary vessels.

The SYNTAX Score is a useful tool to stratify risk outcomes in stable patients with complex CAD who have undergone revascularization by PCI or CABG [14, 15]. A high SYNTAX Score is correlated with a poor prognosis, which is also a marker of systemic atherosclerotic burden [12, 13]. Furthermore, the SYNTAX Score II, which combines anatomical and clinical factors, has been shown to be a better long-term predictor of CV events and all-cause mortality [16]. In the present study, DBP was inversely correlated with both the SYNTAX Score and SYNTAX Score II. Importantly, the frequency of high atherosclerotic burden was significantly highest among patients with a DBP < 60 mm Hg in both the SYNTAX Score and SYNTAX Score II. Interestingly, these data are consistent with findings from recent studies that DBP < 60 mmHg was strongly associated with both subclinical myocardial damage and adverse CV events [10, 11]. Therefore, the current findings provided additional support that over-treatment of hypertension in patients with obstructive CAD may reduce coronary perfusion flow and precipitate myocardial damage that facilitates the development of coronary artery atherosclerotic burdens.

The results of the SPRINT hypothesis seems unlikely to be at odds with the J-curve hypothesis. In contrast, a HOPE-3 (Heart Outcomes Prevention Evaluation) [20] trial reported that BP-lowering therapy among intermediate patients at risk for CV with baseline SBP levels < 130 mmHg and a new meta-analysis [21] showed that among patients with diabetes an SBP less than 140 mmHg, BP-lowering therapy was not beneficial, but tended to cause harm. The results from SPRINT, however, should be interpreted with caution due to the method of BP measurement that used automatic oscillometric monitors after the patients were seated quietly alone and tended to be lower than traditional office BP measurement methods [22].

Based on these findings, it is thus conceivable that potentially severe atherosclerotic burdens of coronary artery vessels may occur in the setting of lowering of DBP. Importantly, the results are reasonable to apply to patients with hypertension and obstructive CAD in that the DBP treatment target should be less aggressive. This was, however, a hypothesis-generated study and further studies into the mechanisms of low DBP leading to an atherosclerotic burden in patients with hypertension and obstructive CAD are warranted.

Limitations of the study

This study was in a single tertiary care center study that recruited patients at the time of cardiac evaluation for coronary angiography. Therefore, it cannot exclude the presence of a selection bias for the patients undergoing evaluation and treatment for CAD. Second, because BP levels were measured at only a single point in time using a digital automatic sphygmomanometer after the patients had rested in a supine position for 15 min in a quiet room of an inpatient unit, pressures then may be similar or slightly lower than the traditional office BP measurement method. The lack of 24-h ambulatory BP measurement was also a limitation of this study. Third, complete information that may be associated with the atherosclerotic burden such as hs-cTnT or central aortic pressure or stiffness were lacking. Therefore, this study was not able to exclude other reasons as to whether the association between low DBP and atherosclerotic burden was due to subclinical myocardial damage, from low DBP, from central aortic stiffness or from a combination of reasons.Furthermore, there was a lack of complete information regarding the history of heart failure and MI; this issue was addressed by enrolling patients who were stable without requiring emergency care. Fourth, intravascular ultrasound or optical coherence tomography to evaluate the stenotic diameters or plaque characteristics were not available. Finally, the relatively low number of the patients in both the intermediate and high SYNTAX Score and SYNTAX Score II tertiles was also a limitation of this study cohort.

Conclusions

A low DBP level had an independent association with high SYNTAX Score and SYNTAX Score II. Lower DBP, particularly < 60 mmHg, may be important to recognize a potential pathophysiological contribution of too low DBP in the development of complexity and an increased atherosclerotic burden, which is identified by the presence of intermediate or high SYNTAX Score and SYNTAX Score II in stable patients with obstructive CAD.

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Conflict of interest: None declared

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