Diastolic blood pressure predicts coronary plaque volume in patients with coronary artery disease

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Abstract

Background and aims—Hypertension is associated with increased clinical and subclinical coronary artery disease (CAD); however, the relationship between blood pressure and coronary plaque volume is unclear. We examined the effect of systolic blood pressure (SBP) and diastolic blood pressure (DBP) on coronary artery plaque volume.

Methods—285 subjects with stable CAD on statin therapy underwent coronary computed tomographic angiography to measure volume of fatty, fibrous, noncalcified, calcified and total coronary plaque.

Results—Mean (SD) age was 63.1 (7.7); mean (SD) LDL-C, 78.7 mg/dL (28.5). Compared to the highest DBP tertile (>76 mmHg), those in the lowest DBP tertile ($\leq$ 68 mmHg) had lower volumes of fatty: 10.0 *vs.* 7.7 mm^3/mm, (*p* trend=0.042), fibrous: 19.6 *vs.* 13.8 mm^3/mm (*p* trend = 0.011), non-calcified: 29.7 *vs.* 22.5 mm^3/mm (*p* trend=0.017) and total plaque: 37.8 *vs.* 25.1 mm^3/mm (*p* trend=0.010) whereas there was no relationship with SBP tertiles. Similarly, when examined as a continuous variable, higher DBP was a significant independent predictor of higher plaque volume after multivariate adjustment: for every 1 mmHg increase in DBP, fibrous plaque increased 0.128 mm^3/mm (*p*=0.022), noncalcified plaque increased 0.176 mm^3/mm (*p*=0.045), calcified plaque increased 0.096 mm^3/mm (*p*=0.001) and total plaque increased 0.249 mm^3/mm (*p*=0.019) whereas SBP ranging from 95 to 154 mmHg did not predict plaque volume.

Conclusions—Level of DBP predicts coronary plaque with a DBP tertile $\leq$ 68 mmHg associated with the least amount of coronary plaque in subjects with LDL-C < 80 mg/dL.

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

1. Introduction

Hypertension is a major risk factor for coronary artery disease (CAD) and is associated with increased cardiovascular morbidity and mortality [1]. Observational studies have demonstrated a direct, graded association between higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) and increased cardiovascular disease (CVD) risk [2,3]. In the Multiple Risk Factor Intervention Trial of over 316,000 men followed for 12 years, strong graded relationships between SBP above 110 mmHg and DBP above 70 mmHg and mortality due to coronary heart disease (CHD) were evident [3]. At every DBP, SBP above 115 mmHg was directly associated with an increasing risk of death from CHD [3]. In a meta-analysis of prospective epidemiologic studies for 1 million adults aged 40 to 70 years, a strong, independent and log-linear association was observed between mortality from CVD and total mortality down to a SBP of at least 115 mmHg [2]. Moreover, each increment of 20 mmHg in SBP or 10 mmHg in DBP was associated with a doubling of the risk of CHD events for blood pressure (BP) of 115/75 to 185/115 mmHg [2]. While the association between hypertension and CHD events is well established, how elevated BP affects coronary plaque volume and characteristics remains a matter of continued investigation. The aim of the current study was to determine the effect of SBP and DBP on overall coronary artery plaque volume and its subtypes measured by coronary computed tomographic angiography (CCTA) in patients with CAD on a stable dose of statin therapy with well-controlled levels of low-density-lipoprotein cholesterol (LDL-C) < 80 mg/dL.

2. Patients and methods

2.1. Study design

This is a cross-sectional analysis at baseline of the Slowing HEART diSease With Lifestyle and Omega-3 Fatty Acids trial. The trial is a randomized, parallel, single-center study of 3.36 g daily of EPA and DHA compared to no EPA and DHA over 30 months. The design has been described previously [4,5]. The protocol was approved by the Beth Israel Deaconess Medical Center Institutional Review Board and all subjects signed an informed consent.

2.2. Study population

Eligible participants were aged 21 to 80 years and had stable, established CAD defined as at least 1 of the following: 50% stenosis in at least 1 coronary artery at catheterization, previous myocardial infarction (MI) (6 months prior) or percutaneous coronary intervention (PCI) (6 months prior), coronary bypass surgery (12 months prior), abnormal exercise treadmill test or an area of reversible ischemia on nuclear imaging, pharmacologic stress or stress echocardiography with subsequent revascularization. All subjects were recommended to be on a stable dose of a statin for at least 3 months. Inclusion

criteria also included a body mass index (BMI) 27 kg/m^2 or a BMI of 25 to 26.9 with either an increased waist circumference or at least 2 components of the metabolic syndrome which include: triglyceride 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL if male or < 50 mg/dL if female, glucose 100 mg/dL or treated hypertension or BP 130/85 mmHg. Additional inclusion criteria included estimated creatinine clearance as measured by the Cockcroft-Gault equation 60 ml/min/1.73 m^2. Exclusion criteria for CCTA were BMI > 35 kg/m^2 (females) or > 40 kg/m^2 (males), contraindication to iodinated contrast agents and serum creatinine > 1.5 mg/dL.

2.3. Blood pressure measurements

Subjects were seated quietly for at least 5 minutes in a chair at 60° to 85° with their feet on the floor and the right arm supported at heart level. A cuff bladder encircling at least 80% of the arm was used to ensure accuracy. Measurements of BP were performed using cycling Dinamaps (GE Medical Systems Information Technologies, Inc, Milwaukee, Wis). Two BP readings were obtained at least 30 seconds apart as in the Treatment of Mild Hypertension Study [6]. If there was more than a 5–mmHg difference in SBP between the 2 readings, a third reading was obtained.

2.4. CCTA Imaging protocol

Imaging was performed at Beth Israel Deaconess Medical Center using a 320-row detector scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) with prospective electrocardiogram gating. The protocol for performance of CCTA, plaque identification and quantification has been previously published [7,8] with image acquisition details and references in Appendix 1 in Supplement 2 of reference 8. Patients were placed in a standard position to enable CT synchronization with the electrocardiogram. Oral or intravenous beta blockade with metoprolol was administered in patients with a heart rate greater than 65 beats per minute to avoid cardiac motion artifacts and assure accurate gated imaging. Sublingual nitroglycerine 0.4 mg was given to all patients just prior to the scan. The starting point of the volume scan and coverage area was cranio-caudally from one centimeter below the tracheal bifurcation to the diaphragm. Prior to the examination, all patients were instructed on quiet breathing and breath holding in order to minimize artifacts during scanning. An intravenous bolus of non-ionic iodinated contrast agent Optiray-350 (70–90 ml) was given at the rate of 4–5 ml per second followed by a bolus of saline. The region of interest was placed over the descending aorta and exposure triggered at 300 Hounsfield units (HU). All patients were imaged at 60–80% of R-R interval using a prospective gating technique. Scanning parameters were determined based upon patient's weight, height and BMI values. Transaxial images were reconstructed with 0.5 mm slice thickness.

2.5. Coronary plaque identification and quantification

CCTA images underwent 3-dimensional reconstruction for coronary segment plaque volume analysis using semiautomated software (SUREPlaque, version 6.3.2, Vital Images, Minnetonka, MN, USA) [9–12]. Analysis was performed for all patients by using standard axial, maximum intensity and multiplanar reformats. The readers had access to scroll through axial images, to interactively perform multiplanar reconstructions, maximum intensity projections, as well as curved multiplanar reformats for both data sets. Using sculpt

tool and various window levels, the main coronary vessels were exposed. The probe feature was then used to quantify plaque in the four major coronary vessels: right coronary artery, left main artery, left anterior descending artery and left circumflex artery. Stents and distal segments with diameter less than 2 mm were not included in analysis, the latter due to limited spatial resolution [13]. Coronary plaque characteristics (fibrous, fatty, and calcified) were analyzed in all patients. Representative images have been previously published (Supplement 2 in reference 8). Segments with prior revascularization or significant calcification causing calcium-bloom artifact were excluded. Noncalcified plaque, the sum of fatty and fibrous plaque, was based on HU densities of fatty (−100 to 49 HU) and fibrous (50 to 150 HU). Calcified plaque was > 150 HU. Plaque volumes were indexed to the length of the plaque lesion; indexed plaque volume was defined as plaque volume (mm^3) divided by artery segment length (mm). The coronary plaque thresholds were based on HU density ranges as reported and validated by others comparing CCTA to intravascular ultrasound [10,12–18] and histopathological comparisons with CCTA [19,20]. Thresholds for coronary plaque quantification were preset in the Vitrea analysis tool before performing the analysis. The software analysis tool provides color coding for lumen and the different plaque components and automatically generates total volume and percentage of different plaque components. Calcified plaque usually causes partial volume artifact in quantifying fibrous and fatty plaque. To avoid calcium blooming artifact, manual adjustments were done by redrawing contours in those particular segments. All analyses were performed by two independent readers (blinded to patient identifiers) to assess the inter-observer and tool reproducibility. The average of both readings was used for final analysis.

2.6. Statistical analysis

Categorical variables were expressed as counts and percentages. Normality tests were conducted using the Shapiro-Wilk test. Continuous variables were reported as the mean and SD for normally distributed variables or median and interquartile range [IQR] for non-normally distributed variables. Plaque volumes were not normally distributed and, therefore, were reported as median [IQR].

Plaque volume was stratified by tertile of SBP and DBP. Proportions according to tertiles were compared using a Chi-square test. A p value for trend was measured for plaque volumes across tertiles of SBP and DBP using linear regression. SBP and DBP were also examined as continuous variables. We examined the association between SBP or DBP and volume of plaque subtypes using linear regression. A backward multivariate linear regression was used to adjust for confounding effects. Variables associated with plaque volume with a $p < 0.1$ in the univariate analysis were included in the fully adjusted backward regression models. These variables included age, sex, BMI, history of MI, history of PCI, coronary artery bypass surgery or hypertension, HbA1c, LDL-C, HDL-C, triglyceride, creatinine clearance and medication use (statin, aspirin, angiotensin converting enzyme inhibitor [ACE-I], angiotensin receptor blocker [ARB], hydrochlorothiazide, furosemide, calcium channel blocker and beta blocker). A 2-sided p value <0.05 was considered statistically significant. Data analyses were performed using SPSS 20.0 (IBM Corp. Armonk, NY).

3. Results

A total of 285 subjects underwent a baseline CCTA evaluation and were included in this analysis. Mean (SD) age was 63.1 (7.7), 18.2% were female, and 240 (84.2%) subjects had a diagnosis of hypertension. In the total group, 272 (95.4%) were on statins with a mean (SD) LDL-C level of 78.7 mg/dL (28.5) and median [IQR] triglyceride level of 117 mg/dL [79, 167].

Baseline characteristics according to systolic and diastolic BP tertiles are shown in Table 1 and Table 2, respectively. Those in the highest tertile of SBP were significantly more likely to be older, have a higher BMI and history of hypertension and use calcium channel blockers whereas those in the lowest tertile of SBP were more likely to have a history of MI. As shown in Supplementary Table 1, those with MI were more aggressively treated to a lower SBP compared to those without MI (121 mmHg vs 126 mmHg, respectively; p=0.002), a finding accounting for the higher prevalence of subjects with MI in the lowest tertile of SBP. In regards to DBP, those in the highest DBP tertile were significantly more likely to be male and less likely to have diabetes or be on a statin or furosemide. A significantly higher percent were receiving any antihypertensive drug in the lowest diastolic BP tertile. There were no current smokers.

Table 3 shows median plaque volumes according to systolic and diastolic BP tertiles. The Intra-observer and Inter-observer agreement indexes for coronary plaque measurements were 0.99 and 0.98, respectively, showing excellent correlation between readings. When examined by tertiles of SBP, there was no significant difference in any of the plaque subtypes. Of note, SBP (mean ± SD) ranged from 108.9±7.4 in the lowest SBP tertile to 139.9±8.2 mmHg in the highest SBP tertile (Table 1). In contrast, when examined by tertiles of DBP, the higher the tertile, the higher the plaque volume. For example, compared to subjects in the highest DBP tertile (> 76 mmHg), subjects in the lowest DBP tertile (≤ 68 mmHg) had lower volumes of fatty: 10.0 *vs.* 7.7 mm^3/mm segment length, respectively, (*p* for trend=0.042), fibrous plaque: 19.6 *vs.* 13.8 mm^3/mm segment length, respectively, (*p* for trend=0.011), noncalcified: 29.7 *vs.* 22.5 mm^3/mm segment length, respectively, (*p* for trend=0.017), calcified plaque: 5.4 *vs.* 4.2 mm3/mm segment length, respectively, (*p* for trend=0.054) and total plaque: 37.8 *vs.* 25.1 mm^3/mm segment length, respectively, (*p* for trend=0.010).

When examined as a continuous variable, in both the univariate and fully adjusted regression models, SBP did not predict the volume of any of the plaque subtypes or total plaque volume (Table 4). The SBP ranged from 95 mmHg to 154 mmHg for 95% of the subjects. On the other hand, DBP predicted volume of all plaque components in the univariate regression model (Table 4). After multivariate adjustment for subject characteristics (Table 4), higher DBP was a significant independent predictor of plaque subtypes: for every 1 mmHg increase in DBP, fibrous plaque increased 0.128 mm^3/mm (95% CI: 0.019 to 0.237: *p*=0.022), noncalcified plaque increased 0.176 mm^3/mm (95% CI: 0.004 to 0.348; *p*=0.045), calcified plaque increased 0.096 mm^3/mm (95% CI: 0.039 to 0.152; *p*=0.001) and total plaque increased 0.249 mm^3/mm (95% CI: 0.041 to 0.457; *p*=0.019). The fully adjusted models for SBP and DBP for total plaque volume are shown in Table 5. Of note, LDL-C did not predict

plaque volume in the univariate or multivariate models for either SBP or DBP. The *p*-values for LDL-C in the univariate model were 0.557 for fatty plaque, 0.594 for fibrous plaque, 0.576 for noncalcified plaque, 0.453 for calcified plaque and 0.603 for total plaque. There was no association between pulse pressure and volume of any of the plaque subtypes.

The analysis was repeated for men only. Supplementary Tables 2 and 3 describe similar results for the tertile analysis (Supplementary Table 2) and multivariate analysis (Supplementary Table 3) as shown for the total group of men and women in Tables 3 and 4.

To determine if a DBP < 68 mmHg, which is the lowest tertile, provided additional benefit on plaque volume, SBP and DBP were plotted versus plaque volume. Locally weighted scatterplot smoothing was used to generate non-linear regression lines. For DBP, Fig. 1A shows that plaque volume continued to decrease as DBP decreased well below 68 mmHg. In contrast, the graph for SBP (Fig. 1B) was flat. Supplementary Figures 1 to 4 show similar findings for fatty, fibrous, noncalcified and calcified plaque. These graphs illustrate a dramatic difference in the effect of DBP versus SBP on plaque volume.

4. Discussion

In the current study, our results using CCTA show a graded increase in coronary plaque volume as DBP tertile increased above 68 mmHg in patients with stable CAD whereas plaque volume did not differ by tertile of SBP. Similar significant results were observed for DBP when examined as a continuous variable and fully adjusted for subject characteristics including LDL-C, again demonstrating a strong direct association between DBP and all plaque components while SBP in the range of 95 mmHg to 154 mmHg (for 95% of the subjects) was not associated with plaque volume. Our findings suggest that level of DBP is an important factor in determining plaque volume whereas SBP in the range in the current study is not. A DBP tertile   68 mmHg was associated with the least amount of coronary plaque volume in these subjects with well controlled LDL-C < 80 mg/dL. Moreover, plaque volume continued to decrease for all plaque types as DBP decreased well below 68 mmHg. In contrast, the graph for SBP was flat. These results illustrate a dramatic difference in the effect of DBP vs SBP on plaque volume. SBP was well-controlled in the majority of our subjects. These findings suggest that in the setting of well-controlled SBP, DBP remains critically important in affecting plaque volume.

The reason for our finding of a graded, direct relationship between DBP and plaque volume, but not between SBP, is unclear. A significantly higher percent were receiving any antihypertensive drug in the lowest DBP tertile, a finding accounting for the lower DBP. Whether the type of antihypertensive treatment affects plaque volume is unknown; however, the only difference in type of antihypertensive medication was use of furosemide. There is no current evidence to support that furosemide may affect plaque volume. Subjects in the lowest tertile for DBP also had a significantly higher prevalence of diabetes. The reason for this difference is unclear but could perhaps be related to more aggressive treatment of blood pressure in subjects with diabetes. Another potential explanation is through the effect of diabetes on arterial stiffness. Diabetes leads to an increase in arterial stiffness which in turn lowers diastolic blood pressure [21]. Diabetes also causes capillary rarefaction in the small

arteries and increases the reflected pulse wave causing a wider pulse pressure and thus lower DBP.

Another explanation that could be hypothesized to account for differences in effect of SBP versus DBP could be due to the fact that flow in the coronary artery occurs mainly during diastole. Higher DBP may be associated with increased coronary flow and alteration in shear stress leading to an increased number of areas with non-laminar flow and the activation of inflammatory pathways leading to plaque formation and growth [22]. Endothelial shear stress can be estimated from CCTA using computational fluid dynamics with sophisticated software [23–25]; therefore, future studies could examine this hypothesis further.

Several prior studies have examined the relationship between BP and volume of coronary plaque. In a cross-sectional study using electron beam computed tomography (EBCT) of subjects with an average age of 40 years in the Rochester Family Heart Study, after adjustment for sex and age, ambulatory systolic and diastolic BP levels were predictive of coronary artery calcification (CAC); however, after additional adjustment for office BP, only the ambulatory DBP level was an independent predictor of CAC whereas SBP was not [26]. Moreover, hypertension was the most important independent risk factor for the presence of CAC and more important than diabetes and hyperlipidemia. In the Muscatine study of 384 subjects ages 20–34 years, in multivariate analysis, DBP independently predicted CAC at ages 29 to 37 years whereas SBP and LDL-C did not predict [27]. In a study of 330 patients examined with intravascular ultrasound, baseline DBP independently predicted an increase in % atheroma volume at 1-year follow-up in the culprit artery [28]. The authors concluded that lowering DBP may retard progression of atherosclerosis and thus reduce CVD events. In a cross-sectional analysis of 100 patients with stable angina using intravascular ultrasound, Iwata et al. [29] reported that DBP predicted plaque volume, but LDL-C was a better predictor. Of note, mean LDL-C levels were 107 ± 30 mg/dL in their study. These findings are in contrast to ours where DBP was a better predictor than LDL-C. LDL-C may not have predicted in our study due to the fact that LDL-C levels were < 80 mg/dL (mean [SD] 78.7 ± 28.5 mg/dL). These low LDL-C levels allowed us to examine factors contributing to plaque volume independently of cholesterol. Our study also differs from that of Iwata et al. [29] in that we used CCTA whereas they used intravascular ultrasound. A limitation of intravascular ultrasound is that it is limited to examining the culprit artery in patients with symptomatic CAD who are undergoing invasive cardiac catheterization in most studies. Therefore, intravascular ultrasound does not provide information on the entire coronary tree whereas CCTA does. To our knowledge, the current study is the first to report the effect of systolic *vs.* diastolic BP on coronary plaque volume measured by CCTA in all coronary arteries.

Because a J-shaped relation between BP and CVD events has been observed in the past, the threshold for DBP has been widely debated. In the Systolic Blood Pressure Intervention Trial (SPRINT), subjects with hypertension were randomized to an intensive strategy of lowering SBP < 120 mmHg versus a standard strategy of lowering SBP < 140 mmHg [30]. Those achieving a SBP < 120 mmHg in the intensively treated arm had a significantly lower rate of CVD events and all-cause mortality compared to those with SBP < 140 mmHg in the standard treatment arm [30]. In the intensive treatment arm, the DBP was lowered from a

mean of 78.2 mmHg to a mean of 68.7 mmHg, a BP similar to the lowest DBP tertile in our analysis which showed the least amount of coronary plaque volume. In SPRINT, a diastolic threshold of < 55 mmHg was associated with increased cardiovascular events in both patients with and without cardiovascular disease [31]. The hazard ratios (95% CI) of DBP < 55 mmHg versus 55 to 90 mmHg were 1.68 (1.16–2.43, *p*=0.006) and 1.52 (0.99–2.34), *p*=0.06 in those without and with CVD, respectively [31]. Thus, the SPRINT results identify a DBP threshold – 55 mmHg – below which increased risk of CVD occurs. Concern has been raised about an increased incidence of dizziness, falls, hypotension and syncope with aggressive BP lowering. In the SPRINT trial, those patients achieving a SBP < 120 mmHg (mean DBP of 68 mmHg) had similar outcome measures as assessed by the Physical Component Summary and Mental Component Summary of the Veterans RAND 12-Item Health Survey, the Patient Health Questionnaire 9-item depression scale, patient-reported satisfaction with their BP care and BP medications, and adherence to BP medications as compared to those who received standard treatment (target BP < 140 mmHg) including among those with decreased physical or cognitive function [32]. Therefore, in addition to being associated with fewer CVD events, the BP levels in the intensive treatment arm in SPRINT were well-tolerated [32]. Thus, the SPRINT data suggest that lowering SBP to 120 mmHg, with a DBP down to 55 mmHg, may be safely achieved. In our study, those in the lowest DBP tertile had no dizziness, falls, hypotension or syncope. Taken together with the SPRINT data, DBP between 55 to 68 mmHg may be safely achieved and may be associated with the least amount of coronary plaque.

Several studies assessing coronary plaque subtypes with CCTA have shown that higher volume of noncalcified plaque and total plaque are associated with higher rates of cardiac death, MI and coronary revascularization [33] and higher rates of acute coronary syndrome [34,35]. Furthermore, evidence from intravascular ultrasound studies shows that progression of plaque atheroma volume is independently associated with higher rates of a composite of cardiac death, MI and coronary revascularization (*p* <0.002) and regression is associated with fewer events [36]. Since plaque volume has been shown to be associated with cardiovascular mortality, our findings further the field by demonstrating a potential mechanism - lower coronary plaque volume - by which DBP reduction lowers cardiovascular mortality. Thus, lowering DBP to 68 mmHg, the mean level for those with SBP < 120 mmHg which showed the most optimal outcome in SPRINT, may be beneficial in preventing CVD events due to lower plaque volume and prevention of plaque rupture. Taken together, these findings suggest that plaque composition and volume predict CVD events and support the potential clinical importance of lower amounts of coronary plaque at DBP 68 mmHg.

Limitations of the study include the small number of subjects; thus, the results are hypothesis generating. Our subjects have clinical coronary artery disease; therefore, the results may be limited to this population.

In conclusion, a graded increase in coronary plaque volume occurred as DBP tertile increased whereas plaque volume did not differ by SBP tertile. Similar results were observed when DBP and SBP were examined as continuous variables. Our findings suggest that level of DBP is an important factor in determining plaque volume whereas SBP in the range in the

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current study is not. Therefore, one would predict that maintaining a DBP in the lowest tertile (68 mmHg) would limit coronary plaque formation the most in those with LDL-C < 80 mg/dL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Coronary plaque volume was measured by coronary computed tomographic angiography

- Coronary plaque volume was higher at higher levels of diastolic blood pressure

- In contrast, systolic blood pressure did not predict coronary plaque volume

- Diastolic blood pressure   68 mm Hg had the lowest coronary plaque volume

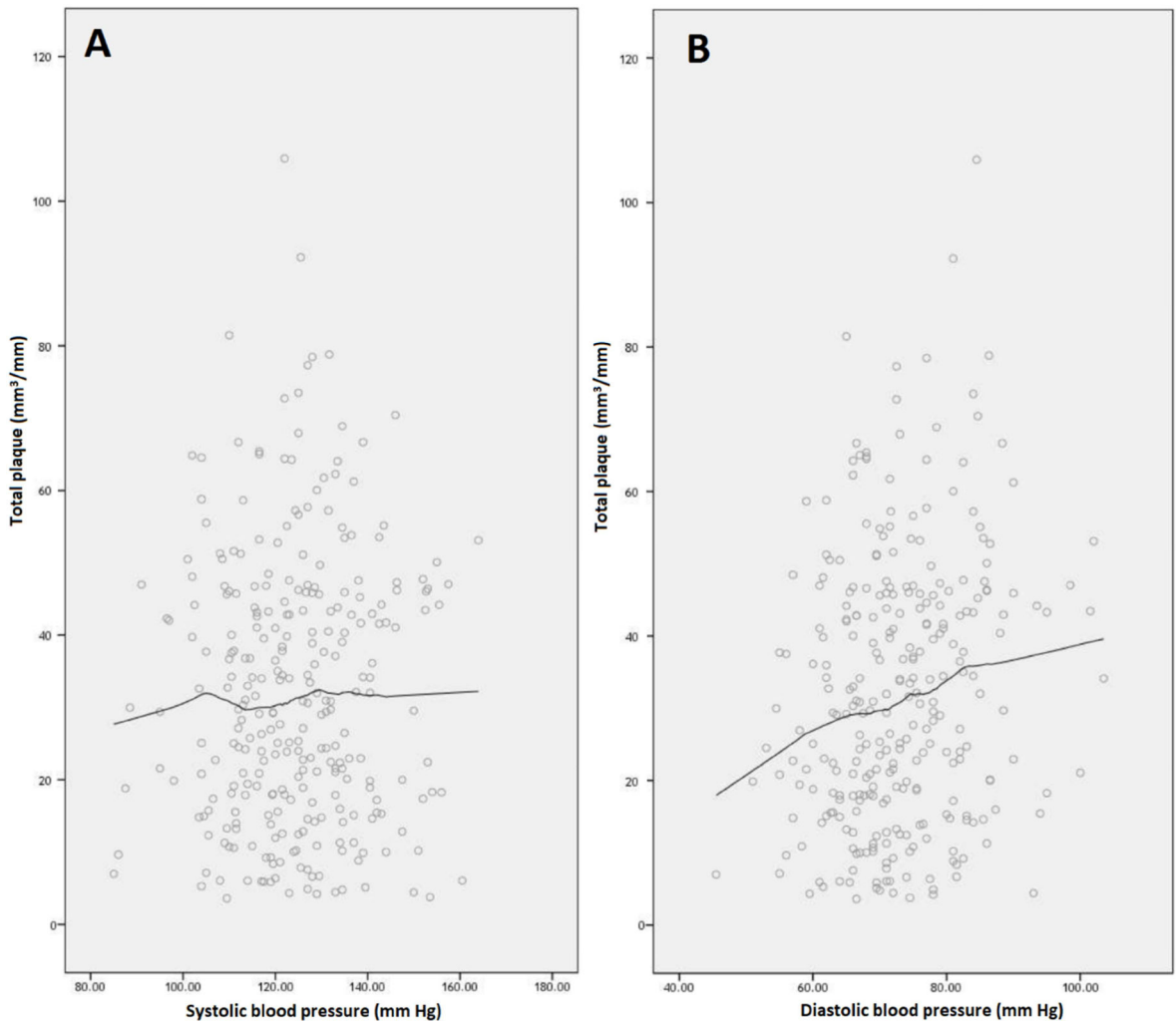- Reduction of diastolic blood pressure to   68 mm Hg may prevent plaque progression

Fig. 1.
Blood pressure.
Systolic blood pressure (A) and diastolic blood pressure (B) graphed *versus* indexed total plaque volume (mm^3/mm).

Table 1

Baseline characteristics according to tertiles of systolic blood pressure.

Characteristics	1st Tertile (118 mmHg) (n = 95)	2nd Tertile (119–130 mmHg) (n = 95)	3rd Tertile (> 130 mmHg) (n = 95)	p for trend
Demographic characteristics				
Age, mean±SD, y	61.7±7.6	62.8±8.6	64.8±6.6	0.007
Male sex, No. (%)	78 (82.1)	79 (83.2)	76 (80.0)	0.708
Inclusion criteria (may have more than one), No. (%)				
History of MI	56 (58.9)	36 (37.9)	38 (40.0)	0.009
History of PCI	62 (65.3)	58 (61.7)	56 (58.9)	0.372
History of CABG	22 (23.2)	22 (23.4)	24 (25.3)	0.735
Cardiovascular risk factors, No. (%)				
Hypertension	66 (69.5)	89 (93.7)	85 (89.5)	<0.001
Diabetes	26 (27.4)	26 (27.4)	30 (31.6)	0.523
Anthropometric and blood pressure, mean±SD				
Weight, kg	90.1±14.8	90.1±13.8	92.8±14.3	0.208
Body mass index, kg/m2*	30.4±3.9	30.2±3.1	31.3±3.7	0.078
Waist circumference, cm	105.8±10.8	105.5±9.6	108.6±10.8	0.069
Systolic BP, mmHg	108.9±7.4	123.9±3.4	139.9±8.2	NA
Diastolic BP, mmHg	66.4±6.7	73.7±7.2	78.8±9.9	<0.001
Pulse pressure, mmHg	42.5±6.7	50.1±7.6	61.1±11.4	<0.001
Complete blood count, mean±SD				
WBC, 10⁹ cells/L	6.6±1.7	6.7±2.7	6.6±1.8	0.986
Monocytes, cells/μL	517.6±158.6	512.7±146.4	548.6±184.3	0.193
Neutrophils, cells/μL	4193.9±1454.4	4109.3±1448.9	4233.1±1604.2	0.857
Lymphocytes, cells/μL	1701.2±554.6	1894.6±2140.4	1672.0±589.0	0.879
Platelets, cells/μL	194.8±52.8	187.8±49.2	195.2±51.2	0.959
Lipids, mean±SD				
Total cholesterol, mg/dL [a]	151.2±32.8	147.3±35.9	158.9±39.5	0.143
Triglyceride, median [IQR], mg/dL [b]	116.5 [77.0,166.0]	122.0 [79.0,167.0]	112.0 [84.0,168.0]	0.880
HDL–C, mg/dL [a]	46.0±13.0	46.6±12.0	48.7±17.3	0.195

Characteristics	1st Tertile (118 mmHg) (n = 95)	2nd Tertile (119–130 mmHg) (n = 95)	3rd Tertile (> 130 mmHg) (n = 95)	p for trend
LDL-C, mg/dL [a]	78.5±25.7	73.7±25.7	83.9±32.7	0.193
Biochemical profile, mean±SD				
Glucose, mg/dL [c]	107.8±41.0	107.1±31.6	106.8±31.3	0.847
HbA1c, % (mmol/mol)	6.2±1.1	6.2±0.9	6.2±.8	0.850
Creatinine clearance (mL/min)	103.0±29.1	100.3±24.7	100.4±27.9	0.512
hs-CRP	0.8 [0.3, 2.6]	0.7 [0.4, 1.8]	0.9 [0.5, 2.6]	0.728
Medication, No. (%)				
Statin	92 (96.8)	91 (95.8)	89 (93.7)	0.299
Aspirin	92 (96.8)	89 (93.7)	92 (96.8)	1.000
ACE-I	49 (51.6)	50 (52.6)	58 (61.1)	0.191
ARB	15 (15.8)	19 (20.0)	17 (17.9)	0.706
Hydrochlorothiazide	15 (15.8)	22 (23.2)	19 (20.0)	0.467
Furosemide	7 (7.4)	11 (11.6)	7 (7.4)	1.000
Calcium channel blocker	16 (16.8)	20 (21.1)	32 (33.7)	0.006
Beta blockers	69 (72.6)	71 (74.7)	66 (69.5)	0.628
On any antihypertensive medication, No. (%)	88 (92.6)	92 (96.8)	87 (91.6)	0.288

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CABG = coronary artery bypass grafting; HbA1c = hemoglobin A1c; HDL-C = high density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; WBC = white blood cell count.

[a] To convert to SI unit (mmol/L), multiply by 0.0259

[b] To convert to SI unit (mmol/L), multiply by 0.0113

[c] To convert to SI unit (mmol/L), multiply by 0.0555

Table 2

Baseline characteristics according to tertiles of diastolic blood pressure.

Characteristics	1st Tertile (68 mmHg) (n=97)	2nd Tertile (69–76 mmHg) (n=93)	3rd Tertile (> 76 mmHg) (n=95)	p for trend
Demographic characteristics				
Age, mean±SD, y	63.5±8.1	63.7±7.8	62.1±7.3	0.204
Male sex, No. (%)	70 (72.2)	81 (87.1)	82 (86.3)	0.011
Inclusion criteria (may have more than one), No. (%)				
History of MI	48 (49.5)	44 (47.3)	38 (40.0)	0.189
History of PCI	55 (56.7)	63 (67.7)	58 (61.7)	0.471
History of CABG	22 (22.7)	28 (30.1)	18 (19.1)	0.579
Cardiovascular risk factors, No. (%)				
Hypertension	79 (81.4)	78 (83.9)	83 (87.4)	0.262
Diabetes	40 (41.2)	22 (23.7)	20 (21.1)	0.002
Anthropometric and blood pressure, mean±SD				
Weight, kg	88.8±14.6	90.5±15.1	93.7±12.9	0.019
Body mass index, kg/m2*	30.6±3.7	30.3±3.5	31.0±3.6	0.417
Waist circumference, cm	105.9±10.7	106.5±10.9	107.5±9.8	0.290
Systolic BP, mmHg	115.0±13.6	125.1±11.9	132.7±11.4	<0.001
Diastolic BP, mmHg	63.3±4.4	72.3±2.2	83.6±6.1	NA
Pulse pressure, mmHg	51.8±12.9	52.9±12.0	49.1±9.7	0.122
Complete blood count, mean±SD				
WBC, 10⁹ cells/L	6.8±1.8	6.8±2.8	6.4±1.6	0.240
Monocytes, cells/µL	532.6±175.7	511.4±145.6	534.5±169.5	0.941
Neutrophils, cells/µL	4291.6±1570.9	4249.0±1534.6	3994.8±1385.1	0.172
Lymphocytes, cells/µL	1722.4±619.9	1877.2±2157.3	1671.6±543.2	0.795
Platelets, cells/µL	192.8±50.2	187.5±52.0	197.3±50.9	0.547
Lipids, mean±SD				
Total cholesterol, mg/dL [a]	150.0±38.7	148.6±30.9	158.8±38.3	0.095
Triglyceride, median [IQR], mg/dL [b]	117.0 [79.0, 167.5]	111.0 [77.0, 161.0]	124.0 [83.0, 175.0]	0.970
HDL-C, mg/dL [a]	46.2±14.1	47.8±15.0	47.3±13.9	0.617

Characteristics	1st Tertile (≤68 mmHg) (n=97)	2nd Tertile (69–76 mmHg) (n=93)	3rd Tertile (> 76 mmHg) (n=95)	p for trend
LDL-C, mg/dL [a]	76.5±29.8	75.4±22.7	84.1±31.4	0.065
Biochemical profile, mean±SD				
Glucose, mg/dL [c]	112.4±38.2	106.4±39.9	102.7±23.6	0.052
HbA1c, % (mmol/mol)	6.3±1.1	6.1±1.0	6.1±.8	0.063
Creatinine clearance (mL/min)	99.0±31.4	102.2±27.1	102.6±22.5	0.363
hs-CRP	0.9 [0.4, 3.2]	0.6 [0.4, 1.5]	0.7 [0.3, 2.3]	0.529
Medication, No. (%)				
Statin	95 (97.9)	91 (97.8)	86 (90.5)	0.014
Aspirin	94 (96.9)	85 (91.4)	94 (98.9)	0.493
ACE-I	56 (57.7)	49 (52.7)	52 (54.7)	0.675
ARB	19 (19.6)	16 (17.2)	16 (16.8)	0.620
Hydrochlorothiazide	19 (19.6)	22 (23.7)	15 (15.8)	0.514
Furosemide	14 (14.4)	7 (7.5)	4 (4.2)	0.012
Calcium channel blocker	22 (22.7)	23 (24.7)	23 (24.2)	0.803
Beta blockers	78 (80.4)	63 (67.7)	65 (68.4)	0.063
On any antihypertensive medication, No. (%)	96 (99.0)	85 (91.4)	86 (90.5)	0.030

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CABG = coronary artery bypass grafting; HbA1c = hemoglobin A1c; HDL–C = high density lipoprotein cholesterol; LDL–C = low density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; WBC = white blood cell count.

[a] To convert to SI unit (mmol/L), multiply by 0.0259

[b] To convert to SI unit (mmol/L), multiply by 0.0113

[c] To convert to SI unit (mmol/L), multiply by 0.0555

Table 3

Comparison of indexed plaque volume components stratified by tertiles of systolic and diastolic blood pressure

	Systolic blood pressure tertiles			
Plaque type [a]	1st Tertile (≤ 118 mmHg) Median [IQR]	2nd Tertile (119–130 mmHg) Median [IQR]	3rd Tertile (> 130 mmHg) Median [IQR]	p value for trend
Fatty	9.3 [5.3,13.7]	8.8 [4.8, 14.0]	9.2 [4.9, 14.3]	0.812
Fibrous	16.5 [9.4, 24.3]	15.1 [8.3, 23.6]	17.1 [9.6, 24.8]	0.758
Noncalcified	25.4 [15.0, 35.9]	23.7 [13.6, 37.5]	26.9 [14.3, 38.9]	0.775
Calcified	4.6 [2.1, 6.8]	3.9 [1.0, 8.8]	4.2 [2.0, 8.6]	0.690
Total	30.0 [18.1, 43.8]	29.3 [15.1, 45.8]	30.9 [17.9, 46.0]	0.645

	Diastolic blood pressure tertiles			
Plaque type [a]	1st Tertile (≤ 68 mmHg) Median [IQR]	2nd Tertile (69–76 mmHg) Median [IQR]	3rd Tertile (> 76 mmHg) Median [IQR]	p value for trend
Fatty	7.7 [5.1,12.9]	9.0 [4.4,13.7]	10.0 [6.1,14.9]	0.042
Fibrous	13.8 [9.0,20.9]	16.5 [8.3,24.5]	19.6 [10.1,25.8]	0.011
Noncalcified	22.5 [14.3,33.5]	25.0 [12.9,37.2]	29.7 [16.4,39.6]	0.017
Calcified	4.2 [2.1,7.3]	3.6 [1.3,6.7]	5.4 [1.8,9.7]	0.054
Total	25.1 [17.2,42.0]	30.6 [16.9,43.8]	37.8 [20.1,47.0]	0.010

[a] Plaque volume expressed as mm^3 per mm artery segment length

Table 4

Systolic and diastolic blood pressures as predictors of plaque volume as a continuous variable.

Systolic blood pressure

	Univariable			Multivariable (fully adjusted)		
	β	95% CI	p	β	95% CI	p
Fatty plaque	0.007	(−0.041 to 0.054)	0.781	0.010	(−0.032 to 0.052)	0.636
Fibrous plaque	0.022	(−0.059 to 0.103)	0.598	0.030	(−0.042 to 0.102)	0.408
Noncalcified plaque	0.028	(−0.099 to 0.155)	0.660	0.040	(−0.072 to 0.152)	0.478
Calcified plaque	0.006	(−0.033 to 0.044)	0.764	0.003	(−0.034 to 0.041)	0.857
Total plaque	0.045	(−0.108 to 0.198)	0.564	0.052	(−0.084 to 0.188)	0.451

Diastolic blood pressure

	Univariable			Multivariable (fully adjusted)		
	β	95% CI	p	β	95% CI	p
Fatty plaque	0.089	(0.018 to 0.159)	0.014	0.029	(−0.036 to 0.094)	0.381
Fibrous plaque	0.192	(0.072 to 0.312)	0.002	0.128	(0.019 to 0.237)	0.022
Noncalcified plaque	0.281	(0.092 to 0.469)	0.004	0.176	(0.004 to 0.348)	0.045
Calcified plaque	0.080	(0.023 to 0.137)	0.006	0.096	(0.039 to 0.152)	0.001
Total Plaque	0.371	(0.145 to 0.598)	0.001	0.249	(0.041 to 0.457)	0.019

Table 5

Fully adjusted models for systolic and diastolic blood pressure for total plaque volume.

Systolic blood pressure			
	β	*p* value	95% C.I.
Constant	53.644	<0.001	(25.735 to 81.552)
Systolic blood pressure	0.052	0.451	(−0.084 to 0.188)
Age	−0.283	0.033	(−0.543 to −0.024)
Gender	−0.782	0.786	(−6.443 to 4.879)
History of CABG	−16.665	<0.001	(−21.326 to −12.004)
Weight	0.224	0.005	(0.067 to 0.382)
Neutrophils	−0.002	0.021	(−0.003 to 0.000)
HbA1c	−3.352	0.001	(−5.406 to −1.297)
On hydrochlorothiazide	4.728	0.059	(−0.177 to 9.632)

Diastolic blood pressure			
	β	*p* value	95% C.I.
Constant	50.740	0.001	(19.823 to 81.656)
Diastolic blood pressure	0.249	0.019	(0.041 to 0.457)
Age	−0.139	0.305	(−0.404 to 0.127)
Gender	0.492	0.864	(−5.164 to 6.149)
History of myocardial infarction	−3.989	0.042	(−7.836 to −0.142)
History of CABG	−16.248	<0.001	(−20.797 to −11.699)
Hypertension	−6.349	0.022	(−11.788 to −0.910)
Weight	0.451	0.001	(0.192 to 0.710)
Waist circumference	−0.362	0.032	(−0.693 to −0.031)
Neutrophils	−0.001	0.078	(−0.002 to 0.000)
HbA1c	−2.543	0.015	(−4.594 to −0.493)
On Hydrochlorothiazide	6.198	0.014	(1.269 to 11.128)

CABG = coronary artery bypass grafting; HbA1c = hemoglobin A1c