Relation of Isolated Systolic Hypertension and Pulse Pressure to High-Sensitivity Cardiac Troponin-T and N-Terminal pro-B-Type Natriuretic Peptide in Older Adults (from the Atherosclerosis Risk in Communities Study)

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Isolated systolic hypertension (ISH) and elevated pulse pressure (PP) are common blood pressure (BP) abnormalities in older adults, reflect poor vascular compliance, and can signify risk for cardiovascular outcomes. We sought to characterize the associations of ISH and widened PP with high-sensitivity Troponin-T (hs-cTnT; a marker of myocardial damage) and N-terminal pro-B-type natriuretic peptide (NT-proBNP; a marker of hemodynamic stress) levels in older adults. We performed a cross-sectional analysis of 5,251 Atherosclerosis Risk in Communities (ARIC) study participants without heart failure who attended visit 5 (2011 to 2013). We used logistic regression to evaluate the association of ISH (systolic BP ≥140 mm Hg and diastolic BP < 90 mm Hg) and quartiles of PP with detectable (≥5 ng/L) and elevated hs-cTnT (≥14 ng/L); as well as elevated NT-proBNP (≥100 pg/mL). The mean age was 75 years, 58% were women, and 78% were white. ISH was present in 24.7% and PP ≥ 70 mm Hg in 30.3% of this cohort. Compared to participants with nonhypertensive BP (<140/90 mm Hg), ISH was independently associated with hs-cTnT and NT-proBNP; adjusted odds ratio of 1.5 (95% confidence interval: 1.1 to 1.9) for detectable hs-cTnT; 1.3 (1.1 to 1.5) for elevated hs-cTnT; and 1.8 (1.6 to 2.1) for elevated NT-proBNP. Increasing quartiles of PP were also significantly associated with both elevated hs-cTnT (p-for-trend <0.0001) and NT-proBNP (p-for-trend <0.0001). These associations were not modified by BP treatment status. In conclusion, ISH and wide PP are relatively common in older adults despite contemporary BP treatment and are associated with abnormalities in hs-cTnT and NT-pro BNP, findings that could guide personalized treatment of older patients with these BP aberrations. **(Am J Cardiol 2019;124:245−252)**

Isolated systolic hypertension (ISH) and increased pulse pressure (PP) are common blood pressure (BP) abnormalities in older adults[1] and reflect structural and functional changes that often occur in the vasculature as part of aging. Previous studies have demonstrated that ISH is independently associated with future cardiovascular disease (CVD) outcomes.[2,3] There is also considerable evidence indicating that elevated PP, another proxy for vascular stiffness, is a strong independent risk factor for CVD risk and mortality in older populations.[4,5] However, while older patients have much to gain from normalizing BP, they are also at highest risk for side effects from intensive BP therapy, highlighting that an individualized approach is paramount.[6] Cardiac biomarkers offer the potential to guide such individualized treatment, in that older adults with elevated biomarkers and either ISH or widened PP are at highest risk and therefore more likely to benefit from more intensive BP therapy. However, the impact of ISH and widened PP on high-sensitivity Troponin-T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in older adults remains poorly characterized.

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Methods

The Atherosclerosis Risk in Communities (ARIC) study is a community-based observational cohort study of adults sampled from 4 US communities: Forsyth Country, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. The initial recruitment and evaluation of 15,792 participants (age 45 to 64 years) occurred between 1987 and 1989. Three subsequent visits took place approximately every 3 years in 1990 to 1992, 1993 to 1995, and 1996 to 1998. A fifth study visit was completed between 2011 and 2013, and a sixth study visit between 2016 and 2017. All baseline values for this analysis were measured at visit 5. The details of the study design and examination protocols for the ARIC Study have been previously described in detail elsewhere.[7] Institutional review boards at all of the study sites approved the study and all participants provided informed written consent.

Of the 6544 participants who attended visit 5, we excluded those with an existing diagnosis of heart failure at or before this visit (n = 371) and those who were missing data regarding heart failure (HF) diagnosis (n = 6). Prevalent heart failure was ascertained a number of ways at ARIC visit 5: (1) adjudicated prior hospitalization since 2005 but before visit 5, as previously established[8]; or (2) by International Classification Diseases ninth Revision, Clinical Modification 428 code for hospitalizations before 2005[9]; or (3) by self-reported HF before visit 5.

We also excluded those patients with missing values for exposure variables (baseline systolic and diastolic BP values), missing values of outcome variables (hs-cTnT and NT-proBNP), and those who were missing other clinical covariates of interest. Per standard ARIC practice, African-Americans in the Minnesota and Washington County cohorts were also excluded (n = 24). We additionally excluded the 18 participants who were not of white or black race. Consequently, a total of 5,251 patients were available for our analysis (Online Supplement, eFigure 1). Medical history, demographic data, anthropometric data, BP measurements, and fasting lipid assessments were obtained during ARIC visit 5 at the same time as the blood draw for the biomarker measurements.

BP was measured with an automatic sphygmomanometer (OMRON HEM-907) at visit 5 by a certified trained technician using an appropriately sized cuff as outlined in the ARIC manual of procedures.[10] We defined ISH as systolic BP (SBP) ≥ 140 mm Hg and diastolic BP (DBP) < 90 mm Hg.[11] We calculated PP as the difference between SBP and DBP in mm Hg. Mean arterial BP was calculated as (2 * DBP + SBP)/3, in mm Hg.

For measurement of NT-proBNP and hs-cTnT, assays were processed at the Baylor College of Medicine in 2011 to 2013. Hs-cTnT was measured using the highly sensitive assay (Elecsys Troponin T Gen 5 STAT, Roche Diagnostics, Indianapolis, Indiana) in stored plasma samples that were collected at visit 5. As per the manufacturer package insert, the limit of detection of this assay is 5 ng/L. This hs-cTnT assay measures values in the range of 3 to 100,000 ng/L. For a "healthy" reference group of patients aged 20 to 70, hs-cTnT values ≥14 ng/L represent the 99th percentile and the 90th percentile in the ARIC sample.[12] The interassay coefficient of variance for hs-cTnT was 6.4% for a mean control level of 29 ng/L.[13] We examined established categories of detectable hs-cTnT (≥5 ng/L) and elevated hs-cTnT (≥14 ng/L). Given the advanced age of participants, we also used age- and gender-specific 99th percentile reference values for adults >65 years of age to define elevated hs-cTnT: >31 ng/L for men and >17 ng/L for women.[14] We measured plasma NT-proBNP at visit 5 using electrochemiluminescent immunoassay (Roche Diagnostics). The lower limit of detection for this assay is 5 pg/ml with a measurement range of 5 to 35,000 pg/ml. The interassay coefficient of variance for NT-proBNP was 7.4% for a mean control level of 134 pg/ml. We defined elevated NT-proBNP as a concentration of 100 pg/ml or higher.[15–17]

Socio-demographic and cardiovascular risk factors were obtained using standardized protocols at ARIC visit 5.[7] Alcohol use and smoking status were self-reported. Body mass index (BMI) was calculated from measured weight and height. Diabetes was defined as either a self-reported physician diagnosis of diabetes or using medication for diabetes or hemoglobin A1C value ≥6.5 %. Hypertension medication use was defined by either self-reported use of antihypertensive medications in the last 4 weeks or by review of medications brought to the visit. Fasting total cholesterol, high-density lipoprotein cholesterol, and triglyceride measurements were obtained. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[18] Estimated glomerular filtration rate was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[19]

We categorized our sample based on BP level as follows: "nonhypertensive or normotensive" (SBP <140 mm Hg and DBP < 90 mm Hg); ISH (SBP ≥ 140 mm Hg and DBP < 90 mm Hg); or hypertensive (SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg). All of these categories included patients with and without antihypertensive medication use at baseline. We used the category of "nonhypertensives or normotensives" as our reference category for the ISH analyses. We excluded 16 patients with isolated diastolic hypertension (SBP < 140 mm Hg and DBP ≥ 90 mm Hg) from this categorical analysis. We also categorized our full sample by quartile of PP (quartile 1: PP of 7 to 54 mm Hg; quartile 2: PP of 54.5 to 62 mm Hg; quartile 3: PP of 62.5 to 72 mm Hg; quartile 4: 72.5 to 158 mm Hg), with the first quartile as reference category. We summarized participant characteristics using mean (standard deviation) or median (25th and 75th percentiles) for continuous variables and percentages for categorical variables. Baseline continuous variables were compared between groups using one-way analysis of variance. Pearson's chi-square test was used for comparison of categorical variables.

Demographic- and multivariable-adjusted logistic regression models were used to calculate odds ratios (ORs) for each of the biomarker outcomes. Separate models were run for ISH category and PP quartiles. Model 1 included age, gender, and, per usual ARIC procedures, race-center (blacks from Jackson, blacks from Forsyth County, whites from Forsyth County, whites from Minneapolis, and whites from Washington County). Model 2 included all variables in model 1 plus BMI, diabetes status, hypertension medication use, use of

cholesterol lowering agents, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, estimated glomerular filtration rate, smoking status, drinking status, and a history of CHD. Model 3 included all the variables in Model 2 with additional adjustment for mean arterial pressure. Because of evidence for a nonlinear association of BMI with elevated NT-proBNP, a linear spline term with knot at 25 kg/m^2 was used for BMI in the relevant models. In the PP analyses, we conducted p-for-trend analyses using an ordinal number for each PP quartile and modeled this variable as a linear exposure. In addition, we examined the association of PP continuously with elevated hs-cTnT and NT-proBNP using a restricted cubic spline with 4 knots in the logistic regression model, adjusting for the variables in Model 3.

As a sensitivity analysis, we also repeated each of the above models stratified by hypertension treatment status (with removal of this term from Models 2 and 3) and tested for interaction by hypertension treatment using the likelihood ratio test. Statistical significance was defined as a 2-sided p-value <0.05. All statistical analyses were performed using Stata 15 IC (StataCorp, College Station, Texas).

Results

The mean age of study participants was 75 years, 58% were women, and 78% were white. Approximately 75% of this older study population were on antihypertensive medication. When categorized by BP level, 73.5% of participants were classified as "nonhypertensive or normotensive" (n = 3,850), that is SBP < 140 mm Hg and DBP < 90 mm Hg, 24.8% had ISH (n = 1,298), and 1.5% (n = 87) had SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg (Table 1). In patients with ISH, the mean SBP was 152 mm Hg whereas the mean DBP was 72 mm Hg compared with mean SBP of 122 mm Hg and mean DBP of 64 mm Hg in the reference group.

Patients with ISH and widening PP tended to be older and more likely to be female (Table 1). The prevalence of diabetes was similar between patients with BP in normal range and patients with ISH (27% and 28.3%, respectively). However, the prevalence of diabetes increased with increasing PP and was highest in quartile 4 (32%) compared with quartile 1 (24%), even though the BMI was similar in both groups (BMI of 28 kg/m^2 in quartile 4 compared with BMI of 29 kg/m^2 in quartile 1). The proportion of patients with prevalent CHD was 13% in both patients with BP in normotensive range and those with ISH; however, this proportion increased with higher PP, with approximately 16% prevalence in the highest PP quartile compared with 10% in the first (reference) PP quartile.

The crude proportions of patients with elevated hs-cTnT (≥14 ng/L) and NT-proBNP (≥100 pg/mL) were considerably larger in the ISH group when compared with the patients with normal BP levels (Table 1). Similarly, the crude proportions of patients with elevated hs-cTnT and NT-proBNP were larger at higher PP quartiles, reaching the largest proportion (39% for hs-cTnT and 75% for NT-proBNP) in the fourth PP quartiles.

In demographic-adjusted models, older adults with ISH had greater odds of having detectable hs-cTnT, elevated hs-cTnT, and elevated NT-proBNP (Table 2, Model 1) compared with normotensive participants. These associations remained robust to further adjustment in Model 2 and Model 3. Compared with older adults with normal BP levels, the adjusted OR of detectable hs-cTnT was 1.62 (95% confidence interval: 1.14, 2.31) in those with ISH in Model 3. The adjusted ORs of elevated hs-cTnT and NT-proBNP were 1.26 (1.03, 1.56) and 1.98 (1.68, 2.40), respectively, when comparing those with ISH to the reference BP group in Model 3. The association between ISH and elevated hs-cTnT was also present when the age- and gender-specific cut-offs for hs-cTnT were used.

We also found that increasing PP quartile was independently associated with abnormalities in hs-cTnT and NT-proBNP, with strong evidence of a graded increase in risk as PP quartile increased (Table 3). These associations remained similar even on further adjustment for mean arterial pressure for all the outcome measurements. On examining PP continuously with a restricted cubic spline, there was appeared to be a stronger linear association with NT-proBNP than with elevated hs-cTnT (Figure 1).

The above associations between ISH and PP with both cardiac biomarkers were similar in models stratified by antihypertensive medication use (Online Supplement, eTables 1 and 2). We also tested all models for interaction by baseline antihypertensive use; however, we did not observe any statistically significant interactions in any model.

Discussion

In this large community-based cohort of older adults without baseline heart failure, we found that those with ISH or widened PP were more likely to have elevated blood levels of hs-cTnT and NT-proBNP. These findings remained robust when age and gender-specific cut-offs for these biomarkers were applied and on stratifying our study population by baseline antihypertensive medication use.

ISH is the most common form of BP abnormality in older adults.[20] Indeed, some physicians have considered ISH to be a "normal" consequence of aging. Perhaps as a result, approximately 25% of older adults with ISH are not appropriately treated for the condition and our contemporary data from ARIC are no exception to this.[21,22] Although these are, to our knowledge, some of the first data to look at the association between ISH/wide PP and cardiac biomarkers in an elderly sample, it is important to note that numerous studies have already shown that ISH and PP are independently associated with increased risk of myocardial infarction, HF, CVD mortality, and total mortality.[2,3,23,24]

The treatment of hypertension in older adults has evolved over the years yet still remains a challenging task for clinicians. We know that lowering of SBP to 140 to 145 mm Hg with antihypertensive treatment has a significant benefit in reducing all-cause mortality and major cardiovascular and cerebrovascular events in elderly patients with ISH. In contrast, the potential for harm from more intensive BP control in the older populations is also described (e.g., increased risk of orthostasis and falls). Furthermore, lowering of systolic BP in older adults patients with ISH may place them at risk for relative hypotension in the diastolic phase. Diastolic BP below 70 mm Hg and

Table 1
Baseline characteristics of study population according to isolated systolic hypertension (ISH) status and quartiles of pulse pressure, the Atherosclerosis Risk in Communities (ARIC) Study, visit 5 (2011 to 2013)

	Isolated systolic hypertension status		p Value	Pulse pressure quartiles (PP range, mm Hg)				p Value
	Normotensive (n = 3,850)	ISH present (n = 1,298)		Q1(7-54) (n = 1,389)	Q2(54.5-62) (n = 1,256)	Q3(62.5-72) (n = 1,309)	Q4(72.5-158) (n = 1,297)	
Age (years)	75.1 ± 5.0	76.3 ± 5.1	0.45	73.6 ± 4.6	74.8 ± 4.8	75.9 ± 4.9	77.4 ± 5.2	<0.0001
Women	56.8%	63.8%	<0.0001	54.0%	53.0%	61.0%	67.0%	<0.0001
White	80.3%	73.2%	<0.0001	78.0%	79.0%	79.0%	76.0%	0.12
BMI (kg/m^2)	28.6 ± 5.5	28.5 ± 5.7	0.38	29.0 ± 5.8	29.0 ± 5.3	28.4 ± 5.4	28.0 ± 5.7	0.002
Diabetes mellitus	27.2%	28.3%	0.67	24.0%	25.0%	27.0%	32.0%	<0.0001
Hypertension medication use	72.7%	77.1%	0.006	70.0%	70.0%	74.0%	81.0%	<0.0001
Cholesterol-lowering medication use	56.8%	52.7%	0.02	54.9%	55.1%	55.3%	57.0%	0.69
Prevalent coronary heart disease	12.9%	13.0%	0.58	10.0%	12.0%	14.0%	16.0%	<0.0001
Systolic blood pressure (mm Hg)	122.1 ± 11.2	152.3 ± 11.4	<0.0001	114.7 ± 11.5	124.3 ± 10.5	133.2 ± 10.6	149.7 ± 15.5	<0.0001
Diastolic blood pressure (mm Hg)	63.5 ± 9.1	72.6 ± 8.9	<0.0001	66.9 ± 10.5	66.0 ± 10.3	66.2 ± 10.3	66.3 ± 11	0.03
Mean arterial blood pressure (mm Hg)	102.6 ± 9.4	125.7 ± 8.7	<0.0001	82.8 ± 10.5	85.5 ± 10.3	88.5 ± 10.3	94.1 ± 11.7	<0.0001
LDL-cholesterol (mg/dl)	103.4 ± 34.2	107.9 ± 34.4	0.13	105.5 ± 33.8	105.5 ± 36.4	103.4 ± 33.5	104.4 ± 33.8	0.008
HDL-cholesterol (mg/dl)	52.1 ± 13.6	53.8 ± 14.9	<0.0001	52.0 ± 13.4	51.6 ± 13.7	52.8 ± 14	53.6 ± 14.8	0.002
Triglycerides (mg/dl)	110.0 (84-148)	112.0 (85-155)	0.11	109.0 (85-145)	112.0 (85-150)	112.0 (84-151)	108 (83-148)	0.16
eGFR (mL/min/1.73 m^2)	66.9 ± 17.4	65.3 ± 18.5	0.03	68.0 ± 17.3	68.3 ± 16.7	66.4 ± 17.4	63.3 ± 18.7	0.001
Smoker		*0.10*		0.14				
Current	6.1%	5.7%		6.3%	5.3%	6.6%	5.6%	
Former	49.2%	46.3%		49.6%	49.4%	49.5%	45%	
Never	39.2%	41.9%		38.7%	39%	38.4%	43.8%	
Unknown	5.5%	6.1%		5.4%	6.3%	5.5%	5.6%	
Alcohol drinker		*<0.0001*		<0.0001				
Current	51.6%	47.4%		52.1%	55.1%	49.9%	43.7%	
Former	28.2%	27.9%		28.9%	25.9%	28%	30.1%	
Never	20.2%	24.7%		19%	19%	22.1%	26.2%	
Median Hs-cTnT (ng/L)	10 (7-15)	11 (8-17)	<0.0001	9 (6-14)	10 (7-15)	10 (7-16)	11 (8-18)	<0.0001
Elevated Hs-cTnT (i.e., ≥14 ng/L)	28.5%	69.3%	<0.0001	25.9%	30.4%	32.2%	38.9%	<0.0001
Median NT-pro BNP (pg/ml)	113.7 (60.3-225.1)	161.1 (86.6-306.9)	<0.0001	92.0 (48-185)	107.0 (58-197)	139.0 (72-245)	186.0 (100-356)	<0.0001
Elevated NT-pro BNP (i.e., ≥100 pg/ml)	29.3%	68.7%	<0.0001	46.4%	53.0%	62.1%	74.9%	<0.0001

Values are presented as mean ± SD, median (25th to 75th percentile) or %. Hs-cTnT, NT-proBNP, and triglycerides are presented as Median (25th to 75th percentile).
BMI = body mass index; e-GFR = estimated glomerular filtration rate.

Table 2
Adjusted odds ratios (95% CIs) for the association of isolated systolic hypertension (ISH) with elevated or detectable hs-cTnT and elevated NT-pro BNP, n = 5,235*

Outcomes	Isolated systolic hypertension status			
	Normotensive, n = 3,850	ISH, n = 1,298 OR (95%CI)		
		Model 1	Model 2	Model 3
Detectable Hs-cTnT (≥5 ng/L)	1 (Ref)	1.50 (1.15, 1.97)	1.52 (1.15, 2.01)	1.62 (1.14, 2.31)
Elevated Hs-cTnT (≥14 ng/L)	1 (Ref)	1.31 (1.13, 1.52)	1.31 (1.12, 1.53)	1.26 (1.03, 1.56)
Sex-specific Elevated Hs-cTnT levels >17 ng/L (women), >31 ng/L (men)	1 (Ref)	1.35 (1.10, 1.66)	1.30 (1.04, 1.62)	1.53 (1.13, 2.07
NT-proBNP ≥ 100 pg/mL	1 (Ref)	1.80 (1.56, 2.08)	1.88 (1.62, 2.19)	1.98 (1.68, 2.40)

Model 1 included age, gender, and race-center.

Model 2 included all variables in Model 1 plus body mass index, diabetes status, hypertension medication use, cholesterol lowering drug use, LDL-cholesterol, HDL-cholesterol, triglycerides, smoking status, drinking status, estimated glomerular filtration rate, and prevalent coronary heart disease.

Model 3 included all variables in Model 2 plus mean arterial pressure.

* This analysis includes 87 patients with combined systolic-diastolic hypertension who were included in the models but whose results are not shown here.

particularly, below 60 mm Hg can impair myocardial perfusion and has been associated with cardiovascular risk.

Therefore, despite studies suggesting benefits of treatment of ISH in older adults, there often remains uncertainty regarding the optimal individualized target for BP in the elderly and many older adults are undertreated out of concerns for drug complications. In this context, a more personalized, biomarker-guided, approach to BP treatment in this age group may be a preferred alternative. Specifically, because cardiac biomarkers like hs-cTnT and NT-proBNP are known to be associated with adverse cardiovascular outcomes (including stroke) and because our results now demonstrate these biomarkers are also independently associated with ISH and elevated PP in older adults, it is possible that these cardiac biomarkers might be used to identify older adults who would benefit from more intensive BP therapy to reduce ISH or normalize PP (conversely normal levels of these biomarkers might identify older adults who could

Table 3
Adjusted odds ratios (95% CIs) for the association of pulse pressure quartiles with detectable and elevated hs-cTnT and elevated NT-pro BNP, n = 5,251

Detectable Hs-cTnT (≥5 ng/L)	Pulse pressure quartiles (PP range, mm Hg)				*P-for-trend*
	Q1 (7-54) mm Hg, n = 1,389	Q2 (54.5-62) mm Hg, n = 1,256	Q3 (62.5-72) mm Hg, n = 1,309	Q4 (72.5-158) mm Hg, n = 1,297	
Model 1	1 (Ref)	1.03 (0.79, 1.35)	1.09 (0.83, 1.43)	1.62 (1.17, 2.23)	0.005
Model 2	1 (Ref)	1.10 (0.84, 1.46)	1.14 (0.86, 1.52)	1.65 (1.18, 2.30)	0.005
Model 3	1 (Ref)	1.10 (0.83, 1.46)	1.13 (0.84, 1.52)	1.61 (1.12, 2.32)	0.011
Elevated Hs-cTnT (≥14 ng/L)					
Model 1	1 (Ref)	1.10 (0.92, 1.33)	1.19 (0.99, 1.43)	1.49 (1.23, 1.79)	<0.001
Model 2	1 (Ref)	1.22 (1.00, 1.48)	1.25 (1.03, 1.52)	1.44 (1.18, 1.76)	<0.001
Model 3	1 (Ref)	1.20 (0.98, 1.46)	1.20 (0.98, 1.46)	1.33 (1.07, 1.65)	0.012
Sex-specific Elevated Hs-cTnT levels >17 ng/L (women), >31 ng/L (men)					
Model 1	1 (Ref)	1.31 (0.96, 1.79)	1.34 (0.99, 1.82)	1.93 (1.45, 2.57)	<0.0001
Model 2	1 (Ref)	1.47 (1.06, 2.05)	1.35 (0.98, 1.86)	1.73 (1.28, 2.35)	<0.0001
Model 3	1 (Ref)	1.47 (1.06, 2.05)	1.35 (0.97, 1.87)	1.71 (1.23, 2.38)	0.001
NT-proBNP ≥ 100 pg/ml					
Model 1	1 (Ref)	1.15 (0.98, 1.35)	1.51 (1.28, 1.77)	2.47 (2.07, 2.95)	0.002
Model 2	1 (Ref)	1.26 (1.07, 1.49)	1.57 (1.32, 1.86)	2.50 (2.08, 3.01)	<0.0001
Model 3	1 (Ref)	1.24 (1.05, 1.47)	1.51 (1.26, 1.79)	2.31 (1.89, 2.83)	<0.0001

Model 1 included age, gender, and race-center.

Model 2 included all variables in Model 1 plus body mass index, diabetes status, hypertension medication use, cholesterol lowering drug use, LDL-cholesterol, HDL-cholesterol, triglycerides, smoking status, drinking status, estimated glomerular filtration rate, and prevalent coronary heart disease.

Model 3 included all variables in Model 2 plus mean arterial pressure.

Pulse pressure ranges by quartiles: Q1: Quartile 1; Q2: Quartile 2; Q3: Quartile 3; Q4: Quartile 4.

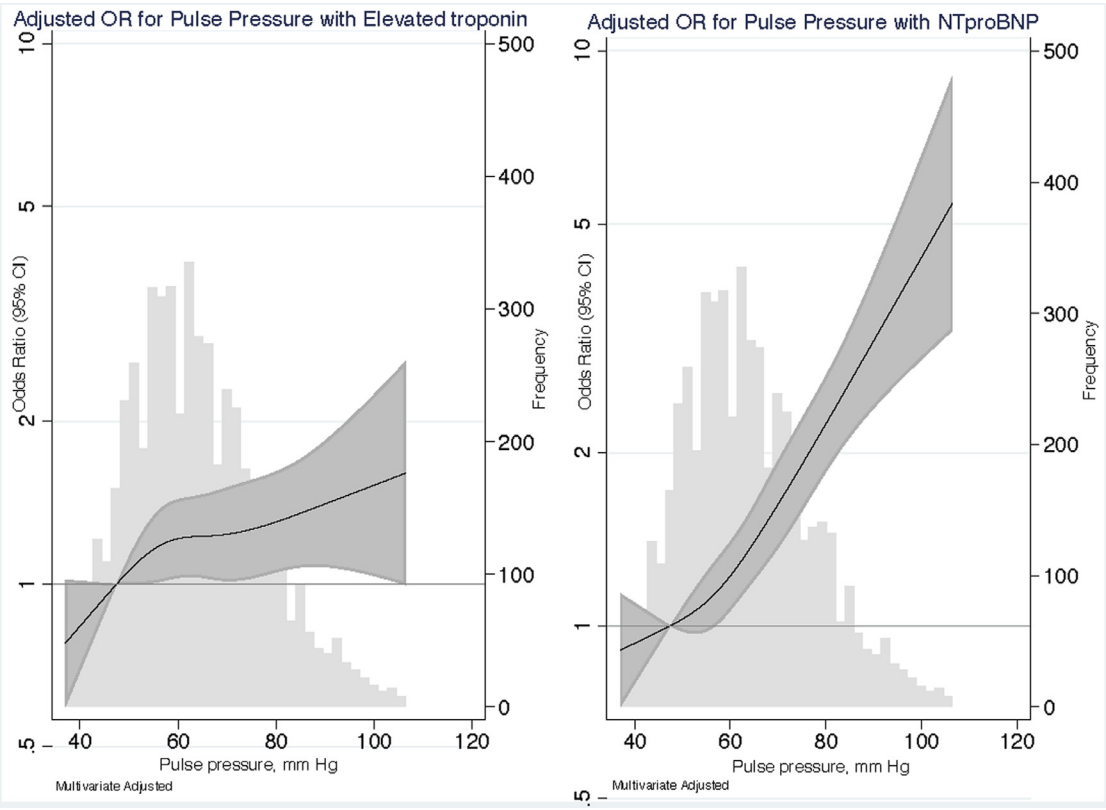

Figure 1. Adjusted odds ratio (95% CI) for association of pulse pressure with (A) elevated hs-cTnT or (B) elevated NT-proBNP. Relation between pulse pressure and elevated high sensitivity cardiac troponin-T (hs-c-TnT ≥ 14 ng/L), *graph on the left (panel a)* and elevated NT-pro BNP (≥100 pg/ml), *graph on the right (panel b)*. Hs-cTnT and NT-proBNP were modeled using restricted cubic splines with knots at pulse pressures of 44.5, 57, 67.5, and 88 mm Hg. The odds ratio was adjusted for age, gender, and race-center, body mass index, diabetes status, hypertension medication use, cholesterol-lowering drug use, LDL-cholesterol, HDL-cholesterol, triglycerides, smoking status, drinking status, estimated glomerular filtration rate, prevalent coronary heart disease, and mean arterial blood pressure. The distribution (frequency histogram) of pulse pressure is shown in grey in the background. The shaded area around the regression line represents the 95% confidence interval (CI).

avoid more intensive therapy). Whether biomarkers might inform the specific BP treatment agent is to be determined.

There are some limitations of this study that should be considered in the interpretation of our results. First, due to the observational and cross-sectional nature of our study design, we cannot establish the temporality of the observed associations nor fully eliminate the possibility of residual confounding (which would undermine causality). Second, although elevated biomarker values reflect myocardial damage, they do not always indicate the exact underlying pathophysiological mechanisms, and can arise in several disease processes (including both cardiac and noncardiac causes) or even due to physiological stresses in otherwise normal hearts.[25,26] Although we also know that elevated hs-cTnT and NT-proBNP are associated with adverse prognosis in younger cohorts,[27–30] whether the asymptomatic older adults with ISH and PP and higher blood levels of cardiac biomarkers in our sample have worse cardiovascular outcomes (with or without aggressive BP treatment) will require additional longitudinal follow-up (we hope that clinical events after visit 6 from ARIC will be available within the next 1 or 2 years). Third, we cannot exclude the possibility that some of our study participants with elevated levels of cardiac biomarkers could have obstructive coronary disease or subclinical LV dysfunction. However, it is important to note that our study participants were all asymptomatic. Fourth, we did not have access to the following information for our analysis; arterial stiffness/elasticity, ventricular-vascular coupling, myocardial perfusion, echocardiography, physical fitness, or central aortic BP.

In conclusion, our cross-sectional study shows that ISH and widening PP are relatively common in contemporary older community-based population. Older adults with ISH and widened PP were much more likely to have elevated blood levels of important and highly prognostic cardiac biomarkers, hs-cTnT, and NT-proBNP. Our study may have implications for the treatment of these BP changes in older adults and may suggest a more personalized approach of risk stratification with guidance from the blood levels of these biomarkers. Additional prospective studies are needed evaluating targeted BP therapies in these older adults with elevated cardiac biomarkers to further understand the clinical significance of the higher blood levels of cardiac biomarkers in those with ISH and widening PP.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.030.

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