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Relations of Matrix Remodeling Biomarkers to Blood Pressure Progression and Incidence of Hypertension in the Community

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Abstract

Background—Biomarkers of extracellular matrix remodeling are associated with prevalent hypertension in cross-sectional studies but their relations to longitudinal changes in blood pressure (BP) and hypertension incidence are unknown.

Methods and Results—We evaluated 595 non-hypertensive Framingham Offspring Study participants (mean age 55 years; 360 women) without prior heart failure and myocardial infarction, and who underwent routine measurements of plasma tissue inhibitor of metalloproteinase-1 (TIMP-1), metalloproteinase-9 (MMP-9), and protocollagen III N-terminal peptide (PIIINP). We related plasma TIMP-1, PIIINP, and MMP-9 to the incidence of hypertension and progression of BP by ≥1 category (defined based on sixth report of the Joint National Committee on Prevention,

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Clinical Summary: The biomarkers of extracellular matrix remodeling include the matrix metalloproteinases (MMPs, which breakdown collagen), the tissue inhibitors of metalloproteinases (TIMPs, which inhibit the activity of metalloproteinases), and the procollagen peptides (which reflect the turnover of extracellular collagen). We evaluated 595 middle-aged non-hypertensive Framingham Offspring Study participants without prior heart failure or myocardial infarction who had measured blood levels of TIMP-1, MMP-9, and procollagen III N-terminal peptide (PIIINP). We related matrix biomarker levels prospectively to the incidence of hypertension and the progression of blood pressure (BP) to a higher category (as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure). On follow-up (4 years), 81 participants developed hypertension and 198 (114 women) progressed to a higher BP category. Adjusting for standard risk factors for hypertension, higher TIMP-1 levels and detectable MMP-9 both were associated with longitudinal tracking of BP. Individuals in top TIMP-1 tertile had a 2.15-fold risk of hypertension (relative to the lowest tertile) whereas those with detectable MMP-9 had a near two-fold risk of BP progression (compared to those with undetectable levels). Plasma PIIINP was not associated with BP tracking. Overall, these data suggest that higher circulating levels of select matrix remodeling biomarkers may antedate the onset of hypertension, perhaps because they reflect ongoing vascular remodeling that accompanies the evolution of high BP.

Other Disclosures: None

Detection, Evaluation and Treatment of High Blood Pressure). On follow-up (4 years), 81 participants (51 women) developed hypertension and 198 (114 women) progressed to a higher BP category. In multivariable models, one-standard deviation increment of log-TIMP-1 was associated with a 50% higher incidence of hypertension (95% confidence intervals [CI] 1.08-2.08) and a 21% (95% CI 1.00-1.47) higher risk of BP progression. Individuals in top TIMP-1 tertile had a 2.15-fold risk of hypertension (95% CI 0.99-4.68) and 1.68-fold (95% CI 1.05-2.70) risk of BP progression relative to the lowest tertile. Individuals with detectable MMP-9 had a 1.97-fold higher risk of BP progression (95% CI 1.06-3.64) compared to those with undetectable levels. Plasma PIIINP was not associated with hypertension incidence or BP progression.

Conclusions—In our community-based sample, higher TIMP-1 and MMP-9 concentrations were associated with BP progression on follow-up. Additional studies are warranted to confirm our findings.

Keywords

Hypertension; Blood pressure; Tissue Inhibitor of Metalloproteinase-1; Matrix Metalloproteinase-9; Type III procollagen N-terminal peptide

Introduction

The pathophysiological mechanisms underlying vascular remodeling include the processes regulating the turnover of extra cellular matrix collagen.[1] In recent years, scientists have studied many biomarkers of matrix remodeling that closely reflect the ongoing process of continuous matrix breakdown and synthesis. Three such families of biomarkers that are associated with regulation of the extracellular collagen matrix are: matrix metalloproteinases (MMPs), which are associated with degradation of collagen; tissue inhibitors of metalloproteinases (TIMPs), which inhibit the activity of metalloproteinases; and procollagen peptides, which reflect the actual turnover of extracellular collagen.[2-4] Of the numerous biomarkers belonging to these 3 families of matrix biomarkers, MMP-9, TIMP-1 proteins, and plasma procollagen III N-terminal peptide (PIIINP) have been extensively studied in experimental investigations, and have been widely implicated in the complex process of vascular remodeling.[1-4]

In clinical studies, high circulating concentrations of TIMP-1 have been associated with presence of left ventricular (LV) hypertrophy,[5] prevalent hypertension,[6-10] congestive heart failure (CHF)[11] and with increased cardiac mortality.[12] In comparison to studies that have evaluated circulating TIMP-1, cross-sectional investigations relating plasma MMP-9 and PIIINP to hypertension have yielded conflicting results. Some studies reported higher plasma concentrations of MMP-9[6,13,14] and higher plasma PIIINP[15] in hypertensive individuals (compared to their non-hypertensive counterparts), whereas others have noted lower MMP-9 concentrations,[16,17] or observed no association of PIIINP[10] with hypertension status. Of note, a polymorphism in the *MMP9* gene has been associated with systolic hypertension and with arterial stiffness in one study,[18] but the findings remain to be replicated. One challenge inherent in the aforementioned cross-sectional studies is that it is impossible to determine if the altered circulating concentrations of extracellular matrix markers are a consequence of hypertension (and associated vascular remodeling), or if they antedate and participate in the pathophysiological vascular changes that contribute to the development of high blood pressure (BP); only prospective studies can clarify this issue. Accordingly, we examined prospectively the relations of plasma concentrations of 3 biomarkers of extracellular matrix remodeling (TIMP-1, MMP-9 and PIIINP) to the incidence of hypertension and to longitudinal tracking of BP in a community-based sample.

Methods

The Framingham Heart Study began in 1948 with the recruitment of 5209 white individuals of European descent who were residents of Framingham, MA (referred to as the Original cohort).[19] In 1971, the offspring of the Original cohort and their spouses (n=5124) were enrolled in the Framingham Offspring Study.[20] Participants who attended the sixth examination cycle of the Framingham Offspring Study (n=3532) were eligible for the present investigation. At that examination, all attendees underwent routine physical examination, laboratory assessment of cardiovascular disease risk factors, and transthoracic echocardiography. The Framingham Heart Study protocol was approved by the Boston University Medical Center Institutional Review Board, and all participants signed written informed consent.

At the sixth examination cycle, plasma concentrations of TIMP-1, MMP-9 and PIIINP were measured in a subsample, chosen to maximize scientific yield and to permit the judicious use of precious and scarce non-renewable serological resources (given the relative novelty of these biomarkers from the perspective of an epidemiological cohort). Previously, investigators have reported associations of extracellular matrix biomarkers to hypertension and related traits (LV remodeling, hypertrophy, and heart failure)[7,10,11,15] in high-risk samples. So, first we examined the sex-specific distributions of echocardiographic LV internal dimensions (LVID) and LV wall thickness (LVWT) of attendees. Next, we sampled participants with both LVID and LVWT measurements below the 50th sex-specific percentile (the “referent” LV group; n=605), and individuals with either the LVID or LVWT at or above the 90th sex-specific percentile (referred to as ‘remodeled LV group’; n=439), as detailed elsewhere.[21,22] We measured plasma concentrations of the matrix biomarkers in the referent and remodeled LV group, and participants with available biomarkers were eligible for the present investigation (n=1026 for TIMP-1, 943 for PIIINP, 700 for MMP-9). A smaller proportion of individuals had MMP-9 measurements because plasma concentrations were not detectable in a majority of persons, as detailed elsewhere.[5] We excluded participants for the following reasons: prevalent hypertension[23] including the use of antihypertensive medications (n=365); prevalent heart failure (n=3) or myocardial infarction (n=17); serum creatinine >2.0 mg/dl (n=6) or missing covariates (n=4); and non-attendance at the follow up examination (n=36). Thus, after exclusions we had 595 non-hypertensive participants (360 women) in our final sample, all of whom had available plasma concentrations of TIMP-1; of these, 545 individuals had available plasma PIIINP concentrations and 351 had available plasma MMP-9 measurements.

Measurement of risk factors and blood pressure

At the sixth Heart Study examination, attendees underwent physical examination including anthropometry and BP measurements. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meter square. Blood pressure readings were obtained using a mercury column sphygmomanometer and a cuff of appropriate size. The examination BP was the average of two physician-obtained measurements obtained on the left arm of participants after they had rested for 5 minutes in a sitting position. The BP of participants was grouped based on the categories defined by the sixth report of Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure:[24] systolic BP<120 mm Hg and diastolic BP <80 mm Hg; systolic BP 120 to 129 mm Hg or diastolic BP 80 to 84 mm Hg; or systolic BP 130 to 139 mm Hg or diastolic BP 85 to 89 mm Hg.

Measurement of biomarkers

Blood samples were obtained from attendees after an overnight fast (typically between 7.30 AM and 9 AM in the morning), centrifuged and the plasma was frozen at -80 degrees C until assay. All three matrix biomarkers were measured in duplicate, using two-site sandwich ELISA

assays for TIMP-1 and MMP-9, and a radioimmunoassay for PIIINP (Amersham Pharmacia Biotech). Plasma total TIMP-1 assays measured free TIMP-1 and complexes of TIMP-1 with MMPs, whereas the total MMP-9 assay measures MMP-9, ProMMP-9/TIMP-1 and MMP-9 complexed with various TIMPs. Intra-assay coefficients of variation were: <5% for TIMP-1, <18% for MMP-9 and 6% for PIIINP.

Echocardiographic measurements

As noted above, all attendees at the sixth examination cycle underwent routine transthoracic M-mode two-dimensional and Doppler color flow echocardiography using a Sonos 1000 Hewlett-Packard machine. The internal dimensions of the left ventricle (LVIDD), the thicknesses of the posterior wall (PW) and interventricular septum (IVS) at end-diastole, and left atrial size at end-systole were obtained by averaging digital M-mode measurements in 3 cardiac cycles, using a leading edge technique and according to the American Society of Echocardiography guidelines.[25] Left ventricular wall thickness (LVWT) was derived by adding the diastolic thicknesses of the IVS and the PW. LV mass was calculated by using the formula[26]: $0.8[1.04(\text{LVID}+\text{LVWT})^3 - (\text{LVIDD})^3] + 0.6$. The reproducibility of echocardiographic measurements was good as has been reported previously.[27]

Blood Pressure Outcomes on Follow-up

At follow-up, approximately 3 years after the sixth examination, participants attended the seventh examination cycle, at which time they underwent a routine examination including measurement of their BP. Three BP outcomes on follow-up were evaluated: i. progression in BP by one or more categories (as defined by the JNC VI)[24]; ii. development of hypertension, defined as a systolic BP ≥140 mm Hg or a diastolic BP≥90 mm Hg, or use of antihypertensive medications;[23] iii. continuous changes in systolic and diastolic BP.

Statistical Analyses

The baseline characteristics of the participants were assessed by sex, and according to tertiles of plasma TIMP-1 and PIIINP concentrations. Our primary outcome of interest was new-onset of hypertension and progression of BP category at the follow up examination (seventh examination cycle). First, we estimated the unadjusted and the age- and sex-adjusted proportions of individuals developing hypertension and BP progression on follow-up for the overall sample according to tertiles of TIMP-1 and PIIINP, and detectability of MMP-9. Second, multivariable logistic regression models were constructed to analyze the association of plasma TIMP-1, PIIINP and MMP-9 concentrations to the incidence of hypertension and to BP progression. Plasma TIMP-1 and PIIINP levels were assessed both as categorical (tertiles, with the lowest tertile serving as referent) and as continuous variables (natural logarithmically-transformed to normalize the skewed distributions), whereas plasma MMP-9 concentration was modeled as a binary variable (detectable versus undetectable levels). Two sets of models were constructed:

I. Adjusting for age, sex and LV sampling group (referent group versus LV remodeled group)

II. Adjusting for age, sex, baseline systolic and diastolic BP, BMI, percentage weight change on follow-up, smoking, diabetes and LV sampling group (as defined above).

In models incorporating tertiles of TIMP-1 and PIIINP, we compared the incidences of hypertension and BP progression in the second and top tertiles with that in the first tertile that served as referent. We also tested for a trend of rising incidence of hypertension and BP progression across tertiles of these markers.

We performed additional analyses examining the relations of matrix biomarkers to longitudinal changes in systolic and diastolic BP analyzed as continuous variables; censored normal regression[28] was used to account for treatment for high BP at the follow-up examination. These models were adjusted for the covariates noted above (model II).

Secondary Analyses

We repeated all analyses adjusting for LV mass (a composite variable derived from LVID and LVWT, the two variables used to define the sampling scheme) in addition to LV group to reduce the possibility of any residual confounding due to the sampling scheme because higher LV mass has been associated with incident hypertension.[29] To further clarify differences based on sampling group and to analyze if the relations of matrix biomarkers to incidence of hypertension and to progression to a higher BP category are influenced by presence of LV remodeling, we repeated all analyses restricting the sample to the referent group, i.e., those with $<50^{th}$ sex-specific percentile of LVID and LVWT.

All analyses were performed using PROC LOGISTIC procedure in SAS and CNREG routine in STATA.[30] A two sided p-value of 0.05 was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The baseline characteristics of participants are displayed in Table 1. Concentrations of extracellular matrix biomarkers were similar in men and women. The clinical characteristics of our sample according to tertiles of TIMP-1 and PIIINP levels are displayed in Appendix Table 1. Individuals in the highest tertile of TIMP-1 and PIIINP were older, more likely to be men, and had higher mean BMI and systolic BP and a higher prevalence of diabetes. Sample sizes for individuals with availability of each of the 3 matrix biomarkers varied, but an assessment of the clinical characteristics for the samples did not reveal any major differences (Appendix Table 2). Additionally, there were no significant differences in clinical characteristics of participants with measured biomarkers compared to rest of the attendees at the same examination cycle, as previously reported.[21]

On follow up (mean 4 years), 81 participants (51 women) developed hypertension and 198 (114 women) progressed to a higher BP category. We observed modest longitudinal changes in systolic (mean 1.85 mm Hg, SD 11.90) and diastolic BP (mean 0.15 mm Hg, SD 7.63) disregarding the effect of treatment on follow-up.

The proportion of individuals developing hypertension and the proportion progressing to a higher BP category rose (Table 2) with increasing tertiles of plasma TIMP-1 and PIIINP concentrations, and with detectable MMP-9 concentrations (compared to those with undetectable MMP-9).

Association of Plasma TIMP-1 concentrations to blood pressure progression and hypertension

We observed a 31-50% higher incidence of hypertension and a 21% increased risk of progression to higher BP category with increase in one-standard deviation (SD) of log-TIMP-1 (0.15ng/ml; Table 3). These results remained unchanged after excluding participants with atrial fibrillation (n=5). Individuals in the top tertile of TIMP-1 had an over 2-fold higher incidence of hypertension and a 68-74% higher likelihood of progression to a higher BP category (Table 3). We also observed a statistically significant trend of higher incidence of hypertension and progression to higher BP category with increasing TIMP-1 tertiles. These results remained

unchanged in analyses adjusting for LV mass (data not shown). In censored normal regression analyses evaluating change in BP as a continuous variable, plasma TIMP-1 concentration was positively associated with systolic and diastolic BP change, but the results did not reach statistical significance (p =0.082 and 0.317, respectively).

Association of Plasma MMP-9 concentrations to progression of blood pressure and hypertension

In our sample, a majority of individuals did not have a detectable concentrations of MMP-9 (n=293). Individuals with detectable levels of MMP-9 (n=60) had a 2-fold risk of progression to a higher BP category as compared to those with undetectable MMP-9 (Table 3). These results remained unchanged in analyses adjusting for LV mass (data not shown). Individuals with detectable MMP-9 did not have a statistically significant higher risk of developing hypertension in these analyses, although the point estimate of the odds ratios exceeded 1 (Table 3). Plasma MMP-9 was associated with changes in systolic and diastolic BP analyzed as continuous variables (p=0.024 and 0.076, respectively).

Association of PIIINP levels to progression of blood pressure and hypertension

Plasma PIIINP levels were neither related to incident hypertension nor to progression of BP category in any of the models evaluated (Table 3). Analyses of change in systolic and diastolic BP as continuous variables confirmed these findings (p =0.847 and 0.584, respectively).

Because there was no association of plasma PIIINP to BP outcomes, we calculated our statistical power to detect associations. We estimated that we have 80% power (at α =0.05) to detect an association of a magnitude of HR 1.83 and 1.31 for incident hypertension and for progression of BP category, respectively, per SD increment in log-PIIINP (SD=0.62ng/ml).

Secondary Analyses—In the referent LV sub-sample (n=433), 130 participants progressed to a higher BP category and 45 developed hypertension on follow-up. In this sample, one SD increase in log TIMP-1 concentrations was associated with a 28-31% higher risk of progression of BP category (Table 4). Participants in the uppermost tertile of TIMP-1 had about twice the risk of advancing to a higher BP category as compared to those in first tertile (*P* value for trend <0.02 in both models; Table 4). These relations remained unchanged after additional adjustment for LV mass (data not shown). However, TIMP-1 was not associated with hypertension in this sample, although the point estimate of the odds ratios exceeded 1 (Table 4). The positive association of detectable MMP-9 concentrations with progression of BP category was slightly attenuated (Table 4). Detectable MMP-9 was not related to incident hypertension and plasma PIIINP levels were not associated with incident hypertension or with progression of BP in this subgroup of individuals (Table 4).

Discussion

Principal findings

Our principal findings are two-fold. First, higher plasma TIMP-1 was associated with greater risk of progression of BP and incidence of hypertension. Analyses of plasma MMP-9 were hampered by low rates of detectability. Nonetheless, detectable plasma MMP-9 was associated with higher likelihood of BP progression. The associations of TIMP-1 and detectable MMP-9 with BP progression were maintained in analyses restricted to a healthier subsample (referent group), and upon adjustment for LV mass. Analyses of BP change as a continuous variable corroborated these findings. Second, plasma PIIINP was not associated with either BP outcome in multivariable analyses, even though unadjusted analyses demonstrated a trend for increase in rates of BP progression and hypertension incidence; these findings suggest likely confounding of the relations of PIIINP and BP outcomes by covariates such as BMI that are

related both to the biomarker and to BP.[22] Our results may also reflect limited statistical power to detect modest associations of this biomarker with BP tracking.

Mechanisms underlying the observed association of matrix biomarkers and BP outcomes

Experimental and clinical studies have suggested that an increase in vascular collagen volume density occurs in essential hypertension.[31,32] Plasma TIMP-1 blocks the activation of several MMPs and prevents their catalytic activity.[33] Hence, higher plasma TIMP-1 levels likely reflect lesser activity of MMPs and greater accrual of collagen matrix, including within the vascular wall.[4,34] Prior clinical data suggest associations of higher TIMP-1 concentrations with prevalent hypertension.[6-10] Researchers have also observed decreases in plasma TIMP-1 concentrations in patients with hypertension after treatment with antihypertensive drugs.[7] Our prospective observations are consistent with these prior findings.

In contrast, results of investigations relating plasma MMP-9 levels to prevalent hypertension have been inconsistent.[6,13,14,16,17] Human vascular endothelium contains several types of collagen. Plasma MMP-9 is a type of gelatinases B that digests gelatin and type IV & V collagen, which is found in subendothelial basement membrane. Hence, it has been proposed that diminished activity of MMP-9 is associated with accumulation of extracellular matrix in the resistance arteries, thereby contributing to hypertension. However, in our study we observed a positive association of detectable MMP-9 and BP progression, which would seem to be the opposite of what would be expected (based on its biological actions) and warrants explanation. One possibility is that we measured total MMP-9, which includes MMP-9 complexed with TIMPs; so it is conceivable that the association of total MMP-9 may reflect the effects of TIMPs. Such an explanation is rendered less likely because the proportion of individuals with detectable MMP-9 decreased across tertiles of TIMP-1 (Appendix 1). A more likely possibility is that MMP-9 may reflect the increased matrix breakdown and vascular inflammation that characteristic of the early stages of vascular remodeling in experimental models of hypertension.[35,36] As hypertension progresses, increased matrix turnover transitions to greater fibrosis as reflected by increases in TIMP-1 levels.[11,37] Consistent with this proposed temporal course of MMP/TIMP activation in early hypertension is the observation that levels of both TIMP-1 and MMP-9 are higher in patients with hypertension in some reports,[6,9,13] possibly indicating a case mix of individuals at different points along the spectrum of hypertension, vascular remodeling and LV hypertrophy.

Strengths and Limitations

The moderate-sized community based sample, adjustment for multiple covariates, and comprehensive analyses of multiple BP outcomes are strengths of our investigation. However, several limitations must be emphasized. We did not measure matrix markers in individuals with their LVDD and LVWT in an intermediate range (50^{th}-90^{th} percentiles). We also did not adjust for left atrial size or LV diastolic function in our analyses. However, we adjusted for LV group and LV mass (which indirectly accounts for LVDD) in all our analyses. Also, we did not measure the circulating concentrations of other biomarkers such as MMP-1, -2 or other types of TIMP levels (e.g. TIMP-2, -4) to examine their associations with BP tracking and hypertension incidence. In addition, although we did not find any association of PIIINP with BP outcomes, it is possible that other biomarkers of the same family such as carboxy terminal propeptide of procollagen type-I or the N-terminal propeptide of type I collagen may be associated with incident hypertension.[38-40] Additional prospective studies with larger sample sizes and longer follow up durations and which measure other TIMPs, MMPs and markers of collagen turnover are required to confirm our findings and better characterize the contributions of extracellular matrix turnover to BP progression in the community.

We used a single measurement of the biomarkers and their levels may vary over time.[41] Such analyses using single-occasion measurements would result in an underestimation of the true strength of the association of biomarkers with the outcomes studied. It is also noteworthy that prior investigators have reported minimal short-term[11] and long-term[42,43] variability over time for the matrix biomarkers studied in the present investigation in individuals without cardiovascular diseases[11] and in some referral samples with disease.[42,43] A majority of participants in our study were white individuals of European ancestry, which limits the generalizability of our findings to other ethnicities.

Conclusions

In our community-based sample, higher plasma TIMP-1 and MMP-9 concentrations were associated with greater risk of experiencing progression to a higher BP progression and developing hypertension on follow up. Overall, these data support the concept that higher circulating levels of matrix remodeling biomarkers may antedate the onset of hypertension, perhaps because these markers reflect vascular remodeling that accompanies the evolution of high BP. PIIINP levels were neither associated with BP progression nor with incident hypertension.

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Table 1

Baseline Characteristics of Study Participants

Characteristic	Men (N=235)	Women (N=360)
Clinical Data		
Age, yrs	54±9	55±9
Body mass index, kg/m^2	27.1±3.8	25.5±4.9
Systolic blood pressure, mm Hg	119±10	115±13
Diastolic blood pressure, mm Hg	75±7	70±8
Optimal BP, %	48.9	59.7
Normal BP %	27.7	21.7
Diabetes, %	5.5	2.2
Current cigarette smoking, %	14.0	18.1
Weight change, %	0.7±5.3	1.1±6.5
Sex-specific LVID and LVWT distributions, %		
LVID and LVWT <50th percentile	73.6	72.2
LVID or LVWT >90th percentile	26.4	27.8
Matrix remodeling markers, ng/mL		
TIMP-1, median IQR	776 (154)	734 (148)
PIIINP, median IQR	3.08 (1.47)	3.03 (1.55)
MMP-9, % detectable	17.5	17.3

All values are mean ± standard deviation or otherwise indicated

Optimal blood pressure, systolic <120 mm Hg and diastolic <80 mm Hg; normal blood pressure, systolic 120-129 mm Hg or diastolic 80-84 mm Hg; high normal blood pressure, systolic 130-139 mm Hg or diastolic 85-89 mm Hg.

TIMP-1: tissue inhibitor of metalloprotein-1; MMP-9: matrix metalloprotein-9; PIIINP: procollagen III N terminal peptide; LVID: Left ventricular internal dimension; LVWT: left ventricular wall thickness

Table 2

Baseline Matrix Remodeling Biomarkers and Four-Year Incidence of Blood Pressure Outcomes

Matrix Biomarkers	Mean (Standard deviation)	Number at risk	Percentage of Individuals developing hypertension		Percentage of Individuals with increase by ≥1 blood pressure category	
			Unadjusted	Age- and sex-adjusted*	Unadjusted	Age- and sex-adjusted*
TIMP tertile						
T1	643.3 (45.6)	198	8.1	9.9	24.75	26.9
T2	750.5 (29.3)	199	10.6	11.1	32.66	33.2
T3	896.1 (94.6)	198	22.2	18.6	42.42	39.3
PIIINP tertile						
T1	2.03 (0.50)	182	8.8	10.7	28.6	30.6
T2	3.05 (0.26)	181	14.4	13.4	32.6	31.7
T3	7.08 (6.85)	182	15.4	14.0	36.2	35.1
MMP-9 category						
Non-detectable	0	290	13.5	13.9	32.8	33.1
Detectable	45.5 (32.7)	61	24.6	21.8	50.8	49.1

Blood pressure categories: optimal blood pressure, systolic<120 mm Hg and diastolic<80 mm Hg; normal blood pressure, systolic 120-129 mm Hg or diastolic 80-84 mm Hg; high-normal blood pressure, systolic 130-139 mm Hg or diastolic 85-89 mm Hg.

TIMP-1: tissue inhibitor of metalloprotein-1; MMP-9: matrix metalloprotein-9; PIIINP: procollagen III N terminal peptide

*Values are age- and sex-adjusted proportions using logistic regression (sample mean age of 54.6 years and 39% are men).

Table 3

Relations of Matrix Remodeling Biomarkers to Hypertension and Blood Pressure Progression

Markers of Matrix Remodeling	Models			
	TIMP-1			
	Incidence of Hypertension		**Progression of Blood Pressure Category**	
	Age- sex- and LV group-adjusted	**Multivariable-adjusted†**	**Age- sex- and LV group-adjusted**	**Multivariable-adjusted†**
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Log TIMP-1, per SD increment	1.31 (1.01-1.70)*	1.50 (1.08-2.08)*	1.21 (1.00-1.45)**	1.21 (1.00-1.47)**
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	1.11 (0.55-2.24)	0.79 (0.35-1.76)	1.34 (0.86-2.09)	1.25 (0.79-1.99)
Tertile 3	2.10 (1.08-4.06)*	2.15 (0.99-4.68)**	1.74 (1.11-2.74)*	1.68 (1.05-2.70)*
Trend	0.02	0.03	0.01	0.03
	PIIINP			
Log PIIINP, per SD increment	1.17 (0.89-1.54)	1.22 (0.88-1.69)	0.95 (0.79-1.14)	0.95 (0.79-1.15)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	1.35 (0.68-2.71)	1.79 (0.78-4.08)	1.05 (0.66-1.90)	1.04 (0.65-1.68)
Tertile 3	1.35 (0.68-2.70)	1.25 (0.54-2.91)	1.21 (0.76-1.90)	1.15 (0.71-1.87)
Trend	0.42	0.69	0.42	0.56
	MMP-9			
Non-detectable MMP-9	Referent	Referent	Referent	Referent
Detectable MMP-9	1.71 (0.83-3.51)	1.54 (0.62-3.86)	1.91 (1.08-3.37)*	1.97 (1.06-3.64)*

*P <0.05;

**P =0.05

†All multivariable models are adjusted for age, sex, systolic and diastolic blood pressure, BMI, LV sampling group (as described in text), percentage weight change, smoking and diabetes mellitus.
TIMP-1: tissue inhibitor of metalloproteinase-1; MMP-9: matrix metalloproteinase-9; PIIINP: procollagen III N terminal peptide; CI denotes confidence intervals

Table 4

Relations of Matrix Remodeling Biomarkers to Hypertension and Progression of Blood Pressure category in Individuals with < 50th Sex-specific Percentile of LVDD and LVWT

Markers of Matrix Remodeling	Models			
	TIMP-1			
	Incidence of Hypertension		**Progression of Blood Pressure Category**	
	Age- sex- adjusted	**Multivariable-adjusted***	**Age- sex- adjusted**	**Multivariable-adjusted***
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Log TIMP-1, per SD incremen	1.15 (0.82-1.62)	1.32 (0.88-1.99)	1.28 (1.02-1.61)	1.31 (1.04-1.66)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	1.02 (0.43-2.43)	0.58 (0.22-1.55)	1.64 (0.96-2.78)	1.47 (0.85-2.53)
Tertile 3	1.72 (0.76-3.91)	1.72 (0.70-4.20)	2.02 (1.17-3.48)	1.98 (1.13-3.46)
Trend	0.18	0.18	0.01	0.02
	PIIINP			
Log PIIINP, per SD increment	1.10 (0.78-1.55)	1.21 (0.83-1.77)	0.92 (0.75-1.13)	0.94 (0.76-1.16)
Tertile 1	Referent	Referent	Referent	Referent
Tertile 2	1.18 (0.49-2.82)	1.28 (0.47-3.47)	0.95 (0.56-1.63)	0.91 (0.52-1.60)
Tertile 3	0.85 (0.33-2.19)	1.03 (0.34-3.11)	0.97 (0.56-1.70)	1.00 (0.56-1.77)
Trend	0.71	0.96	0.93	0.99
	MMP-9			
Non-detectable MMP-9	Referent	Referent	Referent	Referent
Detectable MMP-9	1.96 (0.55-6.92)	3.08 (0.60-15.77)	1.74 (0.73-4.10)	2.60 (1.01-6.69)

*All multivariable models are adjusted for age, sex, systolic and diastolic blood pressure, BMI, percentage weight change, smoking and diabetes mellitus. TIMP-1: tissue inhibitor of metalloprotein-1; MMP-9: matrix metalloprotein-9; PIIINP: procollagen III N terminal peptide. CI denotes confidence intervals.

Appendix Table 1
Baseline Characteristics According to Tertiles of TIMP-1 and PIIINP

Characteristic	Total	Tertiles of TIMP-1			Tertiles of PIIINP		
		Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Clinical Data							
Age, yrs	54.6±8.9	52.1±7.2	54.0±8.3	57.7±10.1	52.6±8.0	55.9±8.6	55.7±9.7
Women, %	60.5	68.2	62.3	51.0	61.0	62.4	59.3
Body mass index, kg/m^2	26.1±4.6	25.1±3.9	26.1±4.4	27.2±5.2	25.3±3.9	25.9±4.2	27.4±5.5
Systolic blood pressure, mm Hg	117±12	114±12	118±12	118±11	115±12	117±12	118±12
Diastolic blood pressure, mm Hg	72±8	71±8	73±8	73±8	72±8	72±8	73±8
Optimal BP, %	55.5	63.1	50.8	52.5	59.3	51.4	54.4
Normal BP %	24.0	22.7	25.6	23.7	20.9	30.4	20.3
Diabetes, %	3.5	2.5	3.0	5.1	1.7	3.3	5.5
Current cigarette smoking, %	16.5	15.7	17.1	16.7	22.5	12.2	13.7
Weight change, %	1.0	1.3±5.6	0.5±6.6	1.0±6.0	1.1±6.9	0.8±6.0	0.9±5.3
LVDD and LVWT, below sex-specific 50th percentile, %	72.8	78.3	72.4	67.7	75.8	72.9	67.6
LVDD or LVWT, above 90th percentile, %	27.2	21.7	27.6	32.3	24.2	27.1	32.4
Matrix remodeling markers, ng/mL							
TIMP-1, ng/ml median (IQR)	752.5 (155.3)	652.6 (62.0)	752.5 (55.5)	870.0 (87.8)	714.2 (132.2)	756.9 (150.9)	775.7 (161.8)
PIIINP, ng/ml median (IQR)	3.05 (1.49)	2.76 (1.45)	3.06 (1.46)	3.28 (1.54)	2.13 (0.68)	3.05 (0.44)	4.56 (2.20)
MMP-9, % detectable	17.4	21.4	17.9	13.6	14.2	14.1	25.3

All values are mean ± standard deviation or otherwise indicated

Optimal blood pressure, systolic <120 mm Hg and diastolic <80 mm Hg; normal blood pressure, systolic 120-129 mm Hg or diastolic 80-84 mm Hg; high normal blood pressure, systolic 130-139 mm Hg or diastolic 85-89 mm Hg.

TIMP-1: tissue inhibitor of metalloproteinase-1; MMP-9: matrix metalloproteinase-9; PIIINP: procollagen III N-terminal peptide

LVDD: left ventricular internal diastolic dimension; LVWT: left ventricular wall thickness

Appendix Table 2

Baseline Characteristics of the Study Participants According to Measured Biomarkers

Characteristic	Measured Biomarkers			P value
	TIMP-1	MMP-9	PIIINP	
Clinical Data	N=595	N=351	N=545	
Age, yrs	55 ± 9	55 ± 9	55 ± 9	0.40
Women, %	60.5	59.3	60.9	0.60
Body mass index, kg/m^2	26.1 ± 4.6	26.9 ± 4.8	26.2 ± 4.7	<0.0001
Systolic blood pressure, mm Hg	117 ± 12	117 ± 12	117 ± 12	0.43
Diastolic blood pressure, mm Hg	72 ± 8	72 ± 8	72 ± 8	0.56
Optimal BP, %	55.5	52.4	55.1	0.16
Normal BP %	24.0	24.8	23.9	0.82
Diabetes, %	3.5	4.0	3.5	0.76
Current cigarette smoking, %	16.5	14.3	16.2	0.20
Weight change, %	1.0 ± 6.1	1.1 ± 6.6	0.9 ± 6.1	0.82
Matrix remodeling markers, ng/mL				
TIMP-1, ng/ml median (IQR)	753 (155)	758 (154)	752 (157)	0.04
PIIINP, ng/ml median (IQR)	3.05 (1.49)	3.02 (1.32)	3.05 (1.49)	0.11
MMP-9, % detectable	17.4	17.4	17.4	0.98