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Fibrinogen and Left Ventricular Myocardial Systolic Function: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Increasing evidence suggests that elevated plasma fibrinogen is associated with incident heart failure. However, the underlying pathophysiological mechanisms have not been well elucidated.

Methods—We examined the relationship between plasma fibrinogen level and peak systolic mid-wall circumferential strain(Ecc) at the base, mid-cavity and apex of the left ventricle measured by magnetic resonance imaging myocardial tagging in 1,096 participants without clinical cardiovascular disease enrolled in the Multi-Ethnic Study of Atherosclerosis(MESA).

Results—After adjustment for demographics, established risk factors and body-mass-index, elevated fibrinogen was independently associated with reductions in absolute Ecc indicative of impaired systolic function in all regions(all P=0.015). The relationships were consistently significant upon further adjustment for measures of atherosclerosis(all P≤0.024), and were modestly attenuated with regional heterogeneity after additional adjustment for other inflammatory biomarker and N-terminal pro-brain-natriuretic peptide. In this fully-adjusted model, every one-standard deviation (74mg/dL) increment in plasma fibrinogen was independently associated with a reduction in left ventricular absolute Ecc of 0.29%(95%CI=0.03%–0.59%, P=0.048) at the base, 0.22%(95%

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CI=0.006%–0.43%, P=0.044) at mid-cavity, 0.20%(95%CI=−0.035%–0.43%, P=0.097) at the apex, and 0.24%(95%CI=0.05–0.43, P=0.015) overall.

Conclusions—Among asymptomatic individuals without clinical cardiovascular disease, elevated fibrinogen is independently associated with impaired myocardial systolic function. These findings support roles of inflammation, procoagulation and hyperviscosity underlying hyperfibrinogenemia in the pathogenesis of incipient myocardial dysfunction.

Keywords

epidemiology; heart failure; myocardial function; fibrinogen; hyperviscosity; hypercoagulability; magnetic resonance imaging

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Fibrinogen is the major circulating coagulation protein by mass and an important determinant of thrombogenicity and blood viscosity.[1,2] As a non-specific acute phase reactant, fibrinogen is also a downstream component of the inflammatory cascade increasingly implicated in the pathogenesis of atherosclerosis, myocardial injury and heart failure.[3,4] Many epidemiological studies and several meta-analyses have reported that elevated plasma fibrinogen level is associated with coronary artery disease, stroke and other adverse cardiovascular events.[5–10] More recently, elevated fibrinogen has also been demonstrated to be associated with incident heart failure.[11,12] However, the underlying pathophysiological mechanisms have not been well elucidated.

Cardiac magnetic resonance imaging(MRI) is considered the reference standard for assessment of left ventricular(LV) structure and function.[13] In particular, magnetic resonance myocardial tagging can accurately measure subtle alterations in regional myocardial function, which may afford unique pathophysiological insights.[13,14] Accordingly, this study tested the hypothesis that increased plasma fibrinogen, a multifunctional glycoprotein of intrinsic prothrombotic, inflammatory and rheological properties, is associated with subclinical impairment in regional systolic myocardial function as measured by MRI tagging, among a multi-ethnic asymptomatic population without known cardiovascular disease. Detailed characterization of such an association, in consideration with biomarkers related to different pathogenetic pathways, may provide novel insights into the complex mechanisms underlying incipient myocardial dysfunction and the increased risk of heart failure observed with hyperfibrinogenemia.

Methods

Study design and population

The Multi-Ethnic Study of Atherosclerosis(MESA) is a multicenter, prospective cohort study designed to examine the prevalence, correlates and progression of subclinical cardiovascular disease. Details of its rationale and methodology have been previously published.[15] Briefly, the MESA cohort comprised of 6814 men and women of four self-reported ethnicities(African-American, Caucasian, Chinese and Hispanic) between 45–85 years of age without known cardiovascular disease at study entry. The cohort represents a population-based sample recruited from six communities(Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota) between 2000–2002. At baseline, all participants underwent detailed evaluation consisting of clinical questionnaires, physical examination and laboratory tests, which included serum creatinine and lipoprotein profile. In addition, novel biomarkers of reported associations with cardiovascular diseases including homocysteine, C-reactive protein(CRP), N-terminal pro-brain-natriuretic peptide(NT-proBNP) and fibrinogen were collected and analyzed centrally at a core laboratory(University of Vermont, Burlington).

Baseline clinical parameters, biomarkers and subclinical atherosclerosis imaging

At the baseline MESA enrollment examination, designated research personnel collected pre-specified clinical information on risk factors including smoking status(never/former/current) and amount(pack-years), hypertension, diabetes and medication use. Hypertension was defined by the recommendations of the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. Diabetes was diagnosed as per the American Diabetes Association criteria or the use of anti-hyperglycemic therapy.[16] Physical examination, including measurements of blood pressure and anthropometric indices, was conducted in accordance with standardized protocol.

Baseline serum fibrinogen was quantitatively measured by immunoprecipitation of fibrinogen antigen using the BNII nephelometer(N-Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). Its intra- and inter-assay coefficients of variation were 2.7% and 2.6%, respectively. CRP was quantified by a high-sensitivity assay(N-High-Sensitivity CRP; Dade Behring, Deerfield, IL; inter-assay coefficient of variation:2.1–5.7%).

To evaluate the anatomic extent of subclinical atherosclerosis, the maximal intimal-medial thickness(IMT) of the common carotid arteries(mean of maximal IMT across the near and far walls of the left and right common carotid arteries 10mm proximal to the bulb) was measured by high-resolution B-mode ultrasonography.[17,18] Coronary artery calcification as defined by the Agatston score was also determined on computed tomography of the chest, obtained using either an electron-beam or multi-detector scanner with a prospective ECG-triggered acquisition protocol.[19] Details on methodology, standardization and reproducibility of baseline measurements of these validated biomarkers of subclinical atherosclerosis have been previously published.[17–19]

Magnetic resonance imaging of the left ventricle and myocardial tagging

In a MESA ancillary study, a subgroup of 1,178 participants from all six field centers additionally underwent myocardial tagging as part of their baseline(September/2001 to September/2002) MRI examination.[20] All studies were performed using commercially available 1.5T whole-body MR scanners: Signa-LX/CVi (GE Medical Systems, Waukesha, WI) or Symphony/Sonata(Siemens Medical Systems, Erlangen, Germany). After acquisition of standard scout, two- and four- chambers and short-axis untagged cine images, tagged images were acquired using segmented *k*-space, electrocardiogram-triggered fast spoiled gradient echo pulse sequence(SPGR/FLASH) with short echo time and without gradient motion refocusing during 12–18 seconds of breath-hold at resting lung volume. Three tagged short-axis slices between the mitral valve plane and the apex of the LV, namely, the basal, mid-ventricular and apical slices, were imaged with parallel striped tags prescribed separately in two orthogonal orientations (0° and 90°) using spatial modulation of magnetization. Parameters for tagged images: field-of-view:40cm; slice thickness:8–10mm; tag spacing:7mm; matrix size:256x(96–140) with 4–9 phase encoding views/segment; repetition-time:3.5–7.2ms; echo-time:2.0–4.2ms; flip-angle:12°; a resulting yield of 9–27 phases/cardiac cycle and temporal resolution of 36±12ms.[20]

Image analysis and myocardial strain determination by harmonic phase imaging (HARP)

LV structural parameters(end-diastolic and end-systolic volumes, end-diastolic mass) and ejection fraction(measure of global systolic function) were determined from the short-axis cine images using standard commercially available software(MASS 4.2, MEDIS, Leiden, The Netherlands). Details on image analysis, data quality control, calculations and reproducibility of these measurements have been detailed elsewhere.[20,21]

The three short-axis tagged images were analyzed by harmonic phase imaging (HARPv2.0, DiagnoSoft Inc, Palo Alto, CA) -- a validated technique for determination of regional myocardial strain.[22,23] To evaluate LV regional myocardial function, the mid-wall peak systolic circumferential strain(Ecc) at the base, mid-ventricle and apex(average of the septal, anterior, lateral and posterior segments within the respective tagged short-axis slice) of the LV were determined. Global-Ecc was computed as the average of basal, mid-ventricular and apical Ecc. All strain analyses were performed centrally at the MRI core laboratory(Johns Hopkins University). Intra-observer and inter-observer agreement for regional Ecc determined by this technique(intra-class correlation coefficients of 0.84 and 0.81, respectively) was previously reported.[24] By convention, Ecc is negative as it designates systolic circumferential shortening. As such, a more negative value denotes greater systolic function.

Statistical analysis

Continuous variables with normal distributions are presented as mean±standard deviation (SD) (or median and inter-quartile range if otherwise), and categorical variables as frequencies and percentages. Logarithmic transformation was applied to variables with skewed distributions before entry into multivariable regression models. The associations of fibrinogen with clinical and other laboratory parameters, measures of subclinical atherosclerosis as well as regional LV functional parameters were examined by Kendall tau-*b* or *chi*-square for trend tests as appropriate across the study cohort stratified by fibrinogen tertiles.

Multivariable linear regression models were constructed in a hierarchical manner to examine the independent association between fibrinogen and (a) LV structural parameters(volumes and mass), (b) global LV systolic function(ejection fraction), and (c) each of the regional functional parameters(basal, mid-ventricular and apical Ecc) and global-Ecc. In the basic model(models-I), adjustment was made for demographics including age, gender and ethnicity. Heterogeneity across gender, ethnicity and sites was tested by introducing corresponding interaction terms with fibrinogen into the basic models. As no significant interaction was observed for all LV parameters(all $P>0.15$), the entire study cohort was analyzed without stratification. In model-II, additional adjustment was made for established risk factors including hypertension, diabetes, cigarette smoking, systolic blood pressure, low-density lipoprotein, total cholesterol, body-mass-index, and treatment with lipid-modifying, anti-hypertensive and anti-hyperglycemic therapies. Selection of these covariates was guided by knowledge of their association with fibrinogen and myocardial function as observed in this and prior studies.[25] To further elucidate the pathogenetic link between fibrinogen and myocardial dysfunction, additional models were constructed with stepwise inclusion of plausible pathogenetic biomarkers. As atherosclerosis is implicated to mediate in part the effects of fibrinogen,[26,27] carotid IMT and coronary artery calcification(Agatston score) were further introduced as additional covariates in model-III. Finally, biomarkers of known association with myocardial dysfunction including serum creatinine, homocysteine and CRP, as well as NT-proBNP as a surrogate biomarker of ventricular wall stress, were added stepwise into a set of more fully adjusted models(model IV-a to IV-d).[21,28,29] To examine the extent of potential confounding or effect mediation by inflammation, the respective independent associations of myocardial function with fibrinogen and CRP, with and without reciprocal adjustment for each other, were determined.

Statistical analyses were performed using SPSS 15.0(SPSS Inc, Chicago, IL). Statistical significance was inferred at 2-sided p-value<0.05.

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Results

Among the 1,178 MESA tagging ancillary study cohort, 1096(93%) had analyzable tagging data with fibrinogen measurement and constituted the present study population.

The mean and standard deviation of plasma fibrinogen level in the study population was 346 ±74 mg/dL. Table-1 shows the baseline characteristics of this cohort stratified by fibrinogen tertiles. Participants with higher fibrinogen levels were older, more likely to be female and having hypertension(all P<0.001 for trend). In addition, they had higher body-mass-index and waist circumference, blood pressure, low-density lipoprotein and total cholesterol, greater anatomic extent of subclinical atherosclerosis with higher carotid IMT and Agatston score, as well as more elevated levels of homocysteine, CRP and NT-proBNP (all P<0.05 for trend).

The regional and global systolic circumferential strain measurements across fibrinogen tertiles are depicted in Table-2. Higher plasma fibrinogen level was associated with reduced regional myocardial systolic function(less negative Ecc) consistently at the base, mid-ventricle and apex of the LV. Fibrinogen was also correlated positively with global Ecc, representing an inverse relationship between fibrinogen and overall LV systolic circumferential strain.

The results of hierarchical multivariable linear regression analyses demonstrating independent associations between fibrinogen and regional myocardial function are summarized in Table-3. For all the LV parameters examined, their relationships with fibrinogen were not heterogeneous across gender, ethnicities or sites (p-value for interaction all >0.15). After adjustment for demographic characteristics (model-I), higher plasma fibrinogen was independently associated with reduced regional Ecc consistently at the base, mid-ventricle and apex of the LV, as well as an overall reduction in LV global-Ecc. Introducing traditional cardiovascular risk factors and use of risk-factor modifying medications into the models(models-II) did not alter the magnitude or significance of the association between fibrinogen and each of these measures of myocardial function. In addition, all these associations remained significant upon further adjustment for subclinical atherosclerosis(models-III). Uniformly across these hierarchical models(models I, II and III), the magnitude of reduction in regional myocardial function independently associated with any given increment in plasma fibrinogen was largest at the base and smallest in the mid-ventricle(Table-3).

In this study cohort, fibrinogen is positively correlated with CRP(Kendall τ-b correlation coefficient=0.34, p<0.001). The set of more fully adjusted models with additional stepwise inclusion of biomarkers are summarized in Table-3(models IV-a to IV-d). Of note, the independent association between each myocardial functional parameter and fibrinogen was not modified by renal function and additionally homocysteine(models IV-a and IV-b, respectively). Upon adjustment for these biomarkers and all previously included covariates, higher CRP was independently associated with reduced global-LV Ecc(regression coefficient=0.38 per 1-unit log[CRP],95%CI=0.04–0.72, p=0.028), but not after additional adjustment for fibrinogen (regression coefficient=0.16 per 1-unit log[CRP],95%CI=−0.22–0.55, p=0.40). In contrast, beyond the same covariates including CRP(models IV-c), elevated fibrinogen remained independently associated with reductions in global and all regional Ecc, although all the associations were attenuated and by the largest degree at the apex, after adjustment for the inflammatory marker CRP. The association was consistent and remained unchanged upon further adjustment for NT-proBNP in the fully-adjusted model (model-IVd, Table-3).

To confirm the robustness of our findings, similar results were obtained in a series of sensitivity analyses using alternative anthropometric indices, substitution of creatinine for estimated glomerular filtration rate, and additional adjustment for LV mass or LV mass index, albuminuria as a marker of subclinical vascular disease. Furthermore, alcohol consumption,

physical activity and educational status as known correlates of plasma fibrinogen level[25] were not found to affect our findings(data not shown).

In contradistinction to regional myocardial systolic function measured by MR tagging, fibrinogen was not significantly associated with regional diastolic function(early and late diastolic circumferential strain), as well as global LV structural(end-diastolic and end-systolic volumes, LV end-diastolic mass) and functional(ejection fraction) parameters in any of the hierarchical(Models I–IV) models(data not shown).

Discussion

In this study of a multi-ethnic asymptomatic population without clinical cardiovascular disease, our principal finding is that higher plasma fibrinogen level was associated with lower regional myocardial systolic circumferential strain, consistently in all anatomical regions of the left ventricle, and independent of demographic characteristics and established cardiovascular risk factors. Importantly, the associations remained significant upon controlling further for surrogates of subclinical atherosclerosis, and were only modestly attenuated after additional adjustment for other inflammatory biomarker and NT-proBNP. These observations suggest additional fibrinogen-related pathophysiological mechanisms, beyond atherosclerosis, inflammation and ventricular filling hemodynamics, may contribute to myocardial dysfunction.

Fibrinogen has been evaluated in epidemiological studies for its cross-sectional relationships with risk factors and prospective associations with cardiovascular outcomes, which appear consistent and generalizable.[5–7,9,10,25] In a meta-analysis of 18 prospective studies encompassing 4,018 cases of coronary heart disease, the relative risk for plasma fibrinogen level in the top versus lowest tertile was 1.8(95%CI=1.6–2.0).[10] A more recent meta-analysis by the Fibrinogen Studies Collaboration suggested that elevated fibrinogen was associated with significant age- and gender-adjusted increased risk for incident coronary artery disease and stroke, albeit the associations were attenuated on further adjustment for established cardiovascular risk factors and CRP.[9] Similar associations have also been extended to incident peripheral arterial diseases.[30] In accordance with these clinical observations, fibrinogen is significantly correlated with the anatomic extent of atherosclerotic diseases, suggesting that fibrinogen may in part mediate the downstream effects of risk factors on atherosclerosis and ultimately atherothrombotic events.[5,7,26,31]

While the association of fibrinogen with subclinical and overt atherosclerotic disease has been well described, very little is known specifically for heart failure until recently, and no information yet exists for its preclinical manifestation.[11,12] In the Swedish Malmő Preventive population-based study of 6071 middle-aged men without clinical cardiovascular disease, higher baseline fibrinogen was found independently predictive of heart failure without interim myocardial infarction.[11] In the larger and more diverse MESA cohort, increased baseline fibrinogen conferred an increased risk for incident heart failure(adjusted hazards ratio=1.25, 95%CI=1.02–1.53 per 1-SD[74mg/dL] increment in fibrinogen) over a median of 4.0-years.[12] Yet, elucidation of the pathophysiologic significance of fibrinogen in the development and progression of heart failure has not been undertaken in these seminal investigations. This present study corroborates these recent clinical observations by demonstrating significant continuous cross-sectional relationships between elevated fibrinogen and reduced regional myocardial systolic function, an increasingly recognized early subclinical manifestation of heart failure.[32]

Plausible pathophysiological mechanisms

Fibrinogen plays a vital role in various interrelated pathophysiological processes with inflammation and atherogenesis being most commonly invoked to explain its link with overt cardiovascular disease. Fibrinogen is a prominent acute-phase reactant, a ligand and up-regulator for intercellular adhesion molecules which enhance monocyte and leukocyte adhesions to endothelial cells.[33] On binding to leukocyte integrin receptor, fibrinogen facilitates chemotaxis vital to the inflammatory response.[34] Fibrinogen also stimulates mononuclear cells expression of proinflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α, which induce nitric oxide-mediated negative inotropic effects and cardiac myocyte apoptosis in experimental animal models.[4,35,36] Upon binding to endothelial cells, fibrinogen also causes release of vasoactive mediators and modulates endothelial cell permeability and migration, in addition to promoting smooth muscle cell proliferation, foam cell and atherosclerotic plaque formation.[37] The complex interplay of these and other processes by which fibrinogen can initiate and contribute to atherogenesis and inflammation as two intricately related pathogenetic mechanisms has been well described.[1,3,38]

Indeed, both subclinical atherosclerosis and inflammation have been shown to be related to incipient myocardial dysfunction and incident heart failure.[4,29,39–42] Nevertheless, the precise pathophysiologic mechanisms by which fibrinogen may affect cardiac function remain incompletely defined. Fibrinogen is known to augment platelet reactivity, aggregation and degranulation in response to adenosine diphosphate, thereby promoting platelet-rich microthrombi formation.[43] Furthermore, elevated plasma fibrinogen promotes the generation of more extensive and less deformable thrombi, while impairing fibrinolysis by interference with plasminogen-receptor binding.[44] The results of platelet hyper-reactivity, hypercoagulability from enhanced thrombogenicity and impaired fibrinolysis, alone and synergistically in combination, predispose to microvascular thrombosis.[38] As a high-molecular weight glycoprotein accounting for more than 50% of plasma and whole blood viscosity, increases in plasma and whole blood viscosity with elevated circulating fibrinogen may also lead to more endothelial shear-stress damage, impaired erythrocyte deformability and reduced microcirculatory blood flow, predisposing to microvascular hypoperfusion, myocardial stunning and recurrent occult ischemia-reperfusion injury.[45]

The persistent independent inverse relationship between fibrinogen and regional myocardial function beyond adjustment for biomarkers of subclinical atherosclerosis, inflammation and ventricular wall stress suggests that these postulated pathogenetic mechanisms, cross-talking at the level of fibrinogen and conceivably in part independent mechanistically of atherosclerosis and inflammation, may contribute to subclinical impairment of myocardial function independent of altered ventricular filling dynamics. The modest attenuation after adjustment for CRP underscores potential confounding, or possible mediation, of some effects of fibrinogen on myocardial function via inflammation.

Methodological considerations

To our best knowledge, the present study is the first to investigate the relationship between hemostatic biomarker and myocardial function in a large asymptomatic population. Although as previously described individuals with elevated fibrinogen levels had more adverse risk factor profile,[25] adjustments for these potential confounders had a negligible impact on the association, lending credence to the notion that fibrinogen may exert downstream detrimental effects on myocardial function. In addition to complementing existing evidence for the pathogenic link between inflammation and the heart failure syndrome continuum,[4,42] our results more importantly raise the novel hypothesis that other haemorrheological alterations related to fibrinogen, notably hypercoagulability and hyperviscosity, may play a role in the pathogenesis of subclinical myocardial systolic dysfunction.

Our finding that the association between fibrinogen and regional myocardial function was differentially weakened upon adjustment for the inflammatory marker CRP is noteworthy. While it was previously reported that the relationship between CRP and myocardial strain was weaker in the region of the left circumflex artery relative to that of the other coronary territories, this regional heterogeneity was unchanged after adjusting for coronary calcium score in the corresponding regions, suggesting that such regional differences is not attributable to underlying atherosclerotic burden.[29] A possible explanation is that the weaker and greater attenuation of fibrinogen-myocardial function association by CRP at the apex may represent regional differences in relative myocardial susceptibility to inflammatory injury, as compared to hypercoagulability or hyperviscosity-related hypoperfusion, and shear-stress insults. The precise pathophysiologic mechanisms for this regional heterogeneity should be explored in future studies. Finally, our study also underscores discrepancies between intrinsic myocardial function measured by MR tagging and conventional index of global LV function such as ejection fraction — the latter may be insensitive to the earliest deterioration in intrinsic myocardial function and thus inferior for the purpose of probing subclinical disease pathophysiology.

Several study limitations should be noted. Because of non-random and thus possible selective enrollment in this tagging ancillary study, our study cohort was not a true population-based sample. Our cross-sectional analyses precluded inferences on temporality and causality of our observations. Although MRI tagging has inferior temporal resolution compared to echocardiography and other technical limitations, it is widely accepted as a valid and useful tool to assess myocardial mechanical function.[22,24] Moreover, the natural history and long-term prognostic significance of regional LV systolic dysfunction associated with increased fibrinogen remain to be determined. In these regards, serial MRI and longitudinal clinical follow-up underway will shed light on these important issues. Nonetheless, the present study affords unique and novel pathophysiologic insights. The strengths of this study include the relatively large sample of diverse individuals from four ethnic groups, availability of comprehensive and standardized clinical data as well as biomarkers, use of reproducible and sensitive techniques for accurate measurements of plasma fibrinogen and myocardial function in blinded core laboratories with extensive experience.[22,24]

In conclusion, among a diverse asymptomatic population without clinical cardiovascular disease, there exists a significant independent inverse relationship between elevated plasma fibrinogen and impaired LV myocardial systolic function, which is only attenuated by further adjustment for other inflammatory biomarker. These findings underscore the notion of a complex interplay between inflammation, procoagulation and hyperviscosity underlying hyperfibrinogenemia in the pathogenesis of myocardial dysfunction. Future studies should examine causality which may have important implications on novel targets for early prevention of myocardial systolic dysfunction and heart failure.

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Table 1

Baseline characteristics of study population according to plasma fibrinogen tertiles

	Plasma fibrinogen levels			P for trend
	First Tertile	Second Tertile	Third Tertile	
Age, years	64±10	66±10	67±9	<0.001
Male,%	67.3	53.6	40.9	<0.001
Ethnicity,%				<0.001
African American	25.7	25.8	32.3	
Asian	11.1	8.2	8.3	
Caucasian	38.1	33.5	27.1	
Hispanic	25.1	32.5	32.3	
Smoking status,%				0.62
Never	50.8	50.7	49.9	
Former	39.4	35.2	38.2	
Current	9.8	14.1	11.9	
Smoking, pack-year	10±21	10±18	13±22	0.46
Diabetes mellitus,%	12.7	15.7	14.9	0.18
Hypertension,%	41.9	45.1	58.6	<0.001
Anti-hypertensive medication, %	38.4	36.0	48.9	0.004
Lipid-modifying medication, %	15.1	19.0	25.1	<0.001
Body mass index, kg/m^2	26.7±4.4	27.9±4.4	28.8±4.9	<0.001
Waist circumference, cm	94±13	98±14	103±15	<0.001
Systolic blood pressure, mmHg	126±20	128±21	131±21	0.001
Diastolic blood pressure, mmHg	73±10	71±10	72±11	0.034
Fasting glucose, mg/dL	98±27	101±26	100±27	0.10
Total cholesterol, mg/dL	189±33	196±34	197±37	0.008
LDL-cholesterol, mg/dL	113±29	119±30	121±31	0.003
HDL-cholesterol, mg/dL	51±15	51±16	51±13	0.67
Triglycerides, mg/dL	128±70	133±76	128±70	0.72
Total cholesterol: HDL ratio	3.97±1.15	4.15±1.29	4.11±1.21	0.29
Serum creatinine, mg/dL	1.0±02	1.0±0.2	1.0±0.5	0.50
C-reactive protein (CRP), mg/ L*	0.90(0.50,1.90)	1.86(0.93,3.56)	3.44(1.81,6.65)	<0.001
Homocysteine(umol/L)*	9.0(7.7,10.6)	9.1(7.6,11.0)	10.3(7.8,11.6)	0.030
N-terminal pro-brain-natriuretic-peptide(ρg/ml)*	54(21,108)	68(28,139)	70(34,142)	0.001
Carotid intimal-medial thickness, mm*	0.82(0.71,0.93)	0.85(0.75,0.98)	0.87(0.77,1.01)	<0.001
Agatston coronary artery calcium score*	4(0,125)	11(0,154)	21(0,197)	0.007

Fibrinogen(mg/dL) tertiles: first, 155–312; second, 313–370; third, 371–945.

Continuous variables are presented as mean ± standard deviation unless otherwise stated.

*Variables with skewed distributions and presented as median(inter-quartile range).

Table 2

Regional and global peak systolic circumferential strain by plasma fibrinogen tertiles

	Plasma fibrinogen			
	First Tertile	Second Tertile	Third Tertile	P-value for trend
Basal Ecc	−15.37±0.18	−14.99±0.18	−14.48±0.19	0.001
Mid-ventricular Ecc	−17.40±0.14	−17.11±0.14	−16.90±0.15	0.011
Apical Ecc	−18.02±0.15	−17.68±0.16	−17.54±0.15	0.037
Global Ecc	−16.97±0.12	−16.58±0.13	−16.33±0.13	0.001

Fibrinogen(mg/dL) tertiles: first, 155–312; second, 313–370; third, 371–945.

Ecc=peak systolic circumferential strain. As Ecc designates systolic circumferential shortening and is negative by convention, less negative values indicate worse systolic function.

Data presented as mean±standard error of mean.

Table 3

Independent association between plasma fibrinogen level and regional and global left ventricular systolic circumferential strain

	Basal-Ecc		Mid-ventricular-Ecc		Apical-Ecc		Global-Ecc	
	Regression coefficient for fibrinogen (95%CI)*	P-value	Regression coefficient for fibrinogen (95%CI)*	P-value	Regression coefficient for fibrinogen (95%CI)*	P-value	Regression coefficient for fibrinogen (95%CI)*	P-value
Model I	0.33(0.11–0.55)	0.003	0.25(0.09–0.42)	0.002	0.26(0.08–0.44)	0.004	0.29(0.14–0.44)	<0.001
Model II	0.33(0.10–0.56)	0.005	0.21(0.04–0.38)	0.015	0.26(0.08–0.45)	0.005	0.27(0.11–0.42)	0.001
Model III	0.33(0.10–0.56)	0.005	0.20(0.03–0.37)	0.022	0.27(0.08–0.45)	0.005	0.26(0.11–0.42)	0.001
Model IV-a	0.34(0.11–0.57)	0.004	0.20(0.03–0.38)	0.020	0.27(0.08–0.46)	0.005	0.27(0.11–0.43)	0.001
Model IV-b	0.33(0.10–0.56)	0.005	0.20(0.03–0.37)	0.024	0.25(0.06–0.44)	0.009	0.26(0.10–0.42)	0.001
Model IV-c	0.31(0.04–0.57)	0.022	0.21(0.01–0.40)	0.038	0.18(−0.030−0.40)	0.092	0.22(0.05–0.40)	0.014
Model IV-d	0.29(0.03–0.59)	0.048	0.22(0.006–0.43)	0.044	0.20(−0.035–0.43)	0.097	0.24(0.05–0.43)	0.015

Ecc=peak systolic circumferential strain; 95%CI=95% confidence interval.

Models-I: adjustment for demographics -- age, gender, ethnicity.

Models-II: adjustment for demographics plus cardiovascular risk factors–hypertension, systolic blood pressure, anti-hypertensive medications, diabetes and use of anti-hyperglycemic therapy, smoking(pack-year), levels of low-density lipoprotein and total cholesterol, use of lipid-modifying medications, and body-mass-index(weight in kilogram divided by the square of height in meter).

Models-III: adjustment for demographics, cardiovascular risk factors plus measures of subclinical atherosclerosis–carotid intimal-medial thickness(IMT) and coronary artery calcification(Agatston score).

Models-IV a-d: adjustment for demographics, cardiovascular risk factors, measures of subclinical atherosclerosis plus biomarkers of reported association with myocardial dysfunction and/or incident cardiovascular events among asymptomatic populations – (a) serum creatinine, (b) serum creatinine and homocysteine, (c) serum creatinine, homocysteine and C-reactive protein, (d) serum creatinine, homocysteine, C-reactive protein and N-terminal-pro-brain-natriuretic peptide.

* Regression coefficients represent the absolute change in Ecc (positive values denote reduction in systolic function) per one-standard deviation increment in plasma fibrinogen level(74mg/dL). As Ecc designates systolic circumferential shortening and is negative by convention, positive regression coefficients indicate worse systolic function with higher fibrinogen.