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Matrix Metalloproteinase-2 Associates with Incident Heart Failure and Atrial Fibrillation: the Atherosclerosis Risk in Communities study

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Abstract

Background—Matrix metalloproteinase-2 (MMP-2) participates in extracellular matrix regulation and may be involved in heart failure (HF), atrial fibrillation (AF) and coronary heart disease (CHD).

Methods—Among 4,693 ARIC study participants (mean age 75±5 years; 42% women) without prevalent HF, multivariable Cox proportional hazard models were used to estimate associations of plasma MMP-2 levels with incident HF, HF with preserved ejection fraction (HFpEF, EF ≥50%), HF with reduced ejection fraction (HFrEF, EF<50%), AF, and CHD. Mediation of the association between MMP-2 and HF was assessed by censoring participants who developed AF or CHD before HF. Multivariable linear regression models were used to assess associations of MMP-2 with measures of left ventricular (LV) and left atrial (LA) structure and function.

Results—Compared to the lower three quartiles, the highest MMP-2 quartile associated with greater risk of incident HF overall (adjusted HR [95% CI]: 1.48 [1.21-1.81]), incident HFpEF (1.44 [1.07-1.94]), incident HFrEF (1.48 [1.08-2.02]), and incident AF (1.44 [1.18-1.77]) but not incident CHD (0.97 [0.71-1.34]). Censoring AF attenuated the MMP-2 association with HFpEF. Higher plasma MMP-2 levels were associated with larger LV end-diastolic volume index, greater

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LV mass index, higher E/e' ratio, larger LA volume index and worse LA reservoir and contractile strains (all P<.001).

Conclusions—Higher plasma MMP-2 levels associate with diastolic dysfunction, LA dysfunction and a higher risk of incident HF and AF. AF is a mediator of MMP-2-associated HFpEF risk.

Keywords

matrix metalloproteinases; heart failure; echocardiography; epidemiology; atrial fibrillation

Introduction

The risk of cardiovascular disease increases with age.[1] Although chronic inflammation due to cardiometabolic comorbidities may underlie the pathophysiology of the most common cardiovascular diseases among older adults, namely heart failure with preserved ejection fraction (HFpEF), atrial fibrillation (AF) and coronary heart disease (CHD),[2] the specific inflammatory pathways responsible are not fully defined. Inflammation promotes activity of the matrix metalloproteinase (MMP) family of zinc-dependent enzymes.[3]

One particular member of the MMP family, MMP-2, exerts pleiotropic effects with potential relevance to HFpEF, AF and CHD. MMP-2 not only targets extracellular matrix proteins involved in left ventricular (LV) and left atrial (LA) fibrosis but also intracellular proteins essential for cardiomyocyte contractility and relaxation, such as troponin and titin, which together may predispose to HF, and in particular HFpEF, by increasing LV stiffness and impairing LV and LA function.[4] MMP-2 may also promote AF generation through connexin-43 and increased LA fibrosis,[5] and CHD through MMP-2-dependent adhesion molecule expression on endothelial cells.[6] Other members of the MMP family have been linked to atherosclerotic plaque vulnerability.[7] AF and CHD are risk factors for HF, which itself is associated with a higher risk of AF.[8] Thus, MMP-2 may represent a shared pathway common to these conditions, but the associations of MMP-2 with HF, AF and CHD are incompletely understood. This study sought to determine the associations of plasma MMP-2 levels with incident HF, AF and CHD in late-life, and with subclinical alterations in cardiac structure and function.

Methods

Data access can be requested at https://aric.cscc.unc.edu/aric9/ through submission of a manuscript proposal to the ARIC Publications Committee.

Study Sample

The Atherosclerosis Risk in Communities (ARIC) study is an ongoing, prospective, longitudinal cohort study that enrolled 15,792 community-dwelling adults between the ages of 45 and 64 years from Forsyth County, North Carolina, Washington County, Maryland, suburban Minneapolis, Minnesota and Jackson, Mississippi between 1987 and 1989.[9] The ARIC study protocol was approved by the institutional review boards at all participating institutions. All participants provided written informed consent. Our study sample included

participants who attended the fifth study visit (2011-2013), had no history of HF and had available MMP-2 and covariate measurements. Analyses of incident AF and incident CHD further excluded participants with a history of AF or CHD at baseline. Participants who reported race other than White or Black (n=18) or those from the Minneapolis and Washington field centers who reported Black race (n=25) were excluded due to small numbers of these individuals.

Matrix Metalloproteinase-2 Measurement

Plasma MMP-2 concentrations were measured on a relative scale using a modified aptamer assay (Somalogic, Boulder, CO) in all Visit 5 participants who consented to such use of their research samples.[10,11] Aptamer-based assay data processing and quality control have been reported previously.[12] MMP-2 levels also were measured using a dual antibody-based proximity extension assay in a substudy of 250 participants with incident HF after Visit 5 and 250 participants who remained free from incident HF after Visit 5.[13] MMP-2 levels measured by the aptamer assay correlated positively with MMP-2 levels measured by the proximity extension assay (N=500; Pearson correlation coefficient [95% CI]: 0.68 [0.62-0.73]; P<.001; Figure S1). The specificity of the MMP-2 aptamer is further supported by the identification of *cis*-protein quantitative trait loci, which suggest that levels of the compound targeted by the MMP-2 aptamer are associated with variants in the MMP-2 gene.[14]

Echocardiography

ARIC Visit 5 echocardiographic measurement procedures have been reported previously.[15,16] Echocardiography was performed at all 4 study field centers by sonographers who received training and certification in the ARIC imaging protocol. The same echocardiographic machines (Philips iE33, Koninklijke Philips, The Netherlands) and probes (Philips XMatrix) were used at all field centers. The echocardiography core laboratory at Brigham and Women's Hospital (Boston, MA) performed all the quantitative measures in a blinded fashion according to American Society of Echocardiography recommendations.[15,16]

HF, AF and CHD Outcomes

Ascertainment of HF events in ARIC has been described previously.[17] The occurrence of a potential HF event was assessed through annual telephone contact through 2012, biennial telephone contact beginning in 2012, and through ongoing manual review of local hospital discharges and health department death certificates. Medical records for hospitalizations with a HF-related International Classification of Diseases (ICD)-9 or ICD-10 codes were abstracted systematically and underwent physician adjudication according to standardized definitions. HFrEF was defined as an adjudicated HF hospitalization with LVEF <50% at the time of hospitalization, while HFpEF was defined when the LVEF at the time of hospitalization was ≥50%. AF cases were identified through review of discharge summary ICD-9 and ICD-10 codes. Incident AF was defined as hospitalization with a discharge diagnosis of AF in the absence of concurrent cardiac surgery.[18] Follow-up for AF continued from Visit 5 through December 31, 2017. Incident CHD included myocardial infarction cases adjudicated by a physician reviewer as definite or probable based upon review

of cardiac pain, electrocardiogram findings and cardiac biomarker levels.[19] Deaths were identified through ARIC surveillance, the National Death Index and hospital discharge lists for in-hospital deaths. Follow-up began on the date of Visit 5 and ended on the occurrence of a HF, AF or CHD event, death, loss to follow-up, or else December 31, 2019 at the Forsyth County, Washington County and suburban Minneapolis Field Centers or December 31, 2017 at the Jackson Field Center (where there have been delays in obtaining more recent information on hospitalizations).

Covariates

Participants self-reported their date of birth, sex and race. Hypertension was defined as anti-hypertensive medication use or study blood pressure measurements indicative of hypertension (≥140/90 mmHg). Diabetes mellitus was defined as self-report of a physician diagnosis of diabetes mellitus, glucose-lowering medication use, fasting glucose level of at least 126 mg/dL or non-fasting glucose level of at least 200 mg/dL. Body mass index (BMI) was calculated as measured body weight in kilograms divided by measured height in meters squared. Estimated glomerular filtration rate (eGFR) was calculated using the 2012 creatinine-cystatin C CKD-EPI equation. Prevalent HF at Visit 5 was identified (for exclusion) by reviewing hospitalization surveillance data (described above). Prevalent CHD and AF at Visit 5 were defined as CHD or AF that occurred before Visit 5 using the same definitions as incident CHD and AF.

Statistical Analysis

Continuous data were summarizing using means and standard deviations if approximately normally distributed or medians and [25^{th}, 75^{th}] percentiles if non-normally distributed. Categorical data were presented as number and percentage. Participant characteristics were compared across quartiles of MMP-2 level using a one-way analysis of variance for normal continuous data, a Kruskal-Wallis test for non-normal data and a chi-squared test for categorical data. MMP-2 relative concentrations were standardized to a mean of 0 and standard deviation of 1 after visual inspection indicated a symmetric distribution. Correlation between the aptamer and proximity extension assays was assessed using Pearson's correlation coefficient.

Based upon a non-linear relationship between the crude incidence rate of HF overall, HFpEF and HFrEF across quartiles of MMP-2 level (similar incidence rate across quartiles 1-3 and a higher incidence in quartile 4), we dichotomized MMP-2 levels into quartiles 1-3 versus quartile 4. Cox proportional hazards regression models were used to estimate the associations between MMP-2 category (quartile 4 vs. quartiles 1-3) and time to incident HF, HFpEF, HFrEF, the composite of HF or death, incident CHD and incident AF. Model 1 included demographic covariates (age, sex, and the combination of race and field center). Model 2 additionally included potentially confounding clinical risk factors (body mass index, diabetes mellitus, CHD [except for models of incident CHD], hypertension, AF [except for models of incident AF], pulse pressure and eGFR). Sensitivity analysis for the incident HF outcomes was performed assuming HF events with LVEF unknown at the time of hospitalization were either HFrEF or HFpEF and by truncating follow-up on December 31, 2017 across all field centers. Continuous, non-linear associations between MMP-2 and

HF outcomes were visualized by modeling MMP-2 relative concentrations with restricted cubic splines. The number of knots for the restricted cubic splines was chosen based upon minimization of the Bayesian information criterion (3 and 4 knots tested). A likelihood ratio test compared the fit of the model with the selected number of knots and the linear model. We then estimated the effect of incident CHD and incident AF on the association between MMP-2 category and incident HF overall, HFpEF and HFrEF by censoring follow-up for incident HF at the time of incident CHD or AF. We also estimated the effect of censoring incident HF on the association between MMP-2 category and incident CHD and incident HF. Visual inspection of scaled Schoenfeld residuals did not suggest deviations from proportionality.

Linear regression models were used to estimate the associations of MMP-2 category (quartile 4 vs. quartiles 1-3) with cardiac structure and function at Visit 5. All linear regression models were adjusted for Visit 5 systolic blood pressure and heart rate, in addition to covariates for Models 1 and 2 above. Continuous, non-linear associations were considered by modeling MMP-2 with restricted cubic splines as described above. All analyses were performed with Stata 17.0 (College Station, TX).

Results

Participant Characteristics

The overall cohort included 4,693 participants (Figure S2). The mean age was 75±5 years and 42% were women (Table 1). Cardiovascular co-morbidities were common, and CHD was prevalent in 13% and AF in 5%. Participants with the highest quartiles of MMP-2 values were older and more likely to be women. The prevalence of CHD and AF increased across quartile of MMP-2.

Associations of MMP-2 with Incident Heart Failure, Coronary Heart Disease and Atrial Fibrillation

Over a mean follow-up of 6.4 years, 459 incident HF events occurred (IR [95% confidence interval] per 1,000 person-years, 15.2 [13.9-16.7]), including 186 incident HFrEF events and 214 incident HFpEF events. Modeling the continuous association of MMP-2 with incident HF using restricted cubic splines demonstrated a non-linear association with greater magnitude of association with incident HF at higher MMP-2 levels (p for non-linearity = .002; Figure S3). Similar associations were observed for incident HFpEF and HFrEF (Figure S3). Concordant with these findings of non-linearity, the highest quartile of MMP-2 was associated with a higher crude incidence rate of incident HF overall (Figure 1A), HFrEF (Figure 1B), and HFpEF (Figure 1C) compared to the lower three quartiles. In fully adjusted models, the fourth MMP-2 quartile associated with a 48% higher risk of HF overall, 48% higher risk of HFrEF, and 44% higher risk of HFpEF compared to the lowest 3 quartiles (Table 2). Results were similar for the association of MMP-2 with the composite of all-cause death or HF (Table 2). Assuming incident HF cases with unknown left ventricular ejection fraction were either all HFrEF or all HFpEF (Table S1) and truncating follow-up on December 31, 2017 for all Field Centers did not alter the results (Table S2).

Using restricted cubic splines to model MMP-2 levels similarly suggested a non-linear association between higher MMP-2 levels and higher incident AF risk (P-nonlinear = 0.052) (Figure S4). The incidence of atrial fibrillation in the fourth MMP-2 quartile (n events=145; IR [95% CI] per 1,000 person-years: 27.5 [23.3-32.3]) was higher than in the lower three quartiles (n=315; IR [95% CI] per 1,000 person-years: 17.9 [16.0-20.0]), and was associated with higher risk of incident atrial fibrillation in the fully adjusted model (HR [95% CI]: 1.44 [1.18-1.77]) (Table 2). In contrast, MMP-2 level did not associate with the incidence of CHD when modeled by quartile (Table 2) or continuously using restricted cubic splines (Figure S4).

Inter-Relationships of MMP-2 and Incident Heart Failure, Incident Atrial Fibrillation and Incident Coronary Heart Disease

Among the 459 participants at Visit 5 who experienced an incident HF event before the end of AF follow-up (December 31, 2017), 75 had an antecedent incident AF event (45 of 144 HFpEF events; 22 of 129 HFrEF events; 8 unknown LVEF) and 49 had an antecedent post-Visit 5 incident CHD event. In models that censored follow-up at the time of incident AF, the highest MMP-2 quartile remained associated with risks of incident HF overall and incident HFrEF, but associations with incident HFpEF were appreciably attenuated and no longer significant (HR [95% CI]: 1.02 [0.63-1.66]; P=.92) (Figure 2). Censoring follow-up at the time of incident CHD did not alter the associations of MMP-2 with incident HF overall, HFrEF and HFpEF (Figure 2). Among the 460 participants at Visit 5 who experienced an incident AF event, 96 had an antecedent incident HF event (35 HFpEF; 49 HFrEF; 12 unknown LVEF). Censoring follow-up at the time of incident HF did not appreciably alter the associations of MMP-2 with incident AF (Table S3). Similarly, of the 216 participants with an incident CHD event, 15 experienced an intercurrent HF event. Censoring follow-up at the time of the incident HF event did not impact the null MMP-2 association with CHD (Table S3).

Association of MMP-2 with Cardiac Structure and Function

Modeling MMP-2 level with restricted cubic splines demonstrated non-linear associations whereby LV mass index, E/e' ratio, pulmonary artery systolic pressure, LA volume index, LA reservoir strain and LA contractile strain worsened at higher MMP-2 levels (Figure 3). Compared to the lower three quartiles, the highest MMP-2 quartile was associated with greater LV end-diastolic volume index, smaller mean wall thickness and greater LV mass index (Table 3). MMP-2 category did not associate with measures of LV systolic function (Table 3). The E/e' ratio and pulmonary artery systolic pressure were significantly higher in the highest MMP-2 quartile compared to the lower three (Table 3). The highest quartile of MMP-2 level was also associated with greater LA volume index and worse LA reservoir and LA contractile strains (Table 3).

Discussion

In this cohort study of older adults (mean age of 75 years) living in four geographically distinct communities across the United States, higher plasma MMP-2 levels associated with a higher risk of incident HFrEF, HFpEF and AF, but not CHD, after adjustment for

demographics and clinical risk factors. The association of MMP-2 with incident HFpEF was attenuated by censoring incident AF events that preceded the incident HFpEF event, but the same was not true for incident HFrEF events. Associations of higher MMP-2 levels with incident AF were unchanged after accounting for intercurrent HF events, which suggests that AF mediates the association of circulating MMP with incident HFpEF, but not HFrEF. Consistent with its observed associations with HFpEF and AF, higher MMP-2 levels also associated with subclinical LV diastolic dysfunction, LA remodeling, and LA dysfunction. MMP-2 levels were not associated with the risk of incident CHD and censoring CHD events did not alter the association between MMP-2 and incident HF events. Together, these findings identify MMP-2 as a biomarker of AF, AF-related HFpEF, and HFrEF and provide insight into the shared pathophysiology linking HF and AF.

MMP-2 is one of 25 enzymes within the MMP family. MMP-2's particular functions may have relevance to the shared mechanisms between HF (especially HFpEF) and AF, which are among the most common cardiovascular diseases in older adults. In addition to extracellular matrix proteins, MMP-2 is believed to target several cardiomyocyte sarcomeric proteins like troponin, titin and myosin light chain..[3] MMP-2's potential effects on connexin-43 and LA fibrosis may contribute to AF pathogenesis.[5] Thus, our study proposes MMP-2 as a potential common contributor to shared pathways among HFpEF and AF. Participants in the highest quartiles of MMP-2 were more likely to be older women with atrial fibrillation and less likely to have coronary heart disease or diabetes. These associations are consistent with prior literature on HF epidemiology in older adults.[1]

Pre-clinical research suggests a role for the MMP family in LA fibrosis and remodeling, although studies on the role of MMP-2 specifically provide inconsistent results.[5,20–22] Nevertheless, the known overlap between aging, fibrosis, AF and HFpEF supports the plausibility of the observed relationships between MMP-2, HF, LA remodeling and AF.[4] Although MMP-2 contributes to atherosclerosis in pre-clinical models[6], we did not find an association of MMP-2 with incident CHD and incident CHD did not appear to mediate the MMP-2 associations with HFrEF or HFpEF.

Previous research has shown that increased MMP-2 can be detected in the hearts of individuals with Stage D, non-ischemic HF[23], while serum pro-MMP-2 levels correlate with severity of diastolic dysfunction in HFpEF[24]. We extend prior work by showing associations between MMP-2 and incident HFrEF and HFpEF as well as cardiac structure and function in people without prevalent HF. The association of MMP-2 with incident HFpEF is supported by the associations of MMP-2 with greater LV mass, greater LV volume, diastolic dysfunction and LA remodeling. MMP-2 plays a role in myocardial fibrosis and inflammation, which may be potential mechanisms through which MMP-2 contributes to the observed LV remodeling.[4] Higher circulating MMP-2 levels were also associated with higher LV filling pressure in our study, consistent with the observed associations with incident HFpEF. Higher MMP-2 levels also associated with higher, rather than lower, e' velocity, which suggests that higher preload, as opposed to impaired active relaxation, was an important factor in higher filling pressures. The association of MMP-2 with greater LV mass related primarily to larger LV volume and an eccentric pattern of LV

remodeling is consistent with observed association with risk of incident HFrEF, and may be related to the degradation of sarcomeric proteins by MMP-2.[3]

Our analyses suggest a non-linear association between circulating MMP-2 levels and incident HF, whereby HF risk increases in the fourth quartile of MMP-2 levels observed in this late-life community-based cohort. These non-linear associations have mechanistic plausibility.[25] Lower MMP-2 levels have been proposed to increase systemic inflammation through decreased inactivation of inflammatory proteins, which in turn initiates organ dysfunction, while higher levels are involved in fibrosis.[25]

There are certain limitations of this study, including its observational design and potential for residual confounding. Plasma MMP-2 levels were measured at a single timepoint on a relative, but not absolute, concentration scale. Correlation between two unique MMP-2 assays and the identification of cis-protein quantitative trait loci for MMP-2 support the specificity of the aptamer-based assay. Factors that may have contributed to the HF hospitalization were not recorded. The ARIC LVEF cutoff to define HFrEF of <50% is higher than the most recently recommended cutoff of <40%. LVEF was unknown at the time of hospitalization in a subset of adjudicated HF events. Overall results were similar in sensitivity analyses that assigned HF events with unknown LVEF to the HFrEF or HFpEF category. LV systolic function was robust overall, which may have limited the power to detect abnormalities in ejection fraction and strain. Incident AF cases did not undergo blinded physician adjudication like incident HF or CHD cases. Plasma MMP-2 levels do not provide insight into specific tissue-level MMP-2 activity. Overlapping actions of other MMP family members cannot be excluded. Assessment of the MMP-tissue inhibitor of metalloproteinase (TIMP) ratio would provide further insight into the MMP-HF relationship beyond assessment of MMPs alone. Although the proteomic assay used in this analysis measures circulating TIMP levels, we did not assess the ratio of MMP-2 to any TIMPs because all concentrations were measured on a relative scale. Whether plasma measurements of MMP-2 can be used as a surrogate of myocardial fibrosis specifically requires correlation between plasma and tissue measurements.[26] The possibility of a causal explanation for the observed MMP-2, HF and adverse cardiac remodeling associations requires further investigation. Nevertheless, our findings provide rationale for further studies investigating the potential for MMP-2 as a therapeutic target, and the extent to which plasma MMP-2 may be used to identify candidates for anti-fibrotic therapies or to monitor responses to anti-fibrotic therapies over time.

Conclusions

Higher plasma MMP-2 levels associate with subclinical diastolic dysfunction and LA remodeling and portend a higher risk of incident HFrEF and HFpEF. Atrial fibrillation is an important mediator of MMP-2-associated HFpEF risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures:

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Non-standard Abbreviations and Acronyms

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
CHD	coronary heart disease
ICD	International Classification of Diseases
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LA	left atrial
LV	left ventricular
LVEF	left ventricular ejection fraction
MMP	matrix metalloproteinase
TIMP	Tissue inhibitor of metalloproteinase

References

1. Roger Veronique L. Epidemiology of Heart Failure: A Contemporary Perspective. Circ Res. 2021;128:1421–1434. [PubMed: 33983838]
2. Triposkiadis F, Xanthopoulos A, Butler J. Cardiovascular Aging and Heart Failure: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;74:804–813. [PubMed: 31395131]
3. DeCoux A, Lindsey ML, Villarreal F, Garcia RA, Schulz R. Myocardial matrix metalloproteinase-2: inside out and upside down. J Mol Cell Cardiol. 2014;77:64–72. [PubMed: 25261607]
4. López B, Ravassa S, Moreno MU, José GS, Beaumont J, González A, Díez J. Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches. Nat Rev Cardiol. 2021;18:479–498. [PubMed: 33568808]
5. Nagibin V, Egan Benova T, Viczenczova C, Szeiffova Bacova B, Dovinova I, Barancik M, Tribulova N. Ageing related down-regulation of myocardial connexin-43 and up-regulation of MMP-2 may

predict propensity to atrial fibrillation in experimental animals. Physiol Res. 2016;65 Suppl 1:S91–s100. [PubMed: 27643943]

6. Momi S, Falcinelli E, Petito E, Ciarrocca Taranta G, Ossoli A, Gresele P. Matrix metalloproteinase-2 on activated platelets triggers endothelial PAR-1 initiating atherosclerosis. Eur Heart J. 2022;43:504–514. [PubMed: 34529782]
7. Johnson JL. Matrix metalloproteinases: influence on smooth muscle cells and atherosclerotic plaque stability. Expert Rev Cardiovasc Ther. 2007;5:265–282. [PubMed: 17338671]
8. Chamberlain AM, Boyd CM, Manemann SM, Dunlay SM, Gerber Y, Killian JM, Weston SA, Roger VL. Risk factors for heart failure in the community: differences by age and ejection fraction. The American Journal of Medicine. 2020;133:e237–e248. [PubMed: 31747542]
9. Wright JD, Folsom AR, Coresh J, Sharrett AR, Couper D, Wagenknecht LE, Mosley TH, Ballantyne CM, Boerwinkle EA, Rosamond WD, Heiss G. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. J Am Coll Cardiol. 2021;77:2939–2959. [PubMed: 34112321]
10. Gold L, Ayers D, Bertino J, Bock C, Bock A, Brody EN, Carter J, Dalby AB, Eaton BE, Fitzwater T, Flather D, Forbes A, Foreman T, Fowler C, Gawande B, Goss M, Gunn M, Gupta S, Halladay D, Heil J, Heilig J, Hicke B, Husar G, Janjic N, Jarvis T, Jennings S, Katilius E, Keeney TR, Kim N, Koch TH, Kraemer S, Kroiss L, Le N, Levine D, Lindsey W, Lollo B, Mayfield W, Mehan M, Mehler R, Nelson SK, Nelson M, Nieuwlandt D, Nikrad M, Ochsner U, Ostroff RM, Otis M, Parker T, Pietrasiewicz S, Resnicow DI, Rohloff J, Sanders G, Sattin S, Schneider D, Singer B, Stanton M, Sterkel A, Stewart A, Stratford S, Vaught JD, Vrkljan M, Walker JJ, Watrobka M, Waugh S, Weiss A, Wilcox SK, Wolfson A, Wolk SK, Zhang C, Zichi D. Aptamer-Based Multiplexed Proteomic Technology for Biomarker Discovery. PLoS One. 2010;5:e15004–e15004. [PubMed: 21165148]
11. Tin A, Yu B, Ma J, Masushita K, Daya N, Hoogeveen RC, Ballantyne CM, Couper D, Rebholz CM, Grams ME, Alonso A, Mosley T, Heiss G, Ganz P, Selvin E, Boerwinkle E, Coresh J. Reproducibility and Variability of Protein Analytes Measured Using a Multiplexed Modified Aptamer Assay. The Journal of Applied Laboratory Medicine. 2019;4:30–39. [PubMed: 31639705]
12. Walker KA, Chen J, Zhang J, Fornage M, Yang Y, Zhou L, Grams ME, Tin A, Daya N, Hoogeveen RC, Wu A, Sullivan KJ, Ganz P, Zeger SL, Gudmundsson EF, Emilsson V, Launer LJ, Jennings LL, Gudnason V, Chatterjee N, Gottesman RF, Mosley TH, Boerwinkle E, Ballantyne CM, Coresh J. Large-scale plasma proteomic analysis identifies proteins and pathways associated with dementia risk. Nature Aging. 2021;1:473–489. [PubMed: 37118015]
13. Assarsson E, Lundberg M, Holmquist G, Björkesten J, Bucht Thorsen S, Ekman D, Eriksson A, Rennel Dickens E, Ohlsson S, Edfeldt G, Andersson A-C, Lindstedt P, Stenvang J, Gullberg M, Fredriksson S. Homogenous 96-Plex PEA Immunoassay Exhibiting High Sensitivity, Specificity, and Excellent Scalability. PLoS One. 2014;9:e95192–e95192. [PubMed: 24755770]
14. Ferkingstad E, Sulem P, Atlason BA, Sveinbjornsson G, Magnusson MI, Styrmisdottir EL, Gunnarsdottir K, Helgason A, Oddsson A, Halldorsson BV, Jensson BO, Zink F, Halldorsson GH, Masson G, Arnadottir GA, Katrinardottir H, Juliusson K, Magnusson MK, Magnusson OT, Fridriksdottir R, Saevarsdottir S, Gudjonsson SA, Stacey SN, Rognvaldsson S, Eiriksdottir T, Olafsdottir TA, Steinthorsdottir V, Tragante V, Ulfarsson MO, Stefansson H, Jonsdottir I, Holm H, Rafnar T, Melsted P, Saemundsdottir J, Norddahl GL, Lund SH, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet. 2021;53:1712–1721. [PubMed: 34857953]
15. Shah AM, Cheng S, Skali H, Wu J, Mangion JR, Kitzman D, Matsushita K, Konety S, Butler KR, Fox ER, Cook N, Ni H, Coresh J, Mosley TH, Heiss G, Folsom AR, Solomon SD. Rationale and Design of a Multicenter Echocardiographic Study to Assess the Relationship Between Cardiac Structure and Function and Heart Failure Risk in a Biracial Cohort of Community-Dwelling Elderly Persons. Circulation: Cardiovascular Imaging. 2014;7:173–181. [PubMed: 24214885]
16. Inciardi RM, Claggett B, Minamisawa M, Shin SH, Selvaraj S, Gonçalves A, Wang W, Kitzman D, Matsushita K, Prasad NG, Su J, Skali H, Shah AM, Chen LY, Solomon SD. Association of Left Atrial Structure and Function With Heart Failure in Older Adults. J Am Coll Cardiol. 2022;79:1549–1561. [PubMed: 35450571]

17. Rosamond WD, Chang PP, Baggett C, Johnson A, Bertoni AG, Shahar E, Deswal A, Heiss G, Chambless LE. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study a comparison of diagnostic criteria. Circulation: Heart Failure. 2012;5:152–159. [PubMed: 22271752]

18. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158:111–7. [PubMed: 19540400]

19. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA, The AI. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: Methods and initial two years' experience. Journal of Clinical Epidemiology. 1996;49:223–233. [PubMed: 8606324]

20. Xu J, Cui G, Esmailian F, Plunkett M, Marelli D, Ardehali A, Odim J, Laks H, Sen L. Atrial extracellular matrix remodeling and the maintenance of atrial fibrillation. Circulation. 2004;109:363–8. [PubMed: 14732752]

21. Moe GW, Laurent G, Doumanovskaia L, Konig A, Hu X, Dorian P. Matrix metalloproteinase inhibition attenuates atrial remodeling and vulnerability to atrial fibrillation in a canine model of heart failure. Journal of Cardiac Failure. 2008;14:768–776. [PubMed: 18995182]

22. Liu Y, Xu B, Wu N, Xiang Y, Wu L, Zhang M, Wang J, Chen X, Li Y, Zhong L. Association of MMPs and TIMPs With the Occurrence of Atrial Fibrillation: A Systematic Review and Meta-analysis. Can J Cardiol. 2016;32:803–13. [PubMed: 26907578]

23. Spinale FG, Coker ML, Heung LJ, Bond BR, Gunasinghe HR, Etoh T, Goldberg AT, Zellner JL, Crumbley AJ. A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure. Circulation. 2000;102:1944–9. [PubMed: 11034943]

24. Martos R, Baugh J, Ledwidge M, O'Loughlin C, Conlon C, Patle A, Donnelly SC, McDonald K. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. Circulation. 2007;115:888–95. [PubMed: 17283265]

25. Hardy E, Hardy-Sosa A, Fernandez-Patron C. MMP-2: is too low as bad as too high in the cardiovascular system? Am J Physiol Heart Circ Physiol. 2018;315:H1332–h1340. [PubMed: 30118342]

26. López B, González A, Ravassa S, Beaumont J, Moreno MU, San José G, Querejeta R, Díez J. Circulating Biomarkers of Myocardial Fibrosis: The Need for a Reappraisal. J Am Coll Cardiol. 2015;65:2449–56. [PubMed: 26046739]

Clinical Implications

- What is new?
  - Matrix metalloproteinase-2 (MMP-2) associates with the risk of incident heart failure with reduced (HFrEF) and preserved (HFpEF) ejection fraction. The MMP-2 association with HFpEF was mediated by a higher risk of atrial fibrillation. MMP-2 associated directly with HFrEF.
- What are the clinical implications?
  - Future research should consider the potential role of MMP-2 as a clinical biomarker. Clinical trials to modulate the MMP-2 pathway may be warranted.

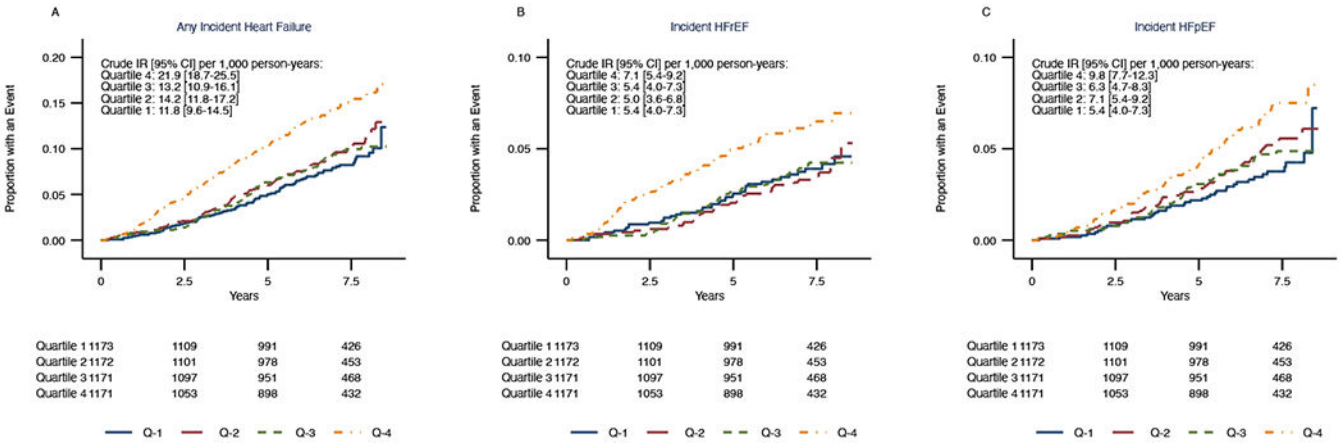

Figure 1.

Incidence of heart failure and heart failure subtypes by quartile of matrix metalloproteinase-2 level

The incidences of heart failure overall (Panel A), HFrEF (Panel B) and HFpEF (Panel C) by quartiles of MMP-2 level.

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IR = incidence rate; MMP-2 = matrix metalloproteinase-2; Q = quartile

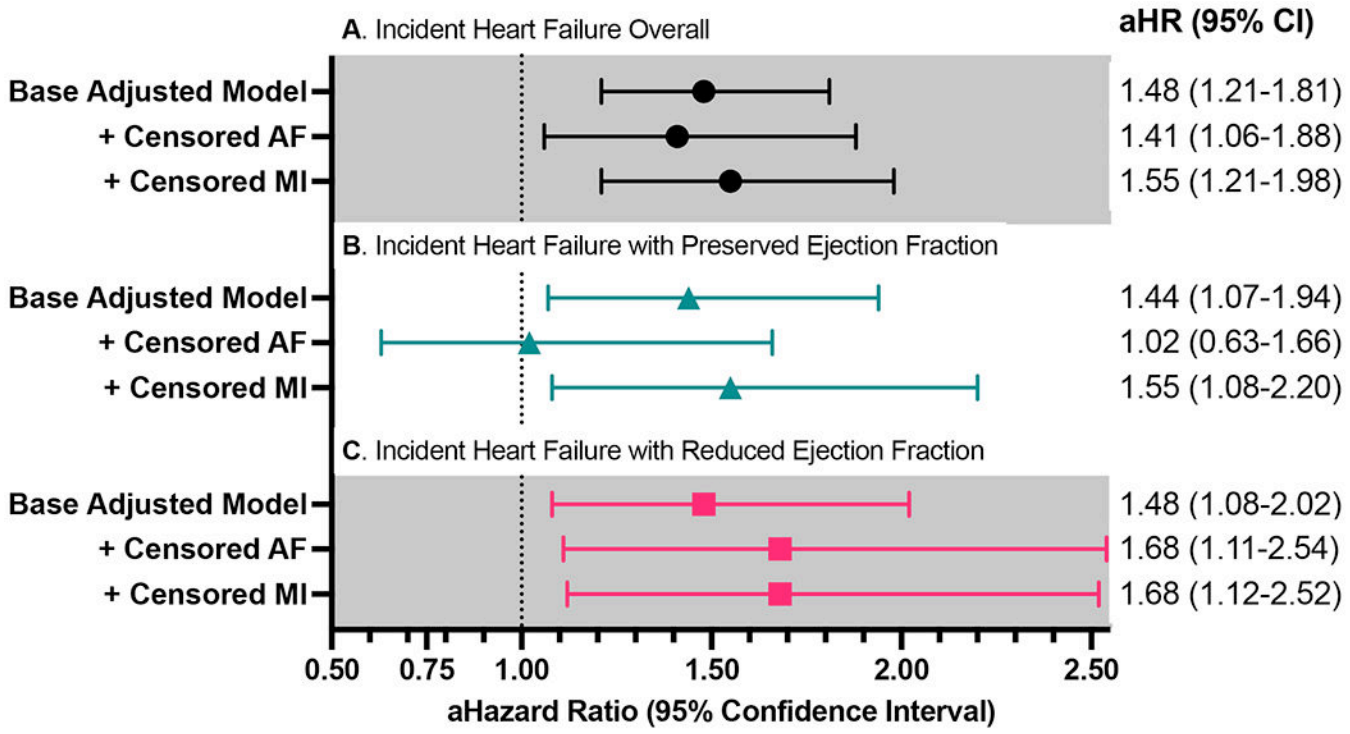

Figure 2.

Risk of heart failure and heart failure subtypes associated with the highest quartile of matrix metalloproteinase-2 level quartiles without and with censoring for incident myocardial infarction and atrial fibrillation

The associations between MMP-2 and any HF, HFpEF and HFrEF (black circles) and after censoring for incident atrial fibrillation (pink squares) and incident myocardial infarction (green triangles) are summarized. Follow-up for incident atrial fibrillation ended on December 31, 2017. Hazard ratios are adjusted for demographics and clinical risk factors. AF = atrial fibrillation; aHR = adjusted hazard ratio; CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; MMP-2 = matrix metalloproteinase-2

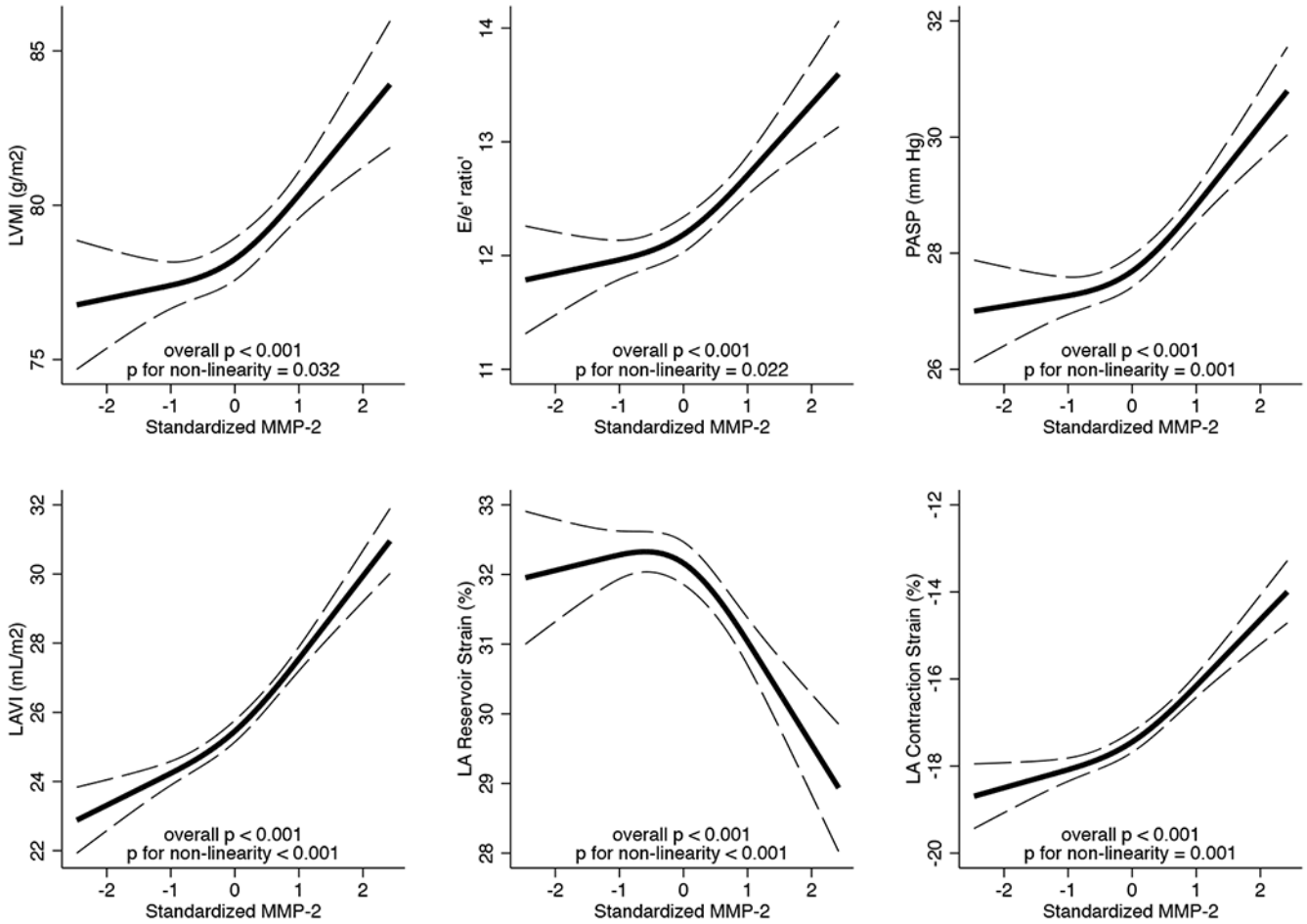

Figure 3.

Restricted cubic splines demonstrating the continuous associations between standardized matrix metalloproteinase-2 level and select measures of cardiac structure and function

This figure depicts non-linear associations between standardized MMP-2 levels and select measures of cardiac structure and function after adjustment for demographics and clinical risk factors. The number of knots was chosen to minimize the Bayesian information criterion.

LA = left atrial; LAVI = left atrial volume index; LVMI = left ventricular mass index; MMP-2 = matrix metalloproteinase-2; PASP = pulmonary artery systolic pressure

Table 1.

Participant characteristics

		Matrix Metalloproteinase-2 Quartiles				
Characteristic	**Overall**	**Quartile 1 (n=1174)**	**Quartile 2 (n=1173)**	**Quartile 3 (n=1173)**	**Quartile 4 (n=1173)**	**P-Value**
Age, years	75 ± 5	74 ± 5	75 ± 5	76 ± 5	77 ± 5	<.001
Women, n (%)	1985 (42.3%)	429 (36.5%)	501 (42.7%)	511 (43.6%)	544 (46.4%)	<.001
Black, n (%)	873 (18.6%)	292 (24.9%)	219 (18.7%)	182 (15.5%)	180 (15.3%)	<.001
Field Center, n (%)						<.001
Forsyth	1141 (24.3%)	202 (17.2%)	251 (21.4%)	301 (25.7%)	387 (33.0%)	
Jackson	803 (17.1%)	270 (23.0%)	204 (17.4%)	164 (14.0%)	165 (14.1%)	
Minneapolis	1458 (31.1%)	328 (27.9%)	386 (32.9%)	390 (33.2%)	354 (30.2%)	
Washington	1291 (27.5%)	374 (31.9%)	332 (28.3%)	318 (27.1%)	267 (22.8%)	
Diabetes, n (%)	1708 (36.4%)	508 (43.3%)	438 (37.3%)	377 (32.1%)	385 (32.8%)	<.001
Hypertension, n (%)	3830 (81.6%)	990 (84.3%)	968 (82.5%)	941 (80.2%)	931 (79.4%)	.008
Coronary heart disease, n (%)	607 (12.9%)	121 (10.3%)	142 (12.1%)	158 (13.5%)	186 (15.9%)	<.001
Stroke, n (%)	141 (3.0%)	38 (3.2%)	34 (2.9%)	24 (2.0%)	45 (3.8%)	.08
Atrial fibrillation, n (%)	252 (5.4%)	37 (3.2%)	47 (4.0%)	56 (4.8%)	112 (9.5%)	<.001
Ever cigarette smoking, n (%)	2876 (61.3%)	731 (62.3%)	731 (62.3%)	696 (59.3%)	718 (61.2%)	.41
Body mass index, kg/m^2	28.5 ± 5.5	29.7 ± 5.7	28.7 ± 5.2	28.1 ± 5.3	27.6 ± 5.6	<.001
Systolic blood pressure, mm Hg	130 ± 18	129 ± 18	130 ± 18	130 ± 17	131 ± 19	.15
Diastolic blood pressure, mm Hg	66 ± 11	67 ± 10	67 ± 10	66 ± 10	65 ± 11	<.001
Pulse pressure, mm Hg	64 ± 14	62 ± 14	63 ± 14	64 ± 14	65 ± 15	<.001
Pulse, beats per minute	65 (11)	68 (11)	65 (11)	64 (11)	63 (11)	<.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	66 ± 17	63 ± 17	66 ± 17	68 ± 17	68 ± 18	<.001
Cardiac troponin T, ng/L	1.1 [0.7, 1.6]	1.0 [0.7, 1.3]	1.0 [0.7, 1.5]	1.1 [0.7, 1.5]	1.2 [0.8, 1.7]	<.001
NT-proBNP, pg/mL	129 [68, 245]	93 [50, 182]	116 [65, 215]	136 [73, 256]	183 [95, 386]	<.001
C-reactive protein, mg/L	1.9 [0.9-4.1]	3.1 [1.4, 6.1]	2.2 [1.1, 4.4]	1.7 [0.9, 3.5]	1.3 [0.7, 2.7]	<.001

Table 2.

Associations between matrix metalloproteinase-2 and incident heart failure, atrial fibrillation and coronary heart disease

	Quartiles 1-3 (n=3520)		Quartile 4 (n=1173)		Model 1		Model 2	
Outcome	**Events (n)**	**IR[#]**	**Events (n)**	**IR[#]**	**HR (95% CI)[*]**	**P**	**HR (95% CI)[*]**	**P**
Any HF	300	13.1 (11.7-14.7)	159	21.9 (18.7-25.5)	1.44 (1.18-1.75)	<.001	1.48 (1.21-1.81)	<.001
HFrEF	120	5.2 (4.4-6.3)	66	9.1 (7.1-11.6)	1.44 (1.06-1.95)	.021	1.48 (1.08-2.02)	.015
HFpEF	143	6.2 (5.3-7.4)	71	9.8 (7.7-12.3)	1.40 (1.04-1.87)	.024	1.44 (1.07-1.94)	.016
Any HF or death	790	34.5 (32.2-37.0)	362	49.8 (44.9-55.2)	1.22 (1.07-1.38)	.002	1.28 (1.13-1.46)	<.001
Incident AF	315	17.9 (16.0-20.0)	145	27.5 (23.3-32.3)	1.37 (1.12-1.68)	.002	1.44 (1.18-1.77)	<.001
Incident CHD	127	5.8 (4.8-6.9)	36	5.1 (3.7-7.1)	0.84 (0.58-1.22)	.36	0.98 (0.67-1.43)	.91

[#]IR = incidence rate per 1,000 person-years

[*]hazard ratios were adjusted for age, sex, race and field center in model 1 and then additionally for smoking, body mass index, hypertension, coronary heart disease, diabetes, pulse pressure, atrial fibrillation and estimated glomerular filtration rate in Model 2

AF = atrial fibrillation; CI = confidence interval; CHD = coronary heart disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; IR = incidence rate; LVEF = left ventricular ejection fraction

Table 3.

Association between matrix metalloproteinase-2 and cardiac structure and function

Measurement	Quartiles 1-3	Quartile 4	Fully Adjusted P-Value
LV structure			
LVEDVI, mL/m^2	42.4 ± 9.5	44.8 ± 10.2	<.001
MWT, cm	0.98 ± 0.13	0.97 ± 0.14	.047
RWT	0.43 ± 0.07	0.42 ± 0.08	.95
LVMI, g/m^2	76.7 ± 17.2	78.6 ± 18.4	<.001
LV systolic function			
LVEF, %	66 ± 6	66 ± 6	.15
GLS, %	−18.1 ± 2.4	−18.2 ± 2.4	.36
GCS, %	−28.0 ± 3.5	−28.0 ± 3.7	.55
LV diastolic function			
E wave, cm/s	64.9 ± 16.4	70.6 ± 19.6	<.001
e', cm/s	5.7 ± 1.4	5.9 ± 1.5	<.001
E/e' ratio	11.9 ± 3.7	12.5 ± 4.7	<.001
PASP, mm Hg	27.4 ± 4.9	28.6 ± 6.1	<.001
LA function			
LAVI, mL/m^2	24.5 ± 7.9	27.6 ± 9.5	<.001
Reservoir (expansion) strain, %	33.0 ± 7.8	31.6 ± 8.9	<.001
Contraction (active) strain, %	−18.2 ± 6.0	−16.3 ± 6.6	<.001

LV GCS = left ventricular global circumferential strain; LV GLS = left ventricular global longitudinal strain; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MWT = mean wall thickness; PASP = pulmonary artery systolic pressure; RWT = relative wall thickness