

Supplementary Online Content

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eFigure. Left Ventricular Mass Index (g/m^2), Mean Left Ventricular Wall Thickness (cm), Left Ventricular End Diastolic Volume Index (ml/m^2), E/e'-ratio and LA Volume Index (ml/m^2) Across Categories of hs-cTnT at Visit 5, Based on hs-cTnT Measurements at Visit 2 and Visit 4 (Marked as Non-detectable [ND] $= < 5 \text{ ng/L}$ and Detectable [D] $= \geq 5 \text{ ng/L}$)

eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Echocardiography

All images were transferred to Brigham and Women's Hospital, Boston, MA, where dedicated and blinded analysts performed all quantitative measures according to recommendations by the American Society of Echocardiography (ASE)/European Society of Echocardiography (ESE).¹ LV mass was calculated from wall thickness and end-diastolic dimension measured on 2D images, and was indexed to height in meters in the allometric power of 2.7 ($\text{height}^{2.7}$) given the high prevalence of elevated BMI in the study population.¹ LV hypertrophy was defined from ASE/ESE-recommended sex-specific cut-offs: LVM indexed to $\text{height}^{2.7} > 48 \text{ g/m}^{2.7}$ for men and $>44 \text{ g/m}^{2.7}$ for women.¹ LV relative wall thickness was calculated as two times the posterior wall thickness divided by the LV end-diastolic diameter. LV and left atrial (LA) volumes were measured by the Simpson's method and were indexed to body surface area (m^2). LV systolic function was assessed by LV ejection fraction (LVEF), global longitudinal strain (GLS), global circumferential strain (GCS) and mid-wall fractional shortening (MWFS). LV diastolic function was assessed based on LA volume index, peak early diastolic myocardial tissue velocity measured from the septal mitral annulus by TDI (e'), and the ratio between early diastolic velocity in transmitral Doppler (E) and e' (E/e'). Mitral annular tissue Doppler were not measured in participants with prior mitral valve replacement or repair (n=11, none of these were included in this study as 9 of them had HF, 1 had a previous stroke and 1 had AF). No participants had moderate or greater mitral stenosis. Diastolic assessment was performed in participants with mitral regurgitation, which was of greater than moderate severity in only 2 participants (0.05%). Diastolic assessment was also performed in participants with ventricular pacing at the time of echocardiography (n=13).

We used sex-specific cut points for diastolic measures established from the ARIC study, as these have previously been shown to improve risk prediction for incident HF compared to ASE/ESE-recommended cut-off values in both ARIC and an independent elderly cohort ²: (1) septal $e' < 4.5$ cm/s or lateral $e' < 5.1$ cm/s for women and septal $e' < 4.6$ cm/s or lateral $e' < 5.4$ cm/s for men, (2) septal $E/e' > 15.1$ or lateral $E/e' > 13.3$ for women and septal $E/e' > 13.3$ or lateral $E/e' > 11.5$ for men and (3) LA volume index > 30 ml/m² for women and LA volume index > 31 ml/m² for men. Diastolic dysfunction was defined by the presence of ≥ 2 of abnormal indices of diastolic function. As a sensitivity analysis, we repeated the primary analysis using the ASE/ESE-recommended classification of diastolic dysfunction as > 2 of the 4 following criteria: (1) septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s, (2) septal $E/e' > 15$ or lateral $E/e' > 13$, (3) LA volume index > 34 ml/m², and (4) tricuspid regurgitation peak velocity > 2.8 m/s.

Blood sampling and troponin measurements

The measurement range was 3 to 100,000 ng/L for the hs-cTnT assay. The intra-assay coefficients of variation (CVs) were 2.1% and 1.0% at a mean concentration of 26 ng/L and 1990 ng/L, and the inter-assay CVs were 6.0% and 3.7% at 25 ng/L and 1940 ng/L for the Visit 2 samples. The intra-assay CVs were 2.1% and 0.76% at 29 ng/L and 2378 ng/L, and the inter-assay CVs were 6.9% and 2.6% at 29 ng/L and 2378 ng/L for the Visit 4 samples. The intra-assay CVs were 1.8% and 1.9% at 29 ng/L and 2227 ng/L, and the inter-assay CVs were 19.3%, 9.8%, 6.4% and 5.6% at 7 ng/L, 14 ng/L, 29 ng/L and 2227 ng/L for the Visit 5 samples. Previous data has demonstrated no significant bias when comparing measurements at the different time points, ³ and the variability related to freeze-thaw cycles and frozen storage has been previously described. ⁴

Statistical analysis

The number of knots for restricted cubic splines were selected based on the lowest Akaike information criterion (3 to 7 knots tested). Restricted cubic splines were adjusted for all Model 2 covariates, with continuous covariates included as cubic spline representations to allow for non-linear associations.

To assess the potential impact of bias due to selective Visit 5 nonattendance among living cohort participants, we performed a sensitivity analysis using inverse probability weights.^{6,7} The likelihood of attendance among ARIC participants known to be alive at the beginning of Visit 5 was modeled using logistic regression with variables assessed at Visit 1 (i.e. age, race, sex, hypertension, diabetes, smoking, BMI, systolic blood pressure, heart rate, and eGFR) as predictors of nonattendance at Visit 5. These inverse probability of attrition weights (IPAW) were incorporated into logistic and linear regression models to assess the association between hs-cTnT and echocardiographic measures in an estimated population representing the full ARIC cohort alive at Visit 5.

eTable 1. Baseline Characteristics and Echocardiographic Measurements According to Categories of hs-cTnT at Visit 5 in the Total Population That Attended Visit 5 (i.e. Not Excluding Prevalent Cardiovascular Disease)

| | Category 1 | Category 2 | Category 3 | Category 4 | Category 5 | Model 1 | Model 2 |
|----------------------------------|-------------------|--------------------|---------------------|---------------------|----------------------|---------|---------|
| | (n=494) | (n=1709) | (n=1390) | (n=1135) | (n=1346) | | |
| Age (y) | 72.8 ± 3.7 | 74.4 ± 4.3 | 75.8 ± 5.0 | 77.2 ± 5.0 | 78.6 ± 5.4 | | |
| Male sex | 80 (16.2%) | 765 (44.8%) | 555 (39.9%) | 586 (51.6%) | 576 (42.8%) | | |
| White race | 421 (85.2%) | 1391 (81.4%) | 1100 (79.1%) | 863 (76.0%) | 969 (72.0%) | | |
| Ever hypertension | 335 (67.8%) | 1307 (76.5%) | 1168 (84.0%) | 996 (87.8%) | 1256 (93.3%) | <0.001 | |
| Ever diabetes | 124 (25.1%) | 525 (30.7%) | 509 (36.6%) | 480 (42.3%) | 646 (48.0%) | <0.001 | |
| Current smoking | 57 (11.8%) | 105 (6.3 %) | 77 (5.7 %) | 50 (4.5 %) | 58 (4.5 %) | 0.002 | |
| BMI (kg/m ²) | 27.5 ± 5.1 | 28.2 ± 5.3 | 28.6 ± 5.6 | 29.1 ± 5.7 | 29.3 ± 6.3 | <0.001 | |
| SBP (mmHg) | 127.1 ± 17.2 | 129.0 ± 17.0 | 130.0 ± 17.7 | 130.5 ± 17.5 | 132.9 ± 19.9 | <0.001 | |
| HR (/min) | 62.5 ± 8.8 | 61.6 ± 10.1 | 62.3 ± 10.4 | 62.6 ± 10.8 | 64.1 ± 11.1 | <0.001 | |
| eGFR (ml/min) | 78.8 ± 12.6 | 74.7 ± 13.9 | 71.3 ± 15.5 | 67.5 ± 16.5 | 59.3 ± 19.7 | <0.001 | |
| NT-proBNP (ng/L) | 86.9[46.4, 154.5] | 95.7 [52.2, 171.6] | 129.9 [72.1, 236.0] | 150.0 [76.3, 314.1] | 264.9 [123.8, 641.3] | <0.001 | |
| Mean LV WT (cm) | 0.93 ± 0.10 | 0.96 ± 0.12 | 0.98 ± 0.13 | 1.00 ± 0.13 | 1.05 ± 0.17 | <0.001 | <0.001 |
| LVEDV index (ml/m ²) | 40.4 ± 8.4 | 43.1 ± 9.8 | 43.9 ± 11.2 | 45.0 ± 11.2 | 46.5 ± 14.1 | <0.001 | <0.001 |
| LVM index (g/m ^{2.7}) | 34.4 ± 7.8 | 35.7 ± 8.8 | 37.7 ± 10.4 | 39.1 ± 10.2 | 43.0 ± 13.6 | <0.001 | <0.001 |
| LV relative WT | 0.42 ± 0.06 | 0.42 ± 0.06 | 0.42 ± 0.07 | 0.43 ± 0.07 | 0.45 ± 0.10 | <0.001 | <0.001 |
| LVEF (%) | 66.6 ± 5.2 | 65.9 ± 5.6 | 65.2 ± 6.6 | 64.7 ± 7.2 | 63.4 ± 8.6 | <0.001 | 0.08 |
| GLS (%) | -18.4 ± 2.2 | -18.2 ± 2.3 | -18.0 ± 2.6 | -17.7 ± 2.8 | -17.1 ± 3.1 | <0.001 | 0.17 |
| GCS (%) | -28.2 ± 3.7 | -27.8 ± 3.6 | -27.7 ± 3.9 | -27.5 ± 4.0 | -27.0 ± 4.8 | <0.001 | 0.55 |
| TDI e' (cm/sec) | 6.0 ± 1.5 | 5.9 ± 1.5 | 5.7 ± 1.4 | 5.5 ± 1.4 | 5.3 ± 1.6 | <0.001 | <0.001 |
| E/e ² -ratio | 11.6 ± 3.5 | 11.6 ± 3.8 | 12.1 ± 3.9 | 12.8 ± 4.6 | 14.4 ± 6.2 | <0.001 | <0.001 |
| LAVi (ml/m ²) | 23.0 ± 6.4 | 24.2 ± 7.3 | 25.7 ± 7.9 | 27.3 ± 10.7 | 29.7 ± 12.0 | <0.001 | <0.001 |

Values are presented as mean ± standard deviation, n (%) or median (Q1-Q3) and the P-value is for trend from Category 1 to Category 5. **Model 1:** Adjusted for age, gender and race. **Model 2:** Adjusted for Model 1 + body mass index, hypertension, diabetes mellitus, smoking, systolic blood pressure, heart rate, estimated glomerular filtration rate and (ln) NT-proBNP. *Abbreviations: BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro brain natriuretic peptide; HF, heart failure; LV, left ventricular; WT, wall thickness; LVEDV, left ventricular end diastolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global longitudinal strain; TDI, tissue Doppler imaging; LAVi, left atrial volume index.

eTable 2. Echocardiographic Measurements According to Sex-Blinded Categories by Stratifying the Total Population in Quintiles of hs-cTnT at Visit 5, Irrespective of Sex

| | Category 1 | Category 2 | Category 3 | Category 4 | Category 5 | Model 1 | Model 2 |
|----------------------------------|-------------|-------------|-------------|-------------|-------------|---------|---------|
| | n=1024 | n=719 | n=857 | n=803 | n=708 | | |
| <i>hs-cTnT range</i> | ≤6 ng/L | 7-8 ng/L | 9-11 ng/L | 12-15 ng/L | ≥17 ng/L | | |
| Septal WT (cm) | 1.00 (0.00) | 1.01 (0.01) | 1.03 (0.01) | 1.03 (0.01) | 1.08 (0.01) | <0.001 | <0.001 |
| LV posterior WT (cm) | 0.89 (0.00) | 0.91 (0.00) | 0.92 (0.00) | 0.93 (0.00) | 0.96 (0.01) | <0.001 | <0.001 |
| LVEDD | 4.29 (0.01) | 4.32 (0.02) | 4.36 (0.02) | 4.39 (0.02) | 4.43 (0.02) | <0.001 | 0.17 |
| LVM (g) | 133.3 (1.2) | 137.4 (1.4) | 142.0 (1.2) | 145.5 (1.3) | 157.2 (1.4) | <0.001 | <0.001 |
| LVM index (g/m ^{2.7}) | 34.3 (0.3) | 35.6 (0.3) | 36.8 (0.3) | 37.3 (0.3) | 40.2 (0.4) | <0.001 | <0.001 |
| LV hypertrophy | 9.9% (0.9) | 11.8% (1.2) | 16.4% (1.3) | 20.3% (1.5) | 28.3% (1.9) | <0.001 | 0.01 |
| LV relative WT | 0.42 (0.00) | 0.42 (0.00) | 0.42 (0.00) | 0.43 (0.00) | 0.44 (0.00) | <0.001 | <0.001 |
| LVEDV index (ml/m ²) | 42.2 (0.3) | 42.2 (0.3) | 43.0 (0.3) | 43.1 (0.3) | 44.9 (0.4) | <0.001 | <0.001 |
| LVEF (%) | 66.3 (0.2) | 66.2 (0.2) | 65.9 (0.2) | 66.0 (0.2) | 65.6 (0.2) | 0.03 | 0.58 |
| GLS (%) | -18.3 (0.1) | -18.3 (0.1) | -18.3 (0.1) | -18.3 (0.1) | -17.8 (0.1) | 0.007 | 0.80 |
| GCS (%) | -27.9 (0.1) | -28.2 (0.2) | -27.9 (0.1) | -28.1 (0.2) | -28.0 (0.2) | 0.88 | 0.22 |
| TDI e' (cm/sec) | 5.97 (0.05) | 5.76 (0.05) | 5.77 (0.05) | 5.55 (0.05) | 5.53 (0.06) | <0.001 | <0.001 |
| E/e' ² -ratio | 11.3 (0.1) | 11.7 (0.1) | 11.7 (0.1) | 12.4 (0.1) | 13.1 (0.1) | <0.001 | <0.001 |
| LAVi (ml/m ²) | 23.4 (0.2) | 23.9 (0.3) | 24.5 (0.2) | 25.1 (0.3) | 26.7 (0.3) | <0.001 | <0.001 |

Values presented as mean or proportion and standard error adjusted for age, race and sex, and P-value is for trend from Category 1 to Category 5 (**Model 1**). Also presented P-values for trend in **Model 2** that was adjusted for Model 1 + body mass index, hypertension, diabetes mellitus, smoking, systolic blood pressure, heart rate, estimated glomerular filtration rate and (ln) NT-proBNP.

*Abbreviations: LV, left ventricular; WT, wall thickness; LVEDV, left ventricular end diastolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global longitudinal strain; MWFS, mid-wall fractional shortening; TDI, tissue Doppler imaging; LAVi, left atrial volume index

eTable 3. Baseline Characteristics Divided in Categories of hs-cTnT at Visit 5 of All Participants Alive at Visit 5 by Inverse-Probability-Weighted Estimation Analysis

| | Category 1 | Category 2 | Category 3 | Category 4 | Category 5 | Model 1 | Model 2 |
|---------------------------------|--------------------|-------------------|----------------------|----------------------|----------------------|---------|---------|
| Age (y) | 73.3 [72.9, 73.7] | 74.9 [74.7, 75.1] | 76.7 [76.4, 77.0] | 86.1 [77.8, 78.4] | 79.8 [79.5, 80.0] | <0.001 | 0.009 |
| Male sex | 15.7% (12.5-18.9) | 43.3% (40.9- | 38.5 (35.9-41.0) | 49.5% (46.6-52.4) | 45.3 (44.3-46.3) | 0.48 | <0.001 |
| White race | 84.2% (80.1-87.6) | 79.4% (77.4- | 77.9% (75.7-80.2) | 74.1% (71.4-76.7) | 67.9% (67.0-68.9) | <0.001 | <0.001 |
| Ever hypertension | 69.9% (65.8-73.9) | 78.4% (76.5- | 84.9% (83.0-86.7) | 89.1% (87.3-90.8) | 94.6% (93.5-95.6) | <0.001 | <0.001 |
| Ever diabetes | 26.3%(22.2-30.3) | 31.2% (29.0- | 37.7% (35.1-40.3) | 44.0% (41.1-46.9) | 51.5%(49.0-54.0) | <0.001 | <0.001 |
| Current smoking | 12.1%(9.1-15.2) | 6.8% (5.5-8.1) | 6.0% (4.6-7.3) | 4.8% 3.5-6.0) | 5.9% (3.8-6.3) | 0.01 | <0.001 |
| BMI (kg/m ²) | 27.7 [27.2, 28.2] | 28.4 [28.1, 28.6] | 28.6 [28.3, 28.9] | 29.2 [28.9, 29.6] | 29.6 [29.2, 29.9] | <0.001 | <0.001 |
| SBP (mmHg) | 128 [126 , 129] | 130 [129 , 130] | 131 [130 , 132] | 131 [130 , 132] | 135 [134 , 136] | 0.001 | 0.005 |
| HR (/min) | 62 [62 , 63] | 62 [61 , 62] | 63 [62 , 63] | 63 [62 , 64] | 64 [64 , 65] | <0.001 | <0.001 |
| eGFR (ml/min) | 78 [77, 80] | 74 [74, 75] | 71 [70, 72] | 67 [66, 68] | 58 [57, 59] | <0.001 | <0.001 |
| Mean LV WT (cm) | 0.93 [0.92, 0.94] | 0.96 [0.96, 0.97] | 0.98 [0.98, 0.99] | 1.00 [0.99, 1.01] | 1.05 [1.04, 1.06] | <0.001 | <0.001 |
| LVEDV index | 40.2 [39.5, 41.0] | 42.8 [42.4, 43.3] | 43.8 [43.2, 44.5] | 44.8 [44.1, 45.5] | 46.4 [45.6, 47.2] | <0.001 | <0.001 |
| LVM index (g/m ^{2.7}) | 34.6 [33.9, 35.4] | 35.8 [35.4, 36.3] | 37.9 [37.3, 38.5] | 39.2 [38.6, 39.9] | 43.3 [42.6, 44.1] | <0.001 | <0.001 |
| LV relative WT | 0.42 [0.41, 0.42] | 0.42 [0.42, 0.42] | 0.43 [0.42, 0.43] | 0.43 [0.42, 0.43] | 0.45 [0.44, 0.45] | <0.001 | <0.001 |
| LVEF (%) | 66.6 [66.2, 67.1] | 65.9 [65.6, 66.2] | 65.2 [64.8, 65.6] | 64.8 [64.3, 65.2] | 63.5 [63.0, 63.9] | <0.001 | 0.05 |
| GLS (%) | -18.3 [-18.5, - | -18.2 [-18.3, - | -17.9 [-18.0, -17.8] | -17.6 [-17.8, -17.5] | -17.1 [-17.3, -16.9] | <0.001 | 0.22 |
| GCS (%) | -28.3 [-28.7, - | -27.8 [-28.0, - | -27.7 [-28.0, -26.5] | -27.5 [-27.8, -27.2] | -27.1 [-27.4, -26.8] | <0.001 | 0.88 |
| TDI e' (cm/sec) | 6.0 [5.9 , 6.1] | 5.9 [5.8 , 5.9] | 5.7 [5.6 , 5.8] | 5.5 [5.4 , 5.6] | 5.3 [5.2 , 5.4] | <0.001 | <0.001 |
| E/e'-ratio | 11.7 [11.3 , 12.0] | 11.7 [11.5 , | 12.2 [12.0 , 12.5] | 13.0 [12.7 , 13.3] | 14.6 [14.2, 14.9] | <0.001 | <0.001 |
| LAV index (ml/m ²) | 23.2 [22.6, 23.9] | 24.3 [24.0, 24.7] | 25.9 [25.4, 26.3] | 27.5 [26.9, 28.2] | 29.9 [29.3, 30.6] | <0.001 | <0.001 |

Continuous variables presented as mean (95% C.I.) and categorical as % (95% C.I.). **Model 1:** Adjusted for age, gender and race. **Model 2:** Adjusted for Model 1 + body mass index, hypertension, diabetes mellitus, smoking, systolic blood pressure, heart rate, estimated glomerular filtration rate and (ln) NT-proBNP. *Abbreviations: BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro brain natriuretic peptide; HF, heart failure; LV, left ventricular; WT, wall thickness; LVEDV, left ventricular end diastolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global longitudinal strain; TDI, tissue Doppler imaging; LAVi, left atrial volume.*

eTable 4. Associations Between hs-cTnT (per 1 Log Unit Increase) at Visit 5 and Measures of Diastolic Dysfunction According to Validated Cut-offs Derived from the ARIC Study²

| | Number of abnormal (%) | OR (95% CI) | P |
|--|-------------------------------|--------------------|----------|
| Abnormal e' | 1,056 (26%) | 1.20 (1.04-1.37) | 0.01 |
| Abnormal E/e' | 1,075 (26%) | 1.25 (1.09-1.44) | 0.001 |
| Abnormal left atrial volume index | 756 (19%) | 1.44 (1.22-1.70) | <0.001 |
| Diastolic dysfunction (>2 abnormal measures) | 761 (19%) | 1.37 (1.16-1.61) | <0.001 |

eTable 5. Associations Between hs-cTnT (per 1 Log Unit Increase) at Visit 5 and Measures of Diastolic Dysfunction According to the Guidelines by American Society of Echocardiography

| | Number of abnormal (%) | OR (95% CI) | P |
|--|-------------------------------|--------------------|----------|
| Abnormal e' | 3911 (95%) | 1.02 (0.78-1.33) | 0.89 |
| Abnormal E/e' | 947 (23%) | 1.31 (1.13-1.52) | <0.001 |
| Abnormal left atrial volume index | 402 (10%) | 1.53 (1.23-1.91) | <0.001 |
| Abnormal tricuspid regurgitation peak velocity | 140 (6%) | 1.42 (1.00-2.03) | 0.049 |
| Diastolic dysfunction (>2 abnormal measures) | 144 (6%) | 1.78 (1.23-2.58) | 0.002 |

eTable 6. Association of Log-transformed hs-cTnT Concentrations at Visit 5 Adjusted for Age, Sex, Race, Hypertension, Diabetes, Obesity and eGFR and Incident Heart Failure (HF), HF With Reduced (HF_rEF) or Mid-range Ejection Fraction (EF_{mr}EF) and HF With Preserved Ejection Fraction (HF_pEF) Without and With Adjustment for Measures of Diastolic Function (Tissue Doppler e', E/e' and Left Atrial [LA] Volume index) and/or Left Ventricular [LV] Mass Index and LV Hypertrophy

Reduction of coefficient is a measure of proportion of the hs-cTnT – outcomes association accounted for by diastolic function and/or LV mass index. Analyses are restricted to participants with available tissue Doppler e', E/e', LA volume index and LV mass index, n=3,936; 96% of the total study population.

| | Incident HF (114 events) | | Incident HF_rEF / HF_{mr}EF (50 events) | | Incident HF_pEF (53 events) | |
|--|-------------------------------------|--|--|--|--|--|
| | <i>HR (95% CI)</i> | <i>Reduction of Coef. (95% CI)</i> | <i>HR (95% CI)</i> | <i>Reduction of Coef. (95% CI)</i> | <i>HR (95% CI)</i> | <i>Reduction of Coef. (95% CI)</i> |
| Adj.* hs-cTnT (log) | 2.35 (1.67-3.32) | REF | 2.55 (1.53-4.27) | REF | 1.83 (1.10-3.03) | REF |
| Adj.* hs-cTnT (log) + diastolic function | 1.80 (1.25-2.58) | -31% (-14% to -60%) | 2.12 (1.23-3.66) | -20% (-21% to 59%) | 1.34 (0.80-2.25) | -51% (-16% to -186%) |
| Adj.* hs-cTnT (log) + LV mass index (m ^{2.7}) | 1.84 (1.28-2.64) | -29% (-16% to -52%) | 1.74 (0.99-3.03) | -41% (-22% to -91%) | 1.57 (0.93-2.63) | -25% (-9% to -99%) |
| Adj.* hs-cTnT (log) + diastolic function + LV mass index (m ^{2.7}) | 1.57 (1.01-1.05) | -47% (-27% to -85%) | 1.70 (0.96-3.02) | -43% (-18% to -110%) | 1.25 (0.74-2.11) | -63% (-24% to -233%) |

*Adjusted for age, race, sex, hypertension, diabetes, obesity, and eGFR

eTable 7. Risk of Incident Heart Failure (HF), HF With Reduced (HF_rEF) or Mid-range Ejection Fraction (EF_{mr}EF) and HF With Preserved Ejection Fraction (HF_pEF) Stratified by the Presence (+) or Absence (-) of Diastolic Dysfunction (DD) and hs-cTnT > Upper Reference Limit (TnT+) After Adjusting for LV Mass Index

(Including 3,989 patients with available data on events , diastolic dysfunction and LV mass)

| | Incident HF | | Incident HF _r EF / HF _{mr} EF | | Incident HF _p EF | |
|-----------------|------------------|------------|---|------------|-----------------------------|------------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| DD- TnT- | <i>REF</i> | <i>REF</i> | <i>REF</i> | <i>REF</i> | <i>REF</i> | <i>REF</i> |
| DD+ TnT- | 1.50 (0.79-2.87) | 0.21 | 2.35 (0.95-5.78) | 0.06 | 0.72 (0.21-2.40) | 0.59 |
| DD- TnT+ | 2.53 (1.55-4.13) | <0.001 | 2.93 (1.36-6.31) | 0.006 | 2.56 (1.30-5.03) | 0.006 |
| DD+ TnT+ | 3.92 (2.22-6.91) | <0.001 | 3.67 (1.45-9.26) | 0.006 | 3.79 (1.69-8.52) | 0.001 |

eTable 8. Risk Incident Heart Failure (HF), HF With Reduced (HF_rEF) or Mid-range Ejection Fraction (EF_{mr}EF) and HF With Preserved Ejection Fraction (HF_pEF) Stratified by the Presence (+) or Absence (-) of Diastolic Dysfunction (DD) Classified According to the American Society of Echocardiography (ASE) Guidelines and hs-cTnT > Upper Reference Limit (TnT+)

(Including 2,303 patients with available data on events and diastolic dysfunction assessed by the ASE guidelines (e', E/e', LA volume index and tricuspid regurgitation peak velocity)

| | Incident HF | | Incident HF _r EF / HF _{mr} EF | | Incident HF _p EF | |
|-----------------|--------------------|------------|---|------------|-----------------------------|------------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| DD- TnT- | <i>REF</i> | <i>REF</i> | <i>REF</i> | <i>REF</i> | <i>REF</i> | <i>REF</i> |
| DD+ TnT- | 1.71 (0.81-3.59) | 0.16 | 1.82 (0.59-5.58) | 0.30 | 1.66 (0.55-5.06) | 0.37 |
| DD- TnT+ | 4.48 (1.87-10.73) | 0.001 | 1.78 (0.23-13.60) | 0.58 | 6.60 (2.17-20.07) | 0.001 |
| DD+ TnT+ | 12.70 (6.38-25.27) | <0.001 | 16.48 (6.26-43.39) | <0.001 | 7.65 (2.20-26.62) | 0.001 |

eTable 9. Incident Rates (per 100 Person-years) of Heart Failure (HF) Overall (114 Events), HF With Mid-Range or Reduced Ejection Fraction (HFmrEF/HFrEFm 50 Events), and HF With Preserved Ejection Fraction (HFpEF, 53 Events) Among Participant Categories Based on the Presence (+) or Absence (-) of Diastolic Dysfunction (DD) and hs-cTnT > Upper Reference Limit (TnT+)

Analysis includes 4,018 patients with available data on hs-cTnT, diastolic dysfunction and incident HF events.

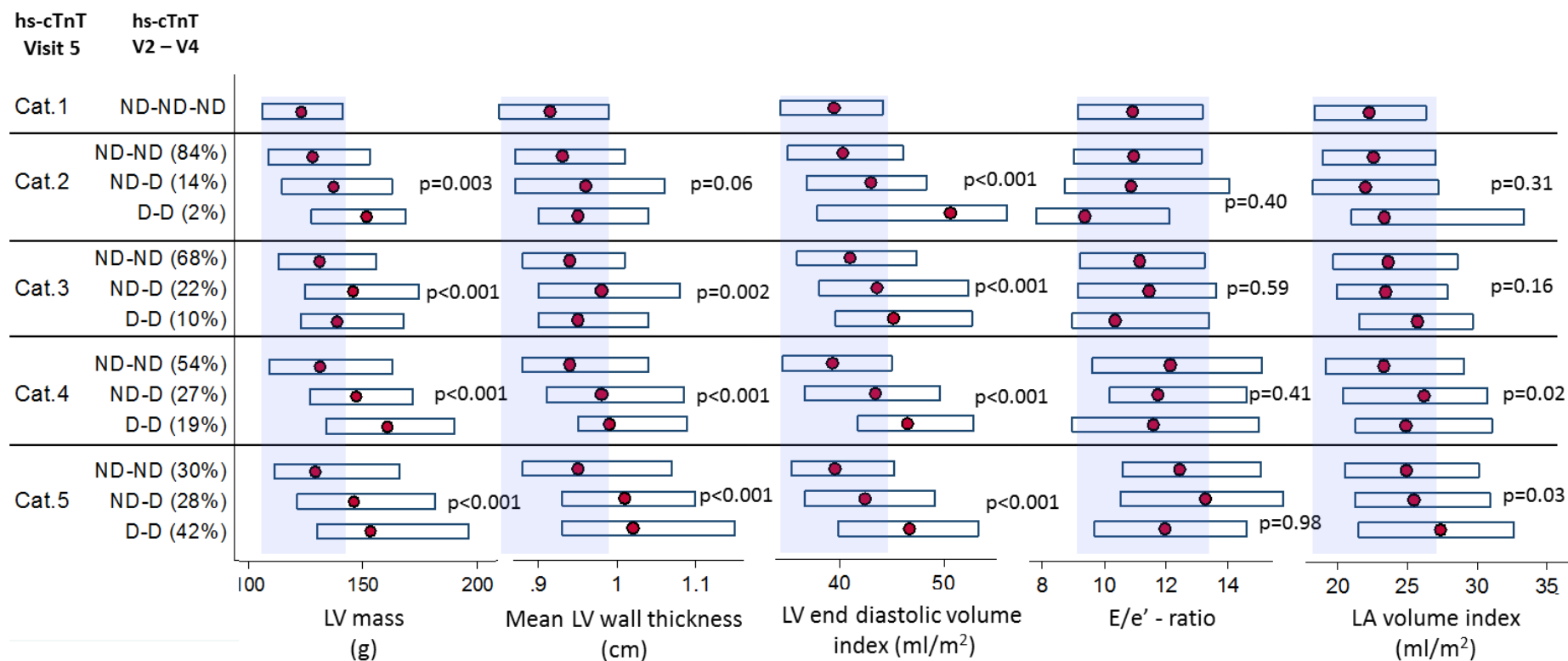
| | | All HF (n=114) | HFpEF (n=53) | HFrEF (n=50) |
|--|----------|-----------------------|---------------------|---------------------|
| Unadjusted | TnT- DD- | REF | REF | REF |
| | TnT+ DD- | 1.96 (1.05-3.64) | 0.84 (0.25-2.81) | 3.23 (1.38-7.55) |
| | TnT- DD+ | 3.68 (2.31-5.87) | 3.45 (1.80-6.61) | 4.60 (2.25-9.43) |
| | TnT+ DD+ | 8.66 (5.29-14.19) | 6.50 (3.09-13.65) | 11.12 (5.26-23.51) |
| Adj. for age, sex, race | TnT- DD- | REF | REF | REF |
| | TnT+ DD- | 1.62 (0.86-3.04) | 0.72 (0.21-2.45) | 2.40 (1.01-5.73) |
| | TnT- DD+ | 3.24 (2.02-5.19) | 3.17 (1.64-6.13) | 3.77 (1.83-7.80) |
| | TnT+ DD+ | 6.60 (3.90-11.18) | 5.35 (2.40-11.91) | 7.21 (3.28-15.84) |
| Adj. for age, sex, race + clinical covariates* | TnT- DD- | REF | REF | REF |
| | TnT+ DD- | 1.25 (0.65-2.39) | 0.53 (0.15-1.84) | 1.80 (0.74-4.39) |
| | TnT- DD+ | 3.07 (1.91-4.95) | 3.04 (1.56-5.94) | 3.50 (1.69-7.26) |
| | TnT+ DD+ | 5.32 (3.07-9.22) | 4.04 (1.78-9.14) | 5.83 (2.52-13.49) |
| Adj. for age, sex, race + clinical covariates* + NT-proBNP | TnT- DD- | REF | REF | REF |
| | TnT+ DD- | 0.89 (0.45-1.74) | 0.46 (0.13-1.60) | 1.00 (0.39-2.59) |
| | TnT- DD+ | 2.10 (1.27-3.48) | 2.15 (1.04-4.47) | 2.26 (1.06-4.80) |
| | TnT+ DD+ | 2.14 (1.17-3.92) | 2.31 (0.97-5.51) | 1.45 (0.56-3.79) |

*Clinical covariates = body mass index, hypertension, diabetes, smoking, systolic blood pressure, heart rate and estimated glomerular filtration rate.

eFigure. Left Ventricular Mass Index (g/m²), Mean Left Ventricular Wall Thickness (cm), Left Ventricular End Diastolic Volume Index (ml/m²), E/e'-ratio and LA Volume Index (ml/m²) Across Categories of hs-cTnT at Visit 5, Based on hs-cTnT Measurements at Visit 2 and Visit 4 (Marked as Non-detectable [ND] = <5 ng/L and Detectable [D] = ≥5 ng/L)

The percentage of participant within each V5 categories displayed. (The participants that went from having detectable to non detectable hs-cTnT concentration [n=293, 8%] were excluded from the figure for simplification.)

The red point represents the median value and the horizontal bar represents the 25th to 75th percentile values. Grey shading indicates the interquartile range for participants with undetectable hs-cTnT at all study visits. P-values represent trend across ND-ND, ND-D, and D-D at Visit 2 and Visit 4, respectively.



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