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ORIGINAL RESEARCH

# Left Ventricular Hypertrophy and Biomarkers of Cardiac Damage and Stress in Aortic Stenosis

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**BACKGROUND:** Left ventricular hypertrophy (LVH) is associated with increased mortality risk and rehospitalization after transcatheter aortic valve replacement among those with severe aortic stenosis. Whether cardiac troponin (cTnT) and NT-proBNP (N-terminal pro-B-type natriuretic peptide) risk stratify patients with aortic stenosis and without LVH is unknown.

**METHODS AND RESULTS:** In a multicenter prospective registry of 923 patients with severe aortic stenosis undergoing transcatheter aortic valve replacement, we included 674 with core-laboratory-measured LV mass index, cTnT, and NT-proBNP. LVH was defined by sex-specific guideline cut-offs and elevated biomarker levels were based on age and sex cut-offs. Adjusted Cox proportional hazards models evaluated associations between LVH and biomarkers and all-cause death out to 5 years. Elevated cTnT and NT-proBNP were present in 82% and 86% of patients with moderate/severe LVH, respectively, as compared with 66% and 69% of patients with no/mild LVH, respectively ( $P<0.001$  for each). After adjustment, compared with no/mild LVH, moderate/severe LVH was associated with an increased hazard of mortality (adjusted hazard ratio [aHR], 1.34; 95% CI 1.01–1.77,  $P=0.043$ ). cTnT and NT-proBNP each risk stratified patients with moderate/severe LVH ( $P<0.05$ ). In a model with both biomarkers and LVH included, elevated cTnT (aHR, 2.08; 95% CI 1.45–3.00,  $P<0.001$ ) and elevated NT-proBNP (aHR, 1.46; 95% CI 1.00–2.11,  $P=0.049$ ) were each associated with increased mortality risk, whereas moderate/severe LVH was not ( $P=0.15$ ).

**CONCLUSIONS:** Elevations in circulating cTnT and NT-proBNP are more common as LVH becomes more pronounced but are also observed in those with no/minimal LVH. As measures of maladaptive remodeling and cardiac injury, cTnT and NT-proBNP predict post-transcatheter aortic valve replacement mortality better than LV mass index. These findings may have important implications for risk stratification and treatment of patients with aortic stenosis.

**Key Words:** biomarkers ■ left ventricular hypertrophy ■ mortality ■ NT-proBNP ■ transcatheter aortic valve implantation ■ transcatheter aortic valve replacement ■ troponin

Left ventricular hypertrophy (LVH) often develops in response to pressure overload from aortic stenosis (AS). Because increased wall thickness reduces wall stress, LVH has long been considered an anticipatory and compensatory response, presumably

advantageous to maintain cardiac performance.<sup>1</sup> However, several studies have challenged the paradigm that hypertrophic remodeling in patients with AS is adaptive.<sup>2–4</sup> Recently, an adverse association between greater left ventricular mass index (LVMI) and

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## CLINICAL PERSPECTIVE

### What Is New?

- In a study with core laboratory measurements of left ventricular (LV) mass index and biomarkers of cardiac damage (cardiac troponin) and stress NT-proBNP (N-terminal pro-B-type natriuretic peptide), elevations in biomarkers were more common as LV mass index increased and among those with concentric or eccentric hypertrophy, but the biomarkers were also frequently elevated in those with no or minimal LV hypertrophy (LVH).
- cTnT and NT-proBNP were useful in risk stratifying patients with moderate/severe LVH and cardiac troponin risk stratified those with no/mild LVH, and in combined models with biomarkers and LVH, the biomarkers were each independently associated with mortality, whereas LVH was not.

### What Are the Clinical Implications?

- As measures of maladaptive remodeling and cardiac injury, cardiac troponin and NT-proBNP predict post-transcatheter aortic valve replacement mortality better than LV mass index, which may have important implications for risk stratification and optimal treatment timing for patients with aortic stenosis.

## Nonstandard Abbreviations and Acronyms

<b>AS</b>	aortic stenosis
<b>cTnT</b>	cardiac troponin
<b>KCCQ</b>	Kansas City Cardiomyopathy Questionnaire
<b>LVH</b>	left ventricular hypertrophy
<b>LVMi</b>	left ventricular mass index
<b>NT-proBNP</b>	N-terminal pro-B-type natriuretic peptide
<b>TAVR</b>	transcatheter aortic valve replacement

worse clinical outcomes was shown among patients with severe AS treated with transcatheter aortic valve replacement (TAVR) in a study with a large number of patients, core laboratory read echocardiograms, and the longest follow-up period for such studies to date.<sup>5</sup> While there was a continuous, linear association between greater LVMi and higher risk, the risk was most clear for those who reached the threshold for moderate or severe LVH. Nonetheless, the risk for these patients was modest.

The adverse prognosis associated with greater LVMi is likely related to the maladaptive remodeling that often accompanies it, characterized by fibrosis, ischemia, capillary rarefaction, and other injurious processes that presage diastolic and systolic dysfunction.<sup>6–8</sup> However, there are also physiologic aspects to LV hypertrophy that presumably are not associated with adverse outcomes. Measurement of LVMi alone, then, does not allow for a distinction between the maladaptive versus adaptive aspects of hypertrophic remodeling in patients with AS. In contrast, the biomarkers cardiac troponin T (cTnT)<sup>9–11</sup> and NT-proBNP (N-terminal pro-B-type natriuretic peptide)<sup>10,12,13</sup> are sensitive and specific circulating measures of cardiac damage and stress that do not reflect adaptive or physiologic cardiac remodeling.<sup>14</sup>

In a multicenter prospective cohort of patients with symptomatic severe AS undergoing TAVR with core laboratory measurement of LVMi, cTnT, and NT-proBNP, we evaluated the relationship between LVH groups (based on degree of increase in LVMi and based on remodeling type) and frequency and severity of biomarker elevations and their respective associations with mortality after TAVR. We hypothesized that the association between LVH and biomarkers would be significant but modest, indicating that they are related but not redundant indicators of myocardial health. Further, we hypothesized that the biomarkers would be more strongly associated with the risk of mortality after TAVR than LVH and would risk stratify both those with minimal and more marked LVH.

## METHODS

The authors will make the data, statistical analyses, and methods available to any researcher for the purposes of replicating the findings herein.

### Study Population

The study population was drawn from a prospective multicenter registry of patients with severe, symptomatic native valve AS who underwent TAVR with a balloon expandable or self-expanding transcatheter heart valve between May 2014 and February 2017. The 11 enrolling centers were all in the United States (listed in Data S1). Severe AS was defined as aortic valve area index  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>, transvalvular mean gradient  $\geq 40$  mm Hg, or peak jet velocity  $\geq 4$  m/sec. For this analysis, we included patients with (1) pre-TAVR echocardiographic images transferred to the coordinating center allowing for centralized measurement of LVMi and (2) measurements of plasma cTnT and NT-proBNP obtained on a pre-TAVR banked blood specimen. Institutional review board approval was obtained at

each enrolling site, and all enrollees provided written, informed consent.

## Biomarkers

Venous blood was collected into EDTA-coated and silicone-coated tubes, centrifuged for 15 minutes at 1500g within 30 minutes of phlebotomy. Plasma aliquots were stored at  $-80^{\circ}\text{C}$  at each local site and at the coordinating center. Biomarkers were collected a mean of  $4\pm 15$  days before TAVR. Frozen samples were shipped on dry ice to the coordinating center where all assays were performed in a single batch on previously unfrozen aliquots. cTnT and NT-proBNP concentrations were measured with electrochemiluminescence immunoassays (Elecsys Troponin T Gen 5 STAT and Elecsys proBNP II, Roche Diagnostics, Basel, Switzerland). Based on assay reference ranges, normal cTnT was defined as  $<14$  and  $<22$  pg/mL for female and male patients, respectively. Normal NT-proBNP was also defined based on assay reference range as  $<125$  and  $<450$  pg/mL for patients aged  $<75$  years and  $\geq 75$  years, respectively.

## Echocardiography

Transthoracic echocardiograms were obtained a mean of  $58\pm 62$  days prior to TAVR. Images were transferred to the coordinating center for centralized review and measurement in a core laboratory. LVMI was calculated with the linear method cube formula using 2D linear measurements from the parasternal long-axis view as recommended by the American Society of Echocardiography (ASE) and was indexed to body surface area.<sup>15–17</sup> Categories of LVH were defined based on sex-specific cut-offs as recommended: no LVH ( $<116$  g/m<sup>2</sup> for male,  $<96$  for female patients); mild LVH ( $\geq 116$  to  $<132$  g/m<sup>2</sup> for male,  $\geq 96$  to  $<109$  g/m<sup>2</sup> for female patients); moderate LVH ( $\geq 132$  to  $\leq 148$  g/m<sup>2</sup> for male,  $\geq 109$  to  $\leq 121$  g/m<sup>2</sup> for female patients); and severe LVH ( $>148$  g/m<sup>2</sup> for male,  $>121$  g/m<sup>2</sup> for female patients).<sup>15</sup> Relative wall thickness (RWT) was calculated as  $\text{RWT} = ((\text{posterior wall thickness} \times 2) / \text{LV end-diastolic dimension})$ . LV remodeling geometry groups—normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy—were also defined based on RWT and sex-based LVMI cut-offs according to ASE criteria.<sup>15</sup>

## Vital Status

Dates of death and dates of last known time alive were obtained through a combination of site report, phone calls, clinic follow-up data in the electronic medical record, or online obituary searches. A final comprehensive assessment for vital status was performed between March and June 2020. Patients were censored at the date last known to be alive.

## Statistical Analysis

For baseline clinical and echocardiographic data, continuous variables were reported as medians with interquartile range, and categorical variables were reported as percent and number of patients. Patients were grouped dichotomously into no/mild and moderate/severe LVH classes based on prior studies associating moderate and severe LVH with increased risk of death and rehospitalization.<sup>5</sup> Patients were also classified as either having “normal” or “elevated” cTnT and NT-proBNP, as described above. Intergroup comparisons were made using Pearson Chi-squared or Kruskal-Wallis test as appropriate. Pairwise tests between groups were performed using the Pearson Chi-squared or Wilcoxon test as indicated.

Survival analysis was conducted to examine the relationships between LVH groups, cTnT, NT-proBNP, and mortality after TAVR. Survival time was calculated from date of TAVR procedure to date of censoring. Kaplan-Meier plots were presented, and intergroup comparisons were made using the log-rank test. In addition, a series of Cox proportional hazard regression models were conducted. Hazard ratio (HR) and 95% CI were calculated to present the associations between risk of all-cause mortality between LVH, cTnT, and NT-proBNP. Adjusted HRs (aHRs) are reported. Covariates in adjusted models were selected a priori based on clinical plausibility and prior studies and included: age, sex, BMI, transvalvular mean gradient, aortic valve area, low flow (stroke volume index  $<35$  mL/m<sup>2</sup>), STS-PROM score, hemoglobin, creatinine clearance, TAVR approach (transfemoral versus non-transfemoral), left ventricular ejection fraction (LVEF), oxygen-dependent lung disease, coronary artery disease, diabetes mellitus, New York Heart Association functional class, mitral regurgitation severity, atrial fibrillation or atrial flutter, and presence of active cancer. Nonlinear terms for continuous covariates were included as restricted cubic spline with 3 knots. There were no missing data for survival, LVMI, cTnT, NT-proBNP, and missingness of adjustment variables was minimal ( $<1\%$ ). In addition, cTnT and NT-proBNP concentrations were log transformed and examined as continuous predictors in Cox models by including restricted cubic spline with 3 knots. Spline plots were also generated with LVMI as a continuous variable, and the data were segregated into those with and without biomarker elevations. Potential interactions between the biomarkers and between the biomarkers and LVH groups were assessed.

Ordinal regressions were conducted to examine the relationships between LVH, cTnT, NT-proBNP and Kansas City Cardiomyopathy Questionnaire (KCCQ) score 30-days post-procedure, and 1-year post-procedure. Baseline KCCQ scores were adjusted for in ordinal regressions. Model-estimated KCCQ score

differences between LVH, cTnT, and NT-proBNP groups at 30-days and 1-year post-procedure were presented.

All statistical computations were performed using R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and associated packages. Statistical significance was defined as a *P*-value <0.05, where all *P*-values were two tailed. Graphics were generated in R or Prism 9 (Graphpad Software, San Diego, CA).

## RESULTS

### Patient Population and Baseline Characteristics

Our multicenter, prospective registry of patients with severe AS who received TAVR included 923 patients. Of these, our analytic cohort included 674 with LVMI measured in the core laboratory and biomarkers measured (Figure S1). Baseline characteristics of included versus excluded patients are shown in Table S1. Baseline characteristics and echocardiographic data are displayed for our analytic cohort in Tables 1 and 2, respectively. The final study population consisted of 44% female patients with median age of 83.5 years and median STS of 4.2. Transfemoral access was used in 88% of procedures and rates of stroke or death prior to discharge were <2%. Median duration of follow-up was 3 years and 279 patients died. Follow-up at 1 year was completed for 564 patients; at 2 years for 439 patients; 3 years for 338 patients; and 4 years for 125 patients. The median (IQR) biomarker concentrations were 25 pg/mL (16–41 pg/mL) for cTnT and 1380 pg/mL (622–3372 pg/mL) for NT-proBNP. Approximately 50% had at least mild hypertrophy and the vast majority had either concentric remodeling (41%) or concentric hypertrophy (41%). Among those with no/mild LVH and moderate/severe LVH, biomarker elevations were associated with higher STS score and reduced kidney function, among other differences (Tables S2 and S3).

### LVH and Biomarker Elevations

Based on sex-specific definitions of LVH, 341 (51%) patients had no LVH (41% of the female, 58% of the male patients), 123 (18%) patients had mild LVH (19% of the female, 18% of the male patients), 88 (13%) patients had moderate LVH (16% of the female, 11% of the male patients), and 122 (18%) patients had severe LVH (24% of the female, 13% of the male patients). When stratified according to LV geometry, 62 (9%) had normal geometry (2% of female, 7% of male patients), 279 (42%) had concentric remodeling (16% of female, 26% of male patients), 278 (41%) had concentric hypertrophy (22% of the female, 19% of the male patients), and 55 (8%) had eccentric hypertrophy (4% of the female, 5% of the male patients).

**Table 1. Baseline Characteristics**

Characteristic	All patients
Patients, No.	674
Age, y	83.5 (77.3–87.8)
Sex, % female (n)	43.8% (295)
Body mass index, kg/m <sup>2</sup>	27.4 (24.0–31.5)
Race, % White (n)	96.4% (650)
STS score	4.2 (3.0–6.4)
Hypertension	92.9% (626)
SBP, mm Hg	130 (118–146)
DBP, mm Hg	68 (61–76)
Diabetes	36.8% (248)
Coronary artery disease	71.1% (481)
Myocardial infarction	22.5% (150)
Coronary revascularization	47.6% (321)
Atrial fibrillation/flutter	41.6% (280)
Creatinine clearance, mL/min	50.8 (36.8–68.2)
Dialysis	3.3% (22)
Heart failure class	
NYHA I	3.6% (23)
NYHA II	25.6% (164)
NYHA III	58.8% (377)
NYHA IV	12.0% (77)
Oxygen-dependent lung disease	9.1% (61)
Active cancer	5.3% (36)
Prior stroke	11.9% (80)
Hemoglobin, g/dL	12.2 (11.0–13.4)
TAVR access, % transfemoral (n)	87.7% (591)
Post-procedural stroke	1.5% (9)
Post-procedural death	1.3% (9)
Plasma cTnT, pg/mL	25.2 (16.2–41.4)
Elevated cTnT	70.9% (478)
Plasma NT-proBNP, pg/mL	1380 (622–3372)
Elevated NT-proBNP	74.2% (500)
Elevated both cTnT and NT-proBNP	57.7% (389)

Data for each characteristic is displayed as either a percentage (number of patients) or as median (IQR<sub>Q1</sub>–IQR<sub>Q3</sub>), where "IQR" is interquartile range.

cTnT indicates cardiac troponin; DBP, diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

The frequency of biomarker elevations in all patients and stratified by sex are shown for LVH groups based on LVMI (Figure 1) and LV remodeling geometry (Figure 2). Absolute concentrations of biomarkers and the distribution of those with 0, 1, and 2 biomarker elevations are shown for these same LVH groups in Figures S2 and S3, respectively. Pair-wise comparisons are reported in Tables S4 and S5. Overall, the frequency of biomarker elevations (individually and combined) and the absolute levels of the biomarkers increase as LVH becomes more severe. With respect to LV remodeling geometry, biomarker elevations are

**Table 2. Baseline Echocardiographic Characteristics**

Characteristic	All patients
LV mass, g	205.1 (164.0–246.0)
LV mass index, g/m <sup>2</sup>	107.4 (90.8–125.9)
LV remodeling type	
Normal geometry	9.2% (62)
Concentric remodeling	41.4% (279)
Concentric hypertrophy	41.2% (278)
Eccentric hypertrophy	8.2% (55)
Left ventricular hypertrophy grade	
No	50.6% (341)
Mild	18.2% (123)
Moderate	13.1% (88)
Severe	18.1% (122)
LV ejection fraction, %	61.4 (52.8–66.1)
LV stroke volume index, mL/m <sup>2</sup>	36.4 (29.3–44.2)
LV end-diastolic diameter, mm	44.2 (40.1–49.5)
LV end-systolic diameter, mm	29.3 (25.2–35.2)
LV relative wall thickness, dimensionless	0.54 (0.45–0.64)
LV septum thickness, mm	12.6 (11.3–14.3)
LV posterior wall dimension, mm	11.9 (10.6–13.4)
LV outflow tract diameter, mm	2.0 (1.9–2.1)
AV area, mm <sup>2</sup>	0.72 (0.59–0.86)
AV area index, mm <sup>2</sup>	0.38 (0.31–0.46)
AV mean gradient, mm Hg	38.3 (31.5–49.2)
Aortic valve peak velocity, m/s	4.1 (3.7–4.5)
Low flow	44.6% (296)
Moderate or severe AR	4.2% (27)
Moderate or severe MR	3.7% (25)

Data for each characteristic is displayed as either a percentage (number of patients) or as median (IQR<sub>Q1</sub>–IQR<sub>Q3</sub>), where “IQR” is interquartile range. AR indicates aortic regurgitation; AV, aortic valve; LV, left ventricular; and MR, mitral regurgitation.

most common in those with concentric hypertrophy or eccentric hypertrophy. These patterns are generally similar in male and female patients. There was a significant, but modest, correlation between log(cTnT) and log(NT-proBNP) levels ( $r=0.49$ ,  $P<0.001$ ) among all patients.

### LVH, Biomarkers, and All-Cause Death

Compared with no/mild LVH with a KM-estimated 5-year mortality of 58.1%, moderate/severe LVH with a KM-estimated 5-year mortality of 69.6% was associated with increased mortality risk, although this was of borderline significance (Figure 3A). After adjustment, compared with no/mild LVH, moderate/severe LVH was independently associated with a higher hazard of mortality (aHR, 1.34; 95% CI 1.01–1.77,  $P=0.043$ ) (Table 3). While the 4-level categorical variable for cardiac remodeling geometry was associated with an

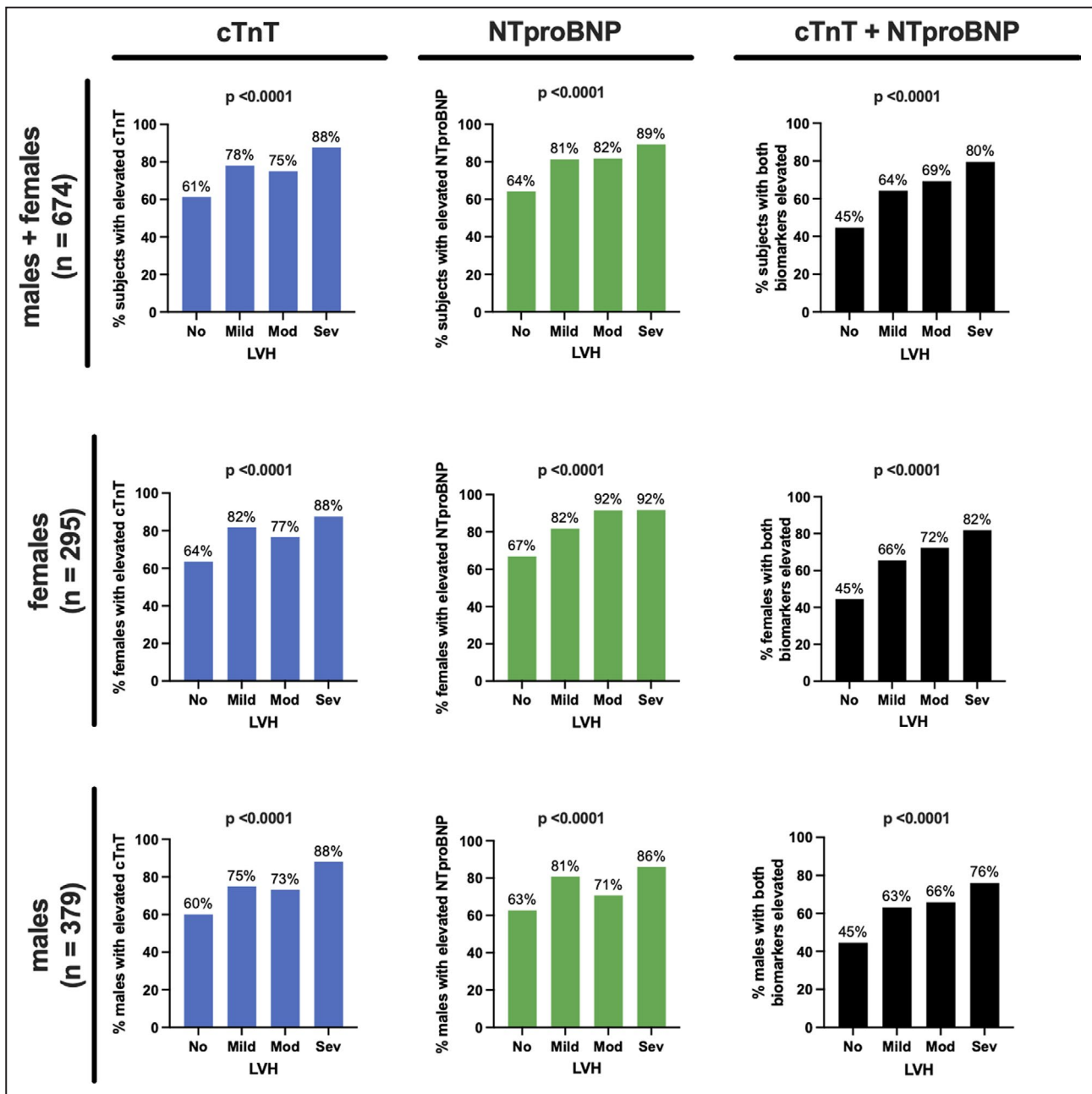
increased risk of mortality (Figure 3B, Table 3), none of the remodeling groups was associated with a significantly increased risk of mortality when compared with normal geometry (Table 3). The associations between elevated cTnT (Figure 3C) and elevated NT-proBNP (Figure 3D) and increased mortality risk were significant in unadjusted and adjusted analyses (Table 3).

We then combined LVH groups and biomarkers in additional analyses. Among those with moderate/severe LVH, compared with those with a normal biomarker level, an increased cTnT or NT-proBNP was associated with increased mortality risk (Table 3 and Figure 4A and 4B). Among those with no/mild LVH, compared with those with a normal biomarker level, an increased cTnT but not an elevated NT-proBNP was associated with increased mortality risk (Table 3 and Figure 4A and 4B). When each biomarker was included in models with LVH, each biomarker was independently associated with increased mortality risk, whereas LVH was not (Table 3). Similarly, in the model with both biomarkers and LVH included, an increased cTnT (aHR 2.08; 95% CI 1.45–3.00,  $P<0.001$ ) and increased NT-proBNP (aHR, 1.46; 95% CI 1.00–2.11,  $P=0.049$ ) were each associated with increased mortality risk, whereas moderate/severe LVH was not ( $P=0.15$ ). There were no significant interactions between each biomarker and LVH category (based on severity or cardiac remodeling geometry) or between cTnT and NT-proBNP.

The associations between continuous LVMi and log-transformed biomarker levels and 5-year survival probability were also evaluated (Figure 5). Irrespective of LVH group, a higher log-transformed cTnT was associated with lower 5-year survival probability until leveling off at a log-transformed cTnT value of  $\sim 4.1$  (corresponding to an absolute level of 60 pg/mL). For those with moderate/severe LVH, the 5-year survival probability was  $\sim 90\%$  for an absolute cTnT value of 4.5 pg/mL and  $\sim 50\%$  for an absolute cTnT value of 22 pg/mL (Figure 5A). Irrespective of LVH group, a higher log-transformed NT-proBNP was linearly associated with a lower probability of 5-year survival. For those with moderate/severe LVH, 5-year survival probability was  $\sim 77\%$  for an absolute NT-proBNP value of 17 versus  $\sim 50\%$  for an absolute NT-proBNP value of 1100 pg/mL (Figure 5B). For both cTnT and NT-proBNP, there was no significant interaction between LVH group and biomarker level. When LVMi was treated as a continuous variable, it was not associated with worsened 5-year survival probability in either those with elevated or normal cTnT or NT-proBNP (Figure 5C and 5D). Likewise, there was no significant interaction between biomarker elevation group and LVMi.

### Quality of Life

After adjusting for baseline KCCQ, there were no significant associations between moderate/severe LVH or



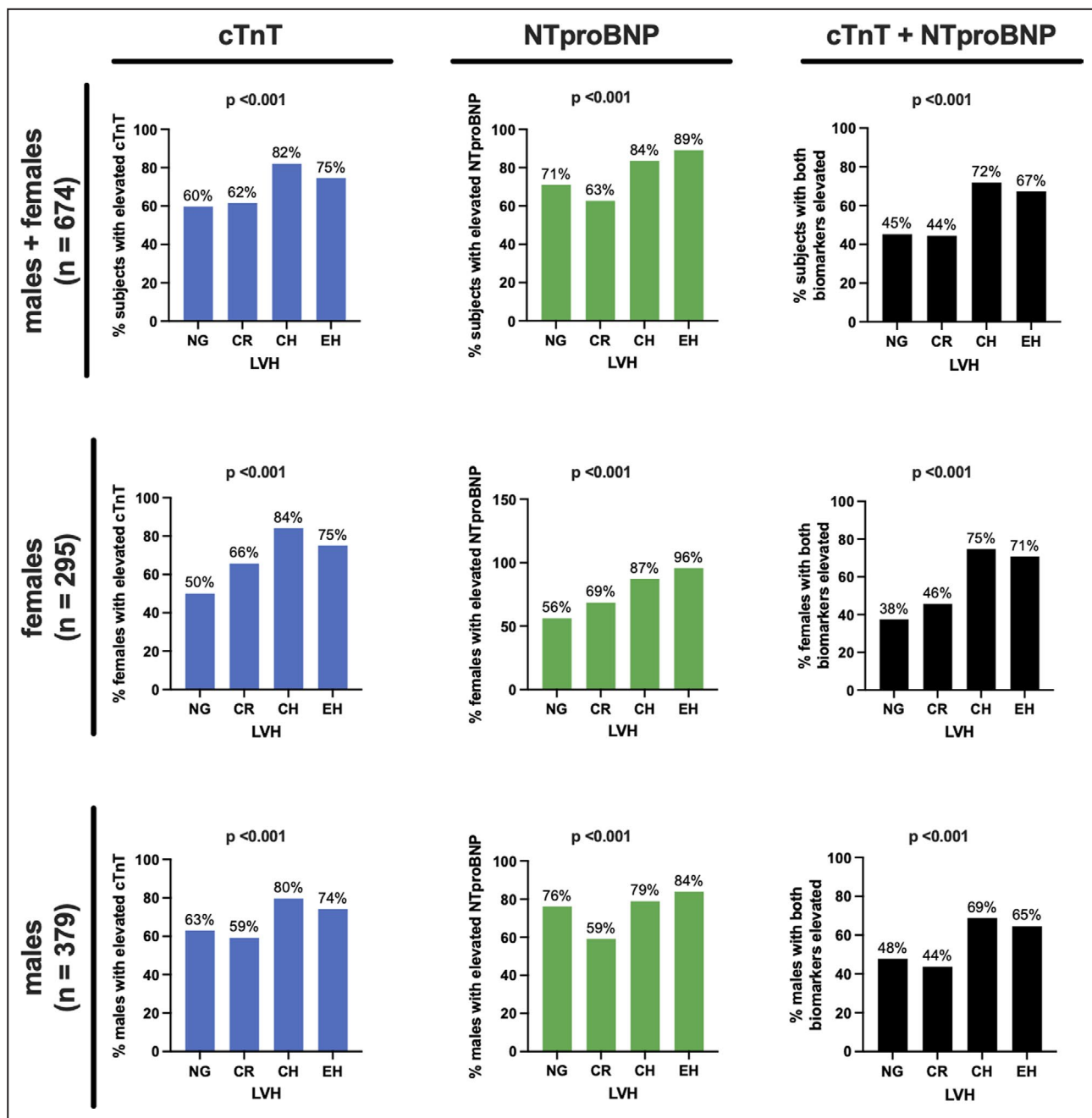
**Figure 1. Sex-stratified distribution of biomarker elevations vs left ventricular hypertrophy (LVH) severity.** The percentage of patients with elevations of cardiac troponin (cTnT), NT-proBNP (N-terminal pro-B-type natriuretic peptide), or both are displayed for each LVH category for female patients, male patients, and female+male patients. P values correspond to the results of the chi square test for trend in proportions. Mod indicates moderate; and Sev, severe.

elevated biomarkers and KCCQ at 30-day or 1-year post-TAVR (Table S6).

## DISCUSSION

In this multicenter prospective registry study of patients with severe, symptomatic AS who underwent TAVR with core-laboratory measurement of LVMi, cTnT, and NT-proBNP, we made several observations. First,

the frequency of biomarker elevations (individually and combined) and the absolute levels of the biomarkers increase as LVH becomes more severe; related to this, biomarker levels are highest in those with concentric hypertrophy or eccentric hypertrophy geometries. Nonetheless, there were many patients with no/mild LVH or normal geometry or concentric remodeling with elevated biomarkers and many with more significant hypertrophy without elevation in biomarkers. Second, our study recapitulates earlier PARTNER trial



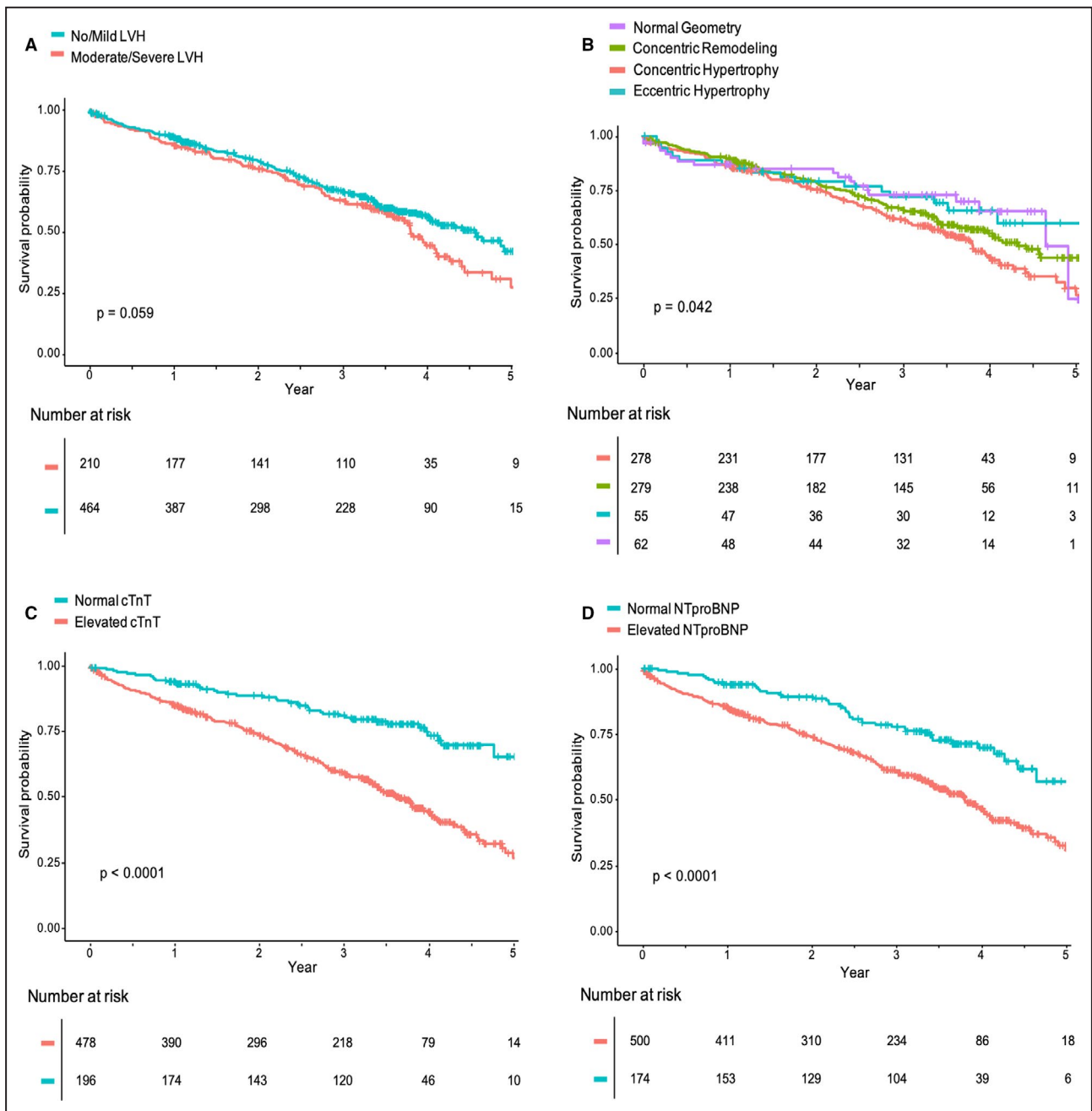
**Figure 2.** Sex-stratified distribution of biomarker elevations vs left ventricular (LV) remodeling geometry.

The percentage of patients with elevations cardiac troponin (cTnT), NT-proBNP (N-terminal pro-B-type natriuretic peptide), or both are displayed for each LV geometry category for female patients, male patients, and female+male patients. *P* values correspond to the results of the chi square test for trend in proportions. CH indicates concentric hypertrophy; CR, concentric remodeling; EH, eccentric hypertrophy; and NG, normal geometry.

data which demonstrated that more marked LVH was associated with an increased hazard of mortality after TAVR.<sup>5</sup> Third, cTnT and NT-proBNP were useful in risk stratifying patients with moderate/severe LVH and cTnT risk stratified those with no/mild LVH. Fourth, in combined models with biomarkers and LVH, the biomarkers were each independently associated with mortality, whereas LVH was not. Collectively, these data indicate

that as more sensitive and specific markers of myocardial damage and stress, cTnT and NT-proBNP predict post-TAVR mortality better than LVMi. They detect patients with no or minimal LVH at increased risk due to myocardial damage and stress from other causes and they identify patients with moderate or severe LVH at lower risk because their hypertrophy is likely more adaptive. These findings may have important





**Figure 3.** Kaplan-Meier estimates of survival probability for (A) no/mild left ventricular hypertrophy (LVH) vs moderate/severe LVH, (B) normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy geometries, (C) elevated cardiac troponin (cTnT) vs normal cTnT, and (D) elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide) vs normal NT-proBNP.

implications for risk stratification and treatment of patients with AS.

Prior studies have separately demonstrated the adverse prognosis associated with significant LVH and biomarkers of cardiac damage and stress (including cTnT and NT-proBNP) in patients with severe AS undergoing aortic valve replacement.<sup>5,18–20</sup> To our knowledge, though, this is the first study that examined the

prognostic significance of LVH and biomarkers together in integrated analyses with LVMi and biomarkers measured in core laboratories. Our finding of an adjusted association between more marked LVH and increased mortality risk after TAVR is consistent with the observation from the PARTNER trial linking increased LVMi to increased 5-year all-cause mortality.<sup>5</sup> Nonetheless, our results also show that the prognostic significance of

**Table 3. Adjusted Cox Proportional Hazard Models for All-Cause Mortality Over 5 Years**

	Adjusted HR (95% CI)	P value
Moderate/severe LVH compared with no/mild LVH ( $X^2=4.1$ , $P=0.043$ )		
Moderate/severe LVH vs no/mild LVH	1.34 (1.01–1.77)	0.043
Patterns of cardiac remodeling ( $X^2=8.55$ , $P=0.036$ )		
1 Normal geometry (referent)	...	...
2 Concentric remodeling	1.35 (0.78–2.34)	0.28
3 Concentric hypertrophy	1.68 (0.98–2.86)	0.059
4 Eccentric hypertrophy	0.85 (0.41–1.75)	0.65
Biomarkers evaluated separately		
cTnT evaluated alone ( $X^2=18.44$ , $P<0.001$ )		
1 Elevated cTnT vs normal cTnT	2.21 (1.54–3.17)	<0.001
NT-proBNP evaluated alone ( $X^2=6.86$ , $P=0.009$ )		
1 Elevated NT-proBNP vs normal NT-proBNP	1.64 (1.13–2.37)	0.009
Biomarkers evaluated (individually) with LVH		
cTnT evaluated with LVH ( $X^2=17.81$ , $P<0.001$ )		
1 Moderate/severe LVH vs no/mild LVH*	1.27 (0.96–1.69)	0.092
2 Elevated cTnT vs normal cTnT*	2.17 (1.51–3.12)	<0.001
Groups according to LVH and cTnT elevation ( $X^2=22.83$ , $P<0.001$ )		
1 No/mild LVH (normal cTnT) (referent)	...	...
2 No/mild LVH (elevated cTnT)	1.92 (1.28–2.88)	0.0016
3 Moderate/severe LVH (normal cTnT)	0.80 (0.35–1.84)	0.60
4 Moderate/severe LVH (elevated cTnT)	2.61 (1.68–4.06)	<0.001
Group 4 vs 3 ( $P=0.004$ ); group 4 vs 2 ( $P=0.04$ )		
NT-proBNP evaluated with LVH ( $X^2=6.67$ , $P<0.036$ )		
1 Moderate/severe LVH vs no/mild LVH*	1.29 (0.97–1.71)	0.075
2 Elevated NT-proBNP vs normal NT-proBNP*	1.59 (1.10–2.31)	0.014
Groups according to LVH and NT-proBNP elevation ( $X^2=11.27$ , $P=0.01$ )		
1 No/mild LVH (normal NT-proBNP) (referent)	...	...
2 No/mild LVH (elevated NT-proBNP)	1.43 (0.95–2.17)	0.090
3 Moderate/severe LVH (normal NT-proBNP)	0.86 (0.37–2.01)	0.72
4 Moderate/severe LVH (elevated NT-proBNP)	1.96 (1.26–3.06)	0.0031
Group 4 vs 3 ( $P=0.046$ ); group 4 vs 2 ( $P=0.04$ )		
Biomarkers evaluated (combined) and LVH		
1 Elevated cTnT vs normal cTnT	2.08 (1.45–3.00)	<0.001
2 Elevated NT-proBNP vs normal NT-proBNP	1.46 (1.00–2.11)	0.049
3 Moderate/severe LVH vs no/mild LVH	1.23 (0.93–1.64)	0.15

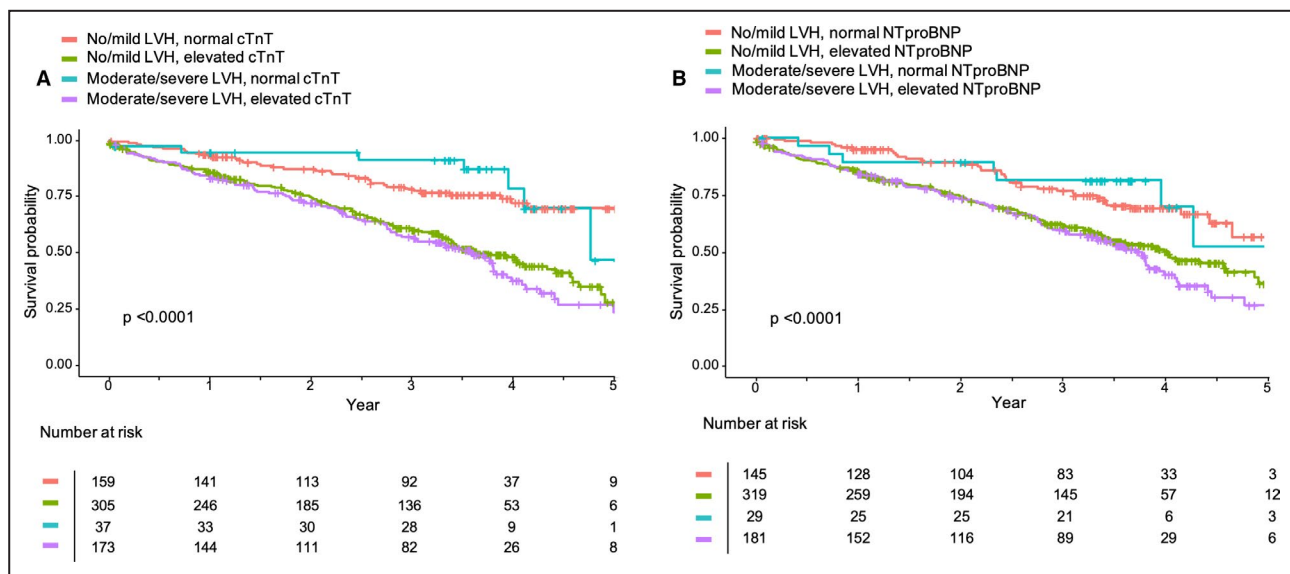
Hazard ratios adjusted for age, sex, Society of Thoracic Surgeons score, body mass index, transvalvular mean gradient, aortic valve area, low flow, transcatheter aortic valve replacement approach, creatinine clearance, diabetes mellitus, coronary artery disease, New York Heart Association functional class, hemoglobin, presence of atrial fibrillation or flutter, oxygen dependence, presence of active cancer, left ventricular ejection fraction and presence of mitral regurgitation.

cTnT indicates cardiac troponin; HR, hazard ratio; LVH, left ventricular hypertrophy; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

\*HRs and P values are based on the models after removing nonsignificant interaction terms.

the biomarkers eclipse that of LVMi alone. Taken as a whole, the risk associated with greater LVH observed in prior studies may be associated with the frequent and severe cardiac damage and stress (indicated by more common and greater elevations in cTnT and NT-proBNP) rather than increased LV mass per se. In non-AS populations, consistent with our findings, others have shown that cTnT and NT-proBNP are useful in risk stratifying individuals with LVH.<sup>14</sup>

We and others have found that greater hypertrophy is associated with more frequent and greater elevations in biomarkers of cardiac damage and stress, but here we also observed frequent elevations in these markers among those without significant LVH.<sup>9</sup> Accordingly, a complex biology is at work contributing to cardiac damage and stress in the pressure overloaded heart; the mechanisms include hypertrophy but also extend beyond it to include other processes. Prior



**Figure 4.** Kaplan-Meier estimates of survival probability in those with moderate/severe vs no/mild left ventricular hypertrophy (LVH) in (A) elevated vs normal cardiac troponin (cTnT) and (B) elevated vs normal NT-proBNP (N-terminal pro-B-type natriuretic peptide).

studies have demonstrated that these mechanisms include fibrosis (diffuse and replacement), inflammation, autophagy and myocyte degeneration, and capillary rarefaction and impaired myocardial flow reserve contributing to ischemia, among others.<sup>8,21–26</sup> Overall, these processes may tend to track with the amount of hypertrophy, but they are not completely overlapping and inter-changeable pathobiologies. The biomarkers of cardiac damage and stress are a more sensitive and specific barometer for all these maladaptive responses to pressure overload, whereas LVMI alone is relatively imprecise.<sup>9,10,23</sup> While some of the processes and pathways that contribute to cardiac damage and stress in the pressure overloaded heart are known, more work is needed to elucidate these and other mechanisms to identify therapeutic targets. Collectively, our findings point to the need to explore the molecular underpinnings of the response to pressure overload from AS to better understand patient risk and potential targets for intervention. These studies ought to include and integrate gross/macrosopic cardiac phenotypes (e.g., LVH, systolic/diastolic function), tissue-level phenotypes (e.g., diffuse and replacement fibrosis), and molecular pathway analysis underlying these cardiac phenotypes.

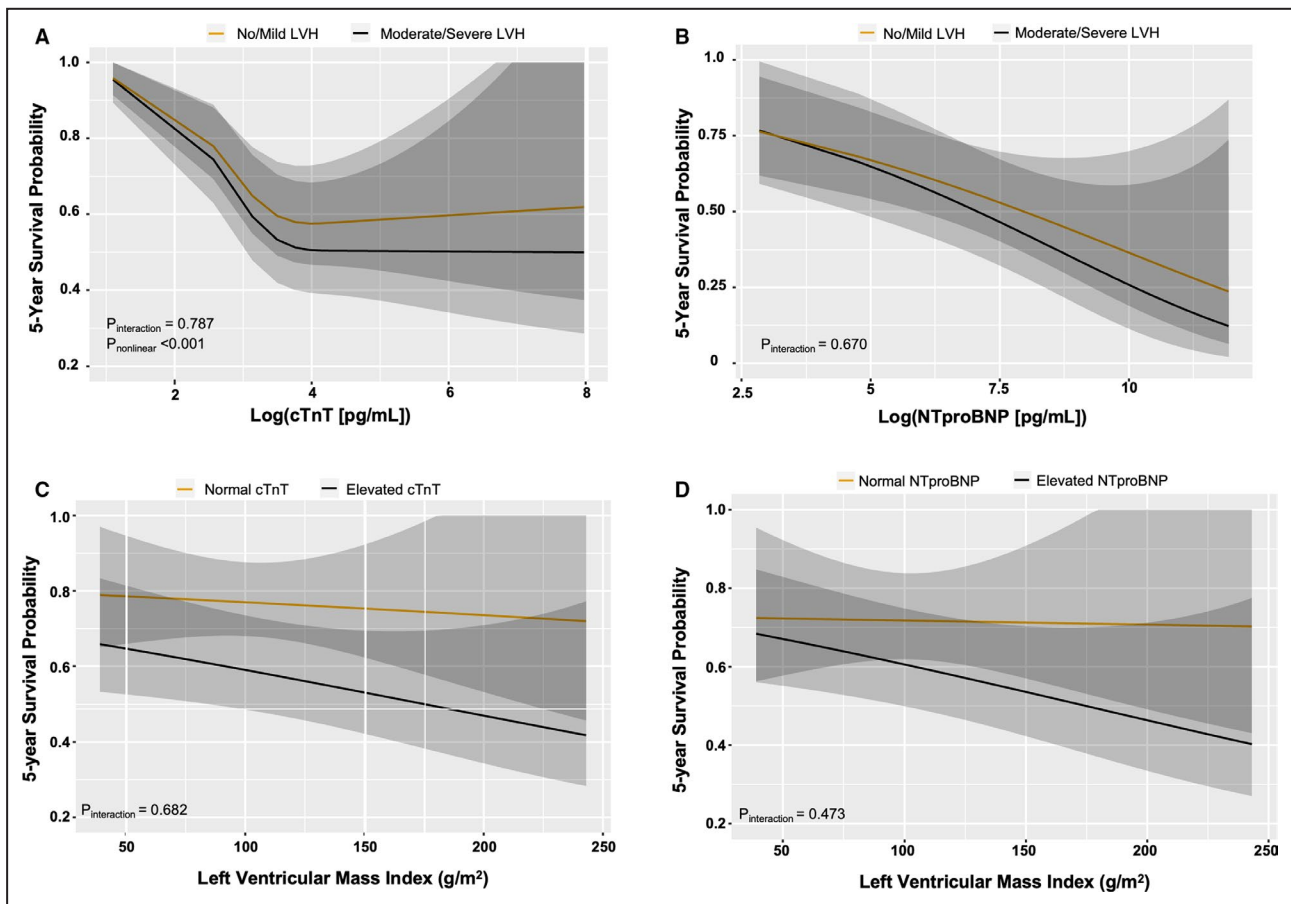
For personalized risk stratification for post-AVR outcomes, the presence and severity of LVH alone is insufficient as LVH is a heterogeneous process. Better than an isolated measure of LVMI, biomarkers of cardiac damage and stress precisely, cheaply, and reliably identify a maladaptive response to pressure overload and risk stratify patients with severe

AS with and without LVH. To mitigate risk from cardiac damage and stress, earlier AVR to unload the heart before cardiac injury develops or becomes more pronounced may improve post-AVR outcomes. Relevant to this, biomarker-based strategies employing cTnT and NT-proBNP have already been proposed to guide treatment decisions for diabetes and hypertension.<sup>27,28</sup> Furthermore, adjunctive medical therapy targeting pathobiological processes that result in cardiac damage and stress—including hypertrophic remodeling but also fibrosis, inflammation, etc.—may protect the heart in the face of pressure overload during progressive AS and yield better post-AVR outcomes.

There are several limitations to consider when interpreting these findings. We may have been underpowered to detect a synergistic relationship between LVH and biomarkers with respect to post-TAVR risk. Our cohort lacks follow-up echocardiographic data to evaluate regression of LVH based on biomarker levels. Data on rehospitalization post-TAVR was not collected. Patients were not systematically assessed for cardiac amyloid and the cohort was not very racially diverse. Finally, all patients had symptomatic severe AS, so any extrapolation to patients without symptoms and potential implications for optimal timing of AVR require additional study.

## CONCLUSIONS

Among patients with severe symptomatic AS undergoing TAVR, elevations in biomarkers of cardiac



**Figure 5. Relationship between 5-year survival and biomarker concentration.**

Shown are the 5-year survival probability with respect to (A) log-transformed cTnT stratified by moderate/severe left ventricular hypertrophy (LVH) and no/mild LVH, where  $P_{\text{interaction}}$  is defined as  $p([\text{cTnT}] * \text{LVMi})$  and (B) log-transformed NT-proBNP (N-terminal pro-B-type natriuretic peptide) stratified by moderate/severe LVH and no/mild LVH, where  $P_{\text{interaction}}$  is defined as  $p([\text{NT-proBNP}] * \text{LVMi})$ . LVMi is a dichotomous variable in both (A and B). 5-year survival probability with respect to continuous LVMi as subdivided by (C) normal cTnT and elevated cTnT level and (D) normal NT-proBNP and elevated NT-proBNP level.  $P_{\text{interaction}}$  is defined as  $p(\text{LVMi} * [\text{cTnT}])$  and  $p(\text{LVMi} * [\text{NT-proBNP}])$  for (C and D), respectively. cTnT indicates cardiac troponin; and LVMi, left ventricular mass index.

damage (cTnT) and stress (NT-proBNP) were more common as LVMi increased and among those with concentric or eccentric hypertrophy, but the biomarkers were also frequently elevated in those with no or minimal LVH. cTnT and NT-proBNP were useful in risk stratifying individuals with and without LVH. In combined models, each of the biomarkers was independently associated with mortality after TAVR, whereas LVH was not. Collectively, these data indicate that as more sensitive and specific markers of myocardial damage and stress, cTnT and NT-proBNP predict post-TAVR mortality better than LVMi. These results should stimulate additional research on mechanisms underlying cardiac damage and stress in the pressure overloaded heart to identify novel therapeutic targets and they inform the risk stratification of patients with severe AS with potential implications for optimizing timing of AVR in asymptomatic patients.

## ARTICLE INFORMATION

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## Supplemental Material

Data S1

Tables S1–S6

Figures S1–S3

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## **Supplemental Material**

**Data S1. List of Enrolling Centers**

Barnes-Jewish Hospital, St. Louis, MO

Cleveland Clinic Foundation, Cleveland, OH

Dartmouth-Hitchcock Medical Center, Lebanon, NH

Intermountain Heart Institute, Murray, UT

Massachusetts General Hospital, Boston, MA

Morristown Medical Center, Morristown, NJ

Stanford Medical Center, Palo Alto, CA

University of Texas Southwestern Medical Center, Dallas, TX

University of Utah Hospital, Salt Lake City, UT

Vanderbilt University Medical Center, Nashville, TN



**Table S1. Baseline characteristics in included versus excluded patients**

Characteristic	Excluded from Study	Included in Study	All Patients	p-value
Patients [N]	249	674	923	
Age [y]	81.7 (74.7 – 86.6)	83.5 (77.3 – 87.8)	83.0 (76.6 – 87.6)	0.006 <sup>1</sup>
Sex [% female (n)]	41.4% (103)	43.8% (295)	43.1% (398)	0.513 <sup>2</sup>
Body mass index [kg / m <sup>2</sup> ]	27.7 (24.5 – 32.6)	27.4 (24.0 – 31.5)	27.5 (24.2 – 31.7)	0.677 <sup>1</sup>
Race [% non-white (n)]	3.6% (5)	3.5% (24)	3.6% (33)	0.47 <sup>2</sup>
STS score	4.1 (2.5 – 6.6)	4.2 (3.0 – 6.4)	4.2 (2.8 – 6.4)	0.085 <sup>1</sup>
Hypertension	92.3% (229)	92.9% (626)	92.7% (855)	0.78 <sup>2</sup>
SBP [mmHg]	131 (118 – 145)	130 (118 – 146)	131 (118 – 146)	0.76 <sup>1</sup>
DBP [mmHg]	69 (60 – 77)	68 (61 – 76)	68 (60 – 76)	0.77 <sup>1</sup>
Diabetes	43.8% (109)	36.8% (248)	38.7% (357)	0.55 <sup>2</sup>
Coronary Artery Disease	61.0% (152)	71.4% (481)	68.6% (633)	0.003 <sup>2</sup>
Myocardial infarction	23.2% (57)	22.5% (150)	22.7% (207)	0.836 <sup>2</sup>
Coronary Revascularization	27.6% (68)	32.6% (219)	31.3% (287)	0.152 <sup>2</sup>
Atrial fibrillation / flutter	36.7% (91)	41.6% (280)	40.3% (371)	0.178 <sup>2</sup>
Creatinine clearance [mL / min]	55.3 (38.7 – 74.4)	50.8 (36.8 – 68.2)	52.1 (37.3 – 70.0)	0.03 <sup>1</sup>
Dialysis	4.0% (10)	3.3% (22)	3.5% (32)	0.579 <sup>2</sup>
Heart failure class				0.225 <sup>2</sup>
NYHA I	2.1% (5)	3.6% (23)	3.2% (28)	
NYHA II	20.5% (48)	25.6% (164)	24.2% (212)	
NYHA III	65.8% (154)	58.8% (377)	60.7% (531)	
NYHA IV	11.5% (27)	12.0% (77)	11.9% (104)	
Oxygen-dependent lung disease	13.7% (34)	9.1% (61)	10.3% (95)	0.041 <sup>2</sup>
Active cancer	5.6% (14)	5.3% (36)	5.4% (50)	0.867 <sup>2</sup>
Prior stroke	10.4% (26)	11.9% (80)	11.5% (106)	0.12 <sup>2</sup>
Hemoglobin [g / dL]	12.3 (11.0 – 13.7)	12.2 (11.0 – 13.4)	12.3 (11.0 – 13.5)	0.222 <sup>1</sup>
TAVR access [% transfemoral (n)]	90.8% (226)	87.7% (591)	88.5% (817)	0.193 <sup>2</sup>
Post-procedural stroke	3.9% (9)	1.5% (9)	2.2% (18)	0.036 <sup>2</sup>
Post-procedural death	0% (0)	3.1% (3)	2.6% (3)	0.465 <sup>2</sup>
Plasma ntProBNP [pg / mL]*	1064 (521 – 2512)	1380 (622 – 3372)	1292 (602 – 3274)	0.069 <sup>1</sup>
Plasma cTnT [pg / mL]*	23.0 (13.7 – 40.7)	25.2 (16.2 – 41.4)	25.1 (15.8 – 41.3)	0.366 <sup>1</sup>
LV mass index [g / m <sup>2</sup> ]*	117.1 (94.3 – 130.9)	107.4 (90.8 – 125.9)	107.9 (91.3 – 127.2)	0.064 <sup>1</sup>
LV mass [g]	213.6 (177.8 – 250.3)	205.1 (164.0 – 246.0)	206.1 (165.8 – 246.2)	0.23 <sup>1</sup>
LV ejection fraction [%]	60.0 (50.0 – 66.6)	61.4 (52.8 – 66.1)	61.2 (52.1 – 66.2)	0.44 <sup>1</sup>
LV stroke volume index [mL / m <sup>2</sup> ]	35.6 (28.5 – 43.9)	36.4 (29.3 – 44.2)	36.4 (29.1 – 44.1)	0.469 <sup>1</sup>
LV end-diastolic diameter [mm]	23.5 (20.8 – 25.9)	23.4 (20.8 – 26.2)	23.4 (20.8 – 26.2)	0.86 <sup>1</sup>
LV end-systolic diameter [mm]	29.6 (24.0 – 36.1)	29.3 (25.2 – 35.2)	29.3 (25.0 – 35.4)	0.823 <sup>1</sup>
LV relative wall thickness [dimensionless]	0.57 (0.47 – 0.69)	0.54 (0.45 – 0.64)	0.54 (0.45 – 0.64)	0.067 <sup>1</sup>
LV septum thickness [mm]	13.5 (11.9 – 15.8)	12.6 (11.3 – 14.3)	12.7 (11.4 – 14.4)	<0.001 <sup>1</sup>
LV posterior wall dimension [mm]	12.4 (10.9 – 14.0)	11.9 (10.6 – 13.4)	11.9 (10.6 – 13.5)	0.101 <sup>1</sup>
LV outflow tract diameter [mm]	1.98 (1.88 – 2.12)	1.99 (1.87 – 2.11)	1.99 (1.87 – 2.12)	0.605 <sup>1</sup>
AV area [mm <sup>2</sup> ]	0.70 (0.60 – 0.85)	0.72 (0.59 – 0.86)	0.72 (0.59 – 0.86)	0.891 <sup>1</sup>
AV area index [mm <sup>2</sup> ]	0.37 (0.30 – 0.44)	0.38 (0.31 – 0.46)	0.38 (0.31 – 0.45)	0.411 <sup>1</sup>
AV mean gradient [mmHg]	40.0 (31.6 – 50.1)	38.3 (31.5 – 49.2)	38.6 (31.5 – 49.3)	0.358 <sup>1</sup>
Aortic valve peak velocity [m / s]	4.1 (3.7 – 4.6)	4.1 (3.7 – 4.5)	4.1 (3.7 – 4.6)	0.661 <sup>1</sup>

<b>Low flow</b>	48.7% (56)	44.6% (296)	45.2% (352)	0.421 <sup>2</sup>
<b>Moderate or severe AR</b>	12.2% (27)	9.2% (62)	9.9% (90)	<0.001 <sup>2</sup>
<b>Moderate or severe MR</b>	13.5% (30)	14.0% (94)	13.8% (124)	<0.001 <sup>2</sup>

Data for each characteristic is displayed as either a percentage (number of patients) or as median (IQR<sub>Q1</sub> – IQR<sub>Q3</sub>). Statistical tests used were <sup>1</sup>Wilcoxon test or <sup>2</sup>Pearson test. LV = left ventricular, AV = aortic valve, AR = aortic regurgitation, MR = mitral regurgitation. \*To be included in the analytic cohort, subjects needed to have NTproBNP, cTnT, *and* LV mass index measured at baseline. Some subjects excluded had one or more of those variables measured: NTproBNP (N=148), cTnT (N=148), and LV mass index (N=86).

**Table S2. Baseline characteristics in the no/mild LVH group with respect to normal versus elevated biomarkers**

Characteristic	No/Mild LVH & Normal cTnT	No/Mild LVH & Elevated cTnT	No/Mild LVH & Normal NTproBNP	No/Mild LVH & Elevated NTproBNP	p-value*	p-value <sup>†</sup>
Patients [N]	159	305	145	319		
Age [y]	82.2 (75.7 – 87.2)	84.0 (77.8 – 87.9)	82.0 (78.1 – 87.2)	84.0 (76.6 – 87.9)	0.083 <sup>1</sup>	0.28 <sup>1</sup>
Sex [% female (n)]	34.0% (54)	40.0% (122)	34.5% (60)	39.5% (126)	0.20 <sup>2</sup>	0.30 <sup>2</sup>
Body mass index [kg / m <sup>2</sup> ]	27.1 (23.9 – 31.6)	27.8 (24.6 – 31.2)	28.0 (25.1 – 31.7)	27.3 (23.8 – 30.8)	0.34 <sup>1</sup>	0.19 <sup>1</sup>
Race [% non-white (n)]	1.3% (2)	3.9% (12)	4.1% (6)	2.5% (84)	0.099 <sup>2</sup>	0.47 <sup>2</sup>
STS score	3.3 (2.2 – 4.7)	4.4 (3.1 – 6.5)	3.3 (2.4 – 4.7)	4.3 (3.0 – 6.4)	<0.001 <sup>1</sup>	<0.001 <sup>1</sup>
Hypertension	90.6% (144)	94.8% (289)	91.0% (132)	94.4% (301)	0.086 <sup>2</sup>	0.18 <sup>2</sup>
SBP [mmHg]	133 (121 – 147)	130 (118 – 148)	130 (120 – 146)	130 (118 – 148)	0.29 <sup>1</sup>	0.40 <sup>1</sup>
DBP [mmHg]	69 (60 – 76)	68 (61 – 75)	67 (62 – 73)	69 (60 – 76)	0.71 <sup>1</sup>	0.52 <sup>1</sup>
Diabetes	26.4% (42)	43.0% (131)	35.2% (51)	38.2% (122)	<0.001 <sup>2</sup>	0.53 <sup>2</sup>
Coronary artery disease	67.9% (108)	74.4% (227)	75.9% (110)	70.5% (225)	0.138 <sup>2</sup>	0.235 <sup>2</sup>
Myocardial infarction	15.8% (25)	26.2% (79)	18.6% (27)	24.4% (77)	0.012 <sup>2</sup>	0.17 <sup>2</sup>
Coronary Revascularization	49.1% (78)	26.2% (79)	53.1% (77)	47.6% (152)	0.93 <sup>2</sup>	0.28 <sup>2</sup>
Atrial fibrillation / flutter	36.5% (58)	45.4% (138)	22.8% (33)	51.3% (163)	0.065 <sup>2</sup>	<0.001 <sup>2</sup>
Creatinine clearance [mL / min]	61.2 (47.3 – 77.5)	47.9 (35.0 – 61.4)	55.5 (45.2 – 72.4)	50.8 (36.1 – 68.0)	0.21 <sup>1</sup>	0.004 <sup>1</sup>
Dialysis	1.3% (2)	3.6% (11)	0.0% (0)	4.1% (13)	0.15 <sup>2</sup>	0.014 <sup>2</sup>
Heart failure class					0.013 <sup>2</sup>	0.005 <sup>2</sup>
NYHA I	3.9% (6)	3.8% (11)	6.7% (9)	2.6% (8)		
NYHA II	29.6% (45)	24.3% (70)	32.8% (44)	23.2% (71)		
NYHA III	62.5% (95)	58.0% (167)	55.2% (74)	61.4% (188)		
NYHA IV	3.9% (6)	13.9% (40)	5.2% (7)	12.7% (39)		
Oxygen-dependent lung disease	5.0% (8)	12.1% (37)	11.0% (16)	9.1% (29)	0.014 <sup>2</sup>	0.51 <sup>2</sup>
Active cancer	8.2% (13)	4.6% (14)	7.6% (11)	5.0% (16)	0.12 <sup>2</sup>	0.27 <sup>2</sup>
Prior stroke	11.4% (18)	10.9% (33)	7.6% (11)	12.6% (40)	0.86 <sup>2</sup>	0.12 <sup>2</sup>
Hemoglobin [g / dL]	12.8 (11.8 – 14.0)	12.0 (10.8 – 13.2)	12.9 (11.7 – 14.0)	12.1 (10.9 – 13.2)	<0.001 <sup>1</sup>	<0.001 <sup>1</sup>
TAVR access [% transfemoral (n)]	91.8% (146)	87.2% (266)	93.1% (135)	86.8% (277)	0.14 <sup>2</sup>	0.047 <sup>2</sup>
Post-procedural stroke	1.4 (2)	2.3 (6)	2.2 (3)	1.8 (5)	0.262	0.072
Post-procedural death	0.6 (1)	2.0 (6)	0.0 (0)	2.2 (7)	--	--
Plasma ntProBNP [pg / mL]	767 (306 – 1338)	1365 (630 – 3032)	344 (206 – 504)	1721 (1036 – 3354)	<0.001 <sup>1</sup>	<0.001 <sup>1</sup>
Elevated NTproBNP	55.3 ( 88)	75.7 (231)	--	--	<0.001	--
Plasma cTnT [pg / mL]	12.6 (9.0 – 16.6)	33.2 (23.7 – 52.5)	19.1 (12.6 – 27.3)	26.1 (16.2 – 48.2)	<0.001 <sup>1</sup>	<0.001 <sup>1</sup>
Elevated cTnT	--	--	51.0 ( 74)	72.4 (231)	--	<0.001
LV mass index [g / m <sup>2</sup> ]	95.1 (79.5 – 106.6)	99.8 (84.7 – 110.3)	94.2 (78.3 – 105.6)	99.8 (86.2 – 110.4)	0.015 <sup>1</sup>	0.001 <sup>1</sup>
LV mass [g]	176.0 (146.4 – 218.0)	185.8 (156.7 – 221.7)	170.8 (147.4 – 216.1)	186.9 (156.8 – 221.5)	0.044 <sup>1</sup>	0.008 <sup>1</sup>
LV remodeling type					0.004	0.002
Normal Geometry	5.7 (25)	12.1 (37)	12.4 (18)	13.8 (44)		
Concentric remodeling	67.3 (107)	56.4 (172)	71.7 (104)	54.9 (175)		
Concentric hypertrophy	12.6 (20)	27.2 (83)	14.5 (21)	25.7 (82)		
Eccentric hypertrophy	4.4 (7)	4.3 (13)	1.4 (2)	5.6 (18)		
LV ejection fraction [%]	62.6 (58.6 – 67.3)	61.6 (54.3 – 66.4)	64.1 (59.8 – 67.6)	61.1 (51.4 – 66.3)	0.030 <sup>1</sup>	<0.001 <sup>1</sup>
LV stroke volume index [mL / m <sup>2</sup> ]	37.1 (29.3 – 45.5)	34.8 (28.6 – 41.9)	40.3 (33.3 – 45.8)	33.4 (27.8 – 39.7)	0.097 <sup>1</sup>	<0.001 <sup>1</sup>
LV end-diastolic diameter [mm]	42.6 (38.6 – 47.4)	43.0 (38.5 – 47.9)	42.3 (38.3 – 46.0)	43.4 (38.8 – 48.4)	0.60 <sup>1</sup>	0.033 <sup>1</sup>
LV end-systolic diameter [mm]	27.9 (24.0 – 31.8)	28.2 (24.4 – 33.8)	26.7 (23.5 – 30.3)	28.8 (24.8 – 34.7)	0.37 <sup>1</sup>	<0.001 <sup>1</sup>

<b>LV relative wall thickness [dimensionless]</b>	0.53 (0.45 – 0.62)	0.55 (0.45 – 0.65)	0.53 (0.45 – 0.64)	0.54 (0.45 – 0.64)	0.26 <sup>1</sup>	0.82 <sup>1</sup>
<b>LV septum thickness [mm]</b>	12.2 (10.6 – 13.5)	12.3 (11.2 – 13.7)	12.4 (11.2 – 13.4)	12.2 (11.0 – 13.8)	0.27 <sup>1</sup>	0.87 <sup>1</sup>
<b>LV posterior wall dimension [mm]</b>	11.3 (10.1 – 12.4)	11.6 (10.5 – 12.9)	11.3 (10.1 – 12.4)	11.5 (10.4 – 12.9)	0.025 <sup>1</sup>	0.069 <sup>1</sup>
<b>LV outflow tract diameter [mm]</b>	2.0 (1.9 – 2.1)	2.0 (1.9 – 2.1)	2.0 (1.9 – 2.1)	2.0 (1.9 – 2.1)	0.75 <sup>1</sup>	0.046 <sup>1</sup>
<b>AV area [mm<sup>2</sup>]</b>	0.74 (0.62 – 0.85)	0.71 (0.58 – 0.86)	0.79 (0.69 – 0.90)	0.69 (0.55 – 0.82)	0.31 <sup>1</sup>	<0.001 <sup>1</sup>
<b>AV area index [mm<sup>2</sup>]</b>	0.38 (0.31 – 0.45)	0.37 (0.31 – 0.45)	0.42 (0.35 – 0.47)	0.36 (0.29 – 0.43)	0.32 <sup>1</sup>	<0.001 <sup>1</sup>
<b>AV mean gradient [mmHg]</b>	37.8 (32.3 – 45.2)	37.6 (29.9 – 48.5)	38.8 (32.3 – 44.9)	37.6 (29.5 – 49.2)	0.78 <sup>1</sup>	0.78 <sup>1</sup>
<b>Aortic valve peak velocity [m / s]</b>	4.0 (3.7 – 4.4)	4.0 (3.6 – 4.5)	4.1 (3.7 – 4.4)	4.0 (3.6 – 4.5)	0.81 <sup>1</sup>	0.42 <sup>1</sup>
<b>Low flow</b>	47.1% (74)	50.3% (150)	32.2% (46)	57.1% (178)	0.516 <sup>2</sup>	<0.001 <sup>2</sup>
<b>Moderate or severe AR</b>	4.7% (7)	4.8% (14)	4.4% (6)	4.9% (15)	0.97 <sup>2</sup>	0.89 <sup>2</sup>
<b>Moderate or severe MR</b>	0.6% (1)	2.6% (8)	0.0% (0)	2.8% (9)	0.14 <sup>2</sup>	0.043 <sup>2</sup>

Data for each characteristic is displayed as either a percentage (number of patients) or as median (IQR<sub>Q1</sub> – IQR<sub>Q3</sub>). Statistical tests used were <sup>1</sup>Wilcoxon test or <sup>2</sup>Pearson test. P-values represent T-tests between the specified groups: no/mild LVH \*(normal cTnT vs elevated cTnT) and †(normal NTproBNP vs elevated NTproBNP). *N* is the number of non-missing values. LV = left ventricular, AV = aortic valve, AR = aortic regurgitation, MR = mitral regurgitation.

**Table S3. Baseline characteristics in the moderate/severe LVH group with respect to normal versus elevated biomarkers**

Characteristic	Mod/Sev LVH & Normal cTnT	Mod/Sev LVH & Elevated cTnT	Mod/Sev LVH & Normal NTproBNP	Mod/Sev LVH & Elevated NTproBNP	p-value*	p-value <sup>‡</sup>
Patients [N]	37	173	29	181		
Age [y]	81.1 (74.3 – 85.9)	84.4 (78.7 – 88.9)	84.2 (80.0 – 86.3)	83.6 (76.9 – 88.8)	0.015 <sup>1</sup>	0.84 <sup>1</sup>
Sex [% female (n)]	54.1% (20)	57.2% (99)	34.5% (10)	60.2% (109)	0.72 <sup>2</sup>	0.009 <sup>2</sup>
Body mass index [kg / m <sup>2</sup> ]	29.2 (25.7 – 33.1)	26.0 (22.9 – 31.7)	31.7 (29.0 – 35.4)	25.9 (22.8 – 30.8)	0.046 <sup>1</sup>	<0.001 <sup>1</sup>
Race [% non-white (n)]	0% (0)	94.2% (10)	3.4% (1)	5.0% (9)	0.33 <sup>2</sup>	0.84 <sup>2</sup>
STS score	3.7 (2.7 – 4.9)	5.4 (3.7 – 7.7)	4.1 (3.1 – 5.9)	5.1 (3.6 – 7.5)	<0.001 <sup>1</sup>	0.034 <sup>1</sup>
Hypertension	89.2% (33)	92.5% (160)	100% (29)	90.6% (164)	0.51 <sup>2</sup>	0.085 <sup>2</sup>
SBP [mmHg]	135 (125 – 154)	132 (118 – 144)	133 (123 – 142)	132.0 (118.0 – 146.0)	0.16 <sup>1</sup>	0.83 <sup>1</sup>
DBP [mmHg]	70 (64 – 78)	68 (60 – 75)	67 (61 – 77)	68 (61 – 76)	0.14 <sup>1</sup>	0.85 <sup>1</sup>
Diabetes	35.1% (13)	36.0% (62)	31.0% (9)	36.7% (66)	0.92 <sup>2</sup>	0.22 <sup>2</sup>
Coronary artery disease	64.9% (24)	70.5% (122)	79.3% (23)	68.0% (123)	0.50 <sup>2</sup>	0.56 <sup>2</sup>
Myocardial infarction	11.1% (4)	24.7% (42)	13.8% (4)	23.7% (42)	0.075 <sup>2</sup>	0.23 <sup>2</sup>
Coronary Revascularization	43.2% (16)	43.9% (76)	58.6% (17)	41.4% (75)	0.94 <sup>2</sup>	0.083 <sup>2</sup>
Atrial fibrillation / flutter	37.8% (14)	40.5% (70)	24.1% (7)	42.5% (77)	0.77 <sup>2</sup>	0.06 <sup>2</sup>
Creatinine clearance [mL / min]	61.2 (45.0 – 71.7)	43.7 (29.7 – 59.1)	58.8 (39.7 – 70.7)	44.3 (31.4 – 60.5)	<0.001 <sup>1</sup>	0.004 <sup>1</sup>
Dialysis	2.7% (1)	4.6% (8)	3.4% (1)	4.4% (8)	0.60 <sup>2</sup>	0.81 <sup>2</sup>
Heart failure class					0.88 <sup>2</sup>	0.082 <sup>2</sup>
NYHA I	2.8% (1)	3.0% (5)	3.6% (1)	2.9% (5)		
NYHA II	25.0% (9)	24.2% (40)	42.9% (12)	21.4% (37)		
NYHA III	61.1% (22)	56.4% (93)	46.4% (13)	59.0% (102)		
NYHA IV	11.1% (4)	16.4% (27)	7.1% (2)	16.8% (29)		
Oxygen-dependent lung disease	2.7% (1)	8.7% (15)	6.9% (2)	7.7% (14)	0.21 <sup>2</sup>	0.87 <sup>2</sup>
Active cancer	8.1% (3)	3.5% (6)	13.8% (4)	2.8% (5)	0.21 <sup>2</sup>	0.006 <sup>2</sup>
Prior stroke	16.2% (6)	13.3% (23)	17.2% (5)	13.3% (24)	0.64 <sup>2</sup>	0.56 <sup>2</sup>
Hemoglobin [g / dL]	11.8 (10.3 – 13.0)	12.1 (10.8 – 13.1)	12.0 (11.3 – 13.3)	12.1 (10.5 – 13.1)	0.59 <sup>1</sup>	0.46 <sup>1</sup>
TAVR access [% transfemoral (n)]	89.2% (33)	84.4% (146)	89.7% (26)	84.5% (153)	0.46 <sup>2</sup>	0.47 <sup>2</sup>
Post-procedural stroke	0.000 (0)	0.007 (1)	0.000 (0)	0.006 (1)	0.511	0.569
Post-procedural death	0.000 (0)	0.012 (2)	0.000 (0)	0.011 (2)		
Plasma ntProBNP [pg / mL]	715 (489 – 1514)	3374 (1686 – 7902)	474 (329 – 622)	3368 (1779 – 7706)	<0.001 <sup>1</sup>	<0.001 <sup>1</sup>
Elevated NTproBNP	62.2 (23)	91.3 (158)			<0.001	
Plasma cTnT [pg / mL]	11.7 (9.6 – 15.4)	33.1 (26.0 – 47.4)	20.4 (14.4 – 31.0)	31.5 (22.1 – 45.5)	<0.001 <sup>1</sup>	<0.001 <sup>1</sup>
Elevated cTnT	--	--	51.7 (15)	87.3 (158)		<0.001
LV mass index [g / m <sup>2</sup> ]	136.1 (117.8 – 146.8)	141.2 (124.0 – 155.1)	138.9 (124.7 – 147.3)	139.4 (122.4 – 154.7)	0.19 <sup>1</sup>	0.87 <sup>1</sup>
LV mass [g]	261.5 (225.9 – 318.1)	257.4 (217.4 – 315.3)	288.7 (254.9 – 331.7)	252.2 (212.2 – 311.5)	0.63 <sup>1</sup>	0.023 <sup>1</sup>
LV remodeling type					0.685	0.655
Normal Geometry	--	--	--	--		
Concentric remodeling	--	--	--	--		
Concentric hypertrophy	81.1 (30)	83.8 (145)	86.2 (25)	82.9 (150)		
Eccentric hypertrophy	18.9 (7)	16.2 (28)	13.8 (4)	17.1 (31)		
LV ejection fraction [%]	64.3 (56.8 – 66.1)	57.5 (44.4 – 63.3)	62.5 (60.6 – 65.5)	57.5 (44.4 – 63.7)	<0.001 <sup>1</sup>	0.001 <sup>1</sup>
LV stroke volume index [mL / m <sup>2</sup> ]	40.3 (35.3 – 49.0)	38.9 (29.9 – 45.8)	41.6 (37.6 – 48.6)	38.9 (30.1 – 45.9)	0.11 <sup>1</sup>	0.084 <sup>1</sup>
LV end-diastolic diameter [mm]	47.0 (42.8 – 53.8)	48.1 (43.2 – 53.9)	49.2 (45.8 – 52.0)	47.8 (42.7 – 54.1)	0.91 <sup>1</sup>	0.34 <sup>1</sup>
LV end-systolic diameter [mm]	28.4 (25.5 – 36.6)	33.2 (29.0 – 40.8)	31.3 (28.3 – 34.2)	33.2 (27.7 – 41.3)	0.024 <sup>1</sup>	0.12 <sup>1</sup>
LV relative wall thickness [dimensionless]	0.57 (0.47 – 0.63)	0.54 (0.46 – 0.65)	0.57 (0.50 – 0.63)	0.54 (0.46 – 0.65)	0.78 <sup>1</sup>	0.78 <sup>1</sup>

<b>LV septum thickness [mm]</b>	14.0 (12.4 – 15.4)	13.8 (12.1 – 15.6)	14.4 (13.5 – 16.4)	13.6 (12.0 – 15.3)	0.53 <sup>1</sup>	0.062 <sup>1</sup>
<b>LV posterior wall dimension [mm]</b>	13.0 (11.8 – 15.0)	13.0 (11.5 – 14.7)	13.2 (12.2 – 15.0)	13.0 (11.5 – 14.7)	0.83 <sup>1</sup>	0.41 <sup>1</sup>
<b>LV outflow tract diameter [mm]</b>	2.07 (1.9 – 2.2)	2.0 (1.9 – 2.1)	2.1 (2.0 – 2.2)	2.00 (1.9 – 2.1)	0.20 <sup>1</sup>	0.007 <sup>1</sup>
<b>AV area [mm<sup>2</sup>]</b>	0.74 (0.64 – 0.90)	0.71 (0.57 – 0.86)	0.85 (0.70 – 0.97)	0.71 (0.57 – 0.84)	0.11 <sup>1</sup>	0.003 <sup>1</sup>
<b>AV area index [mm<sup>2</sup>]</b>	0.40 (0.35 – 0.46)	0.39 (0.31 – 0.47)	0.42 (0.33 – 0.48)	0.39 (0.31 – 0.47)	0.42 <sup>1</sup>	0.20 <sup>1</sup>
<b>AV mean gradient [mmHg]</b>	39.8 (32.4 – 54.3)	40.9 (32.5 – 50.7)	42.5 (35.0 – 50.1)	40.6 (31.6 – 52.0)	0.90 <sup>1</sup>	0.79 <sup>1</sup>
<b>Aortic valve peak velocity [m / s]</b>	4.1 (3.7 – 4.8)	4.1 (3.8 – 4.7)	4.1 (3.8 – 4.4)	4.1 (3.7 – 4.7)	0.80 <sup>1</sup>	0.88 <sup>1</sup>
<b>Low flow</b>	24.3% (9)	36.8% (63)	17.2% (5)	37.4% (67)	0.147 <sup>1</sup>	0.034 <sup>1</sup>
<b>Moderate or severe AR</b>	0% (0)	3.6% (6)	3.4% (1)	2.9% (5)	0.450 <sup>2</sup>	0.28 <sup>2</sup>
<b>Moderate or severe MR</b>	5.4% (2)	8.1% (14)	3.4% (1)	8.3% (15)	0.57 <sup>2</sup>	0.36 <sup>2</sup>

Data for each characteristic is displayed as either a percentage (number of patients) or as median (IQR<sub>Q1</sub> – IQR<sub>Q3</sub>). Statistical tests used were <sup>1</sup>Wilcoxon test or <sup>2</sup>Pearson test. P-values represent T-tests between the specified groups: mod/sev LVH \*(normal cTnT vs elevated cTnT) and †(normal NTproBNP vs elevated NTproBNP). *N* is the number of non-missing values. LV = left ventricular, AV = aortic valve, AR = aortic regurgitation, MR = mitral regurgitation.

**Table S4. Pairwise comparisons between the LVH groups**

	LV Remodeling Type		
	CR	CH	EH
<b>cTnT</b>			
<b>Females</b>			
NG	0.42	0.022	0.26
CR	--	<0.001	0.34
CH	--	--	0.41
<b>Males</b>			
NG	0.73	0.021	0.19
CR	--	0.002	0.13
CH	--	--	0.63
<b>Females + Males</b>			
NG	0.61	0.051	0.31
CR	--	<0.001	0.085
CH	--	--	0.66
<b>NTproBNP</b>			
<b>Females</b>			
NG	0.97	0.021	0.009
CR	--	<0.001	<0.001
CH	--	--	0.34
<b>Males</b>			
NG	0.005	0.23	0.049
CR	--	<0.001	<0.001
CH	--	--	0.29
<b>Females + Males</b>			
NG	0.013	0.016	0.003
CR	--	<0.001	<0.001
CH	--	--	0.14

Pairwise comparisons between the LVH groups in the box-and-whisker plots shown in Supplemental Figure 3. P-values from the Wilcoxon rank sum test are shown in each cell for cTnT and NTproBNP in females, males, and both.

**Table S5. Pairwise comparisons between the LVH groups**

	LVH		
	Mild	Moderate	Severe
<b>cTnT</b>			
<b>Females</b>			
No	0.32	0.036	<0.001
Mild	--	0.18	0.001
Moderate	--	--	0.094
<b>Males</b>			
No	0.012	0.31	0.001
Mild	--	0.31	0.45
Moderate	--	--	0.10
<b>Females + Males</b>			
No	0.052	0.13	<0.001
Mild	--	0.93	0.024
Moderate	--	--	0.026
<b>NTproBNP</b>			
<b>Females</b>			
No	<0.001	<0.001	0.002
Mild	--	0.90	0.29
Moderate	--	--	0.53
<b>Males</b>			
No	0.02	<0.001	<0.001
Mild	--	0.11	<0.001
Moderate	--	--	0.002
<b>Females + Males</b>			
No	<0.001	<0.001	<0.001
Mild	--	0.29	<0.001
Moderate	--	--	0.006

Pairwise comparisons between the LVH groups in the box-and-whisker plots shown in Supplemental Figure 3. P-values from the Wilcoxon rank sum test are shown in each cell for cTnT and NTproBNP in females, males, and both.

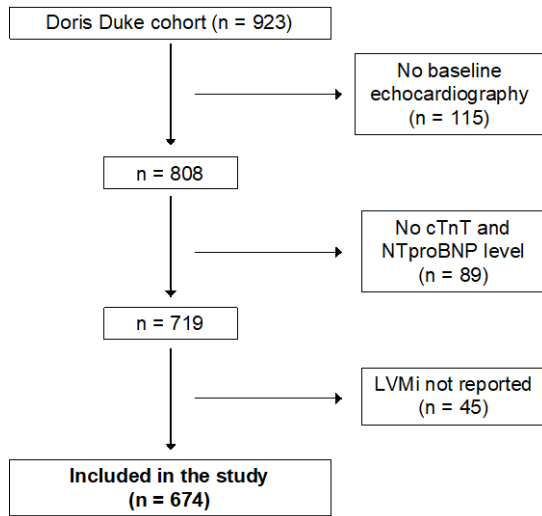


**Table S6. LVH, Biomarkers, and Kansas City Cardiomyopathy Questionnaire (KCCQ) score**

	30-days		1-year	
	estimated KCCQ (95% CI)	p-value	estimated KCCQ (95% CI)	p-value
<b>Model 1: LVH</b>				
Moderate/severe vs. no/mild LVH	-1.04 (-5.11 – 3.12)	0.62	2.38 (-1.69 – 6.66)	0.29
<b>Model 2: cTnT</b>				
Moderate/severe vs. no/mild LVH	-0.75 (-4.61 – 3.55)	0.72	2.65 (-1.33 – 6.78)	0.23
Elevated vs. normal cTnT	-1.99 (-6.37 – 1.95)	0.38	-2.58 (-6.77 – 2.01)	0.25
<b>Model 3: NTproBNP</b>				
Moderate/severe vs. no/mild LVH	-0.62 (-4.56 – 3.70)	0.76	2.81 (-1.20 – 7.25)	0.2
Elevated vs. normal NTproBNP	-2.55 (-7.02 – 1.37)	0.27	-2.67 (-7.81 – 2.38)	0.26
<b>Model 4: cTnT and NTproBNP</b>				
Moderate/severe vs. no/mild LVH	-0.44 (-4.38 – 3.78)	0.83	2.96 (-0.90 – 7.32)	0.18
Elevated vs. normal cTnT	-1.55 (-5.77 – 2.53)	0.49	-2.24 (-7.37 – 2.89)	0.35
Elevated vs. normal NTproBNP	-2.22 (-6.79 – 1.66)	0.38	-2.17 (-6.15 – 2.50)	0.34

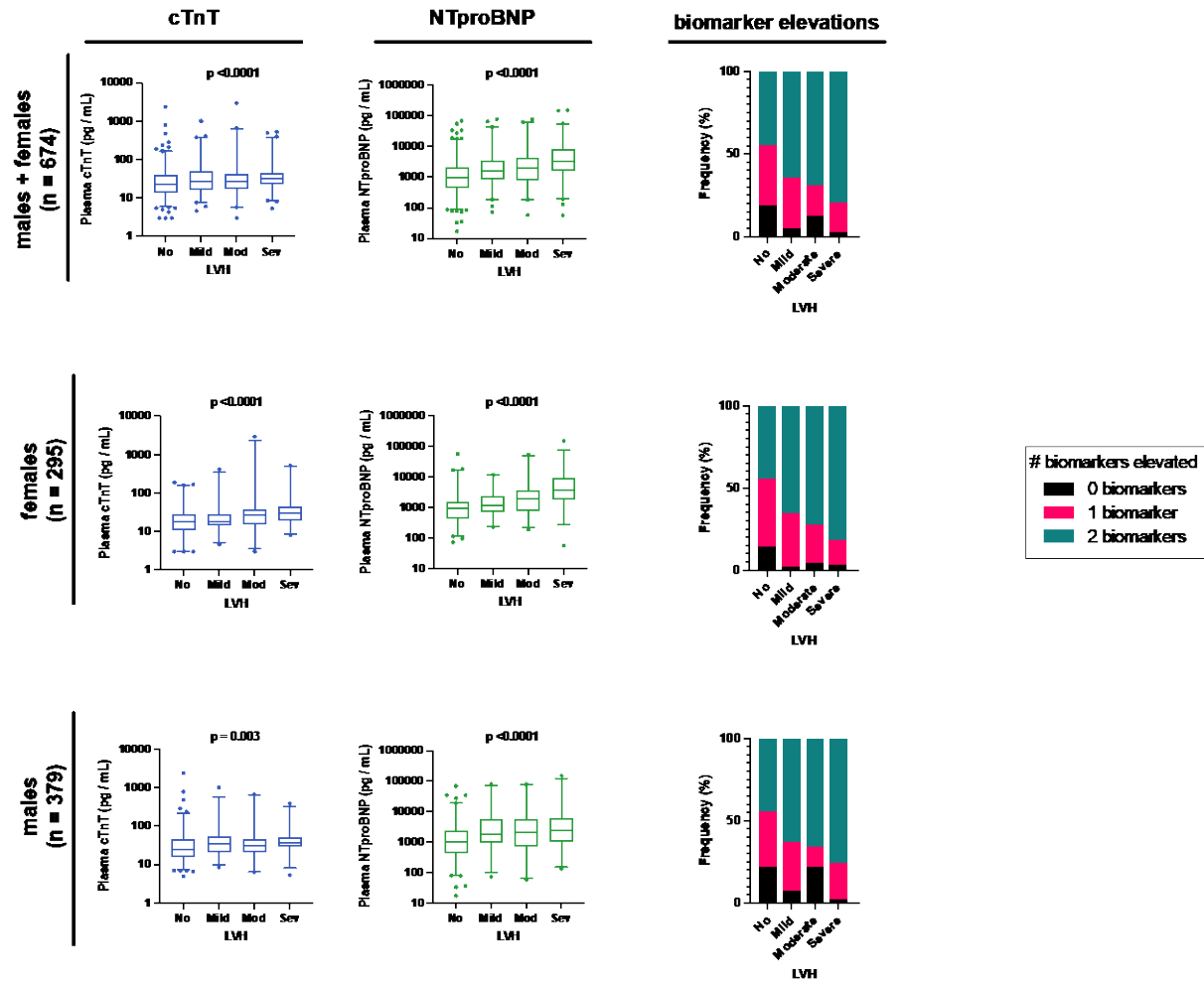
The estimated difference in KCCQ score at 30-days and 1-year post-TAVR are displayed for four models. No KCCQ differences met statistical significance.

**Figure S1. CONSORT diagram**



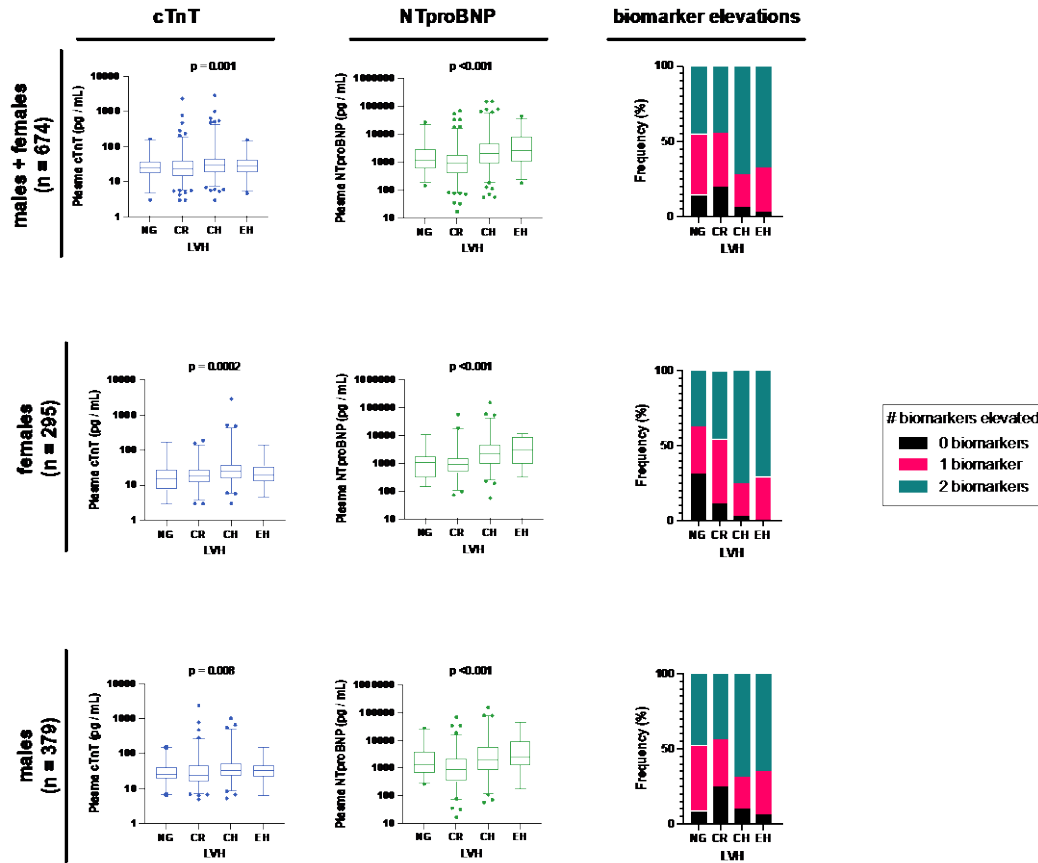
CONSORT diagram displaying patient inclusion and exclusion in the study.

Figure S2. Box-and-whisker plots according to LVH severity



Box-and-whisker plots according to LVH severity of the distribution of plasma cTnT and NTproBNP versus LVH are shown for females, males, and females + males. The horizontal bar in the box denotes the median. The upper and lower whiskers represent the 97.5 and 2.5 percentiles, respectively. Discrete plotted points represent data outside this range. Percentages above bars indicate the frequency of biomarker elevation. P-values were generated from the nonparametric Kruskal-Wallis test and pairwise comparisons from the Wilcoxon rank sum test can be seen in Supplemental Table 4. On the rightmost side of the figure, stacked proportions charts demonstrate the frequency of elevations in 0, 1, or 2 biomarkers with respect to LVH severity in females, males, and both.

Figure S3. Box-and-whisker plots according to LV remodeling geometry



Box-and-whisker plots according to LV remodeling geometry of the distribution of plasma cTnT and NTproBNP versus LVH are shown for females, males, and females + males. The horizontal bar in the box denotes the median. The upper and lower whiskers represent the 97.5 and 2.5 percentiles, respectively. Discrete plotted points represent data outside this range. Percentages above bars indicate the frequency of biomarker elevation. P-values were generated from the nonparametric Kruskal-Wallis test and pairwise comparisons from the Wilcoxon rank sum test can be seen in Supplemental Table 3. On the rightmost side of the figure, stacked proportions charts demonstrate the frequency of elevations in 0, 1, or 2 biomarkers with respect to LV geometry in females, males, and both. ‘NG’ = normal geometry, ‘CR’ = concentric remodeling, ‘CH’ = concentric hypertrophy, and ‘EH’ = eccentric hypertrophy.