Impact of high-sensitivity cardiac troponin T on survival and rehospitalization after transcatheter aortic valve replacement

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Abstract
Background: Constant elevations of the serum concentration of cardiac troponin T (TnT) indicate a myocardial injury that may affect the long-term outcome of transcatheter aortic valve replacement (TAVR).

Objectives: We sought to investigate the impact of pre-TAVR TnT on outcomes after TAVR during long-term follow-up.

Methods: In a retrospective, observational study we compared long term outcomes after TAVR between tertiles of preinterventional high-sensitivity TnT. Systematic follow-up was performed annually for 5 years. The primary endpoint was a composite of all-cause death and any rehospitalization.

Results: Between 2010 and 2018, 2,129 patients with severe aortic valve stenosis underwent TAVR at our institution (mean age 82.6 years, 57.2% female, logistic EuroSCORE 20.5 ± 15.8). Boundaries for TnT tertiles were <21 ng/L and >42 ng/L. The median follow-up was 895 days. Three-year incidences for the primary endpoint were 70.9%, 76.6%, and 81.7% in the low, middle, and high tertile (log rank p < .001). Compared with the first tertile, the corresponding adjusted hazard ratios were 1.23 (95%-CI 1.08–1.40, p < .001) and 1.50 (95%-CI 1.32–1.70, p < .001) for the second and third tertile. We found consistent differences between TnT strata for all-cause death (3-year incidences 23.3%, 33.3%, and 47.1%; adjusted p < .001) and rehospitalization (3-year incidences 64.7%, 68.7% and 72.0%; adjusted p < .001), including significant differences in deaths (p < .001). The association between TnT and outcome was independent of coronary artery disease or low aortic valve gradient.

Conclusions: TnT before TAVR is strongly associated with all-cause death and rehospitalization during 3-year follow-up.

Keywords
coronary artery disease, mortality, rehospitalization, transcatheter aortic valve replacement, troponin T
1 | INTRODUCTION

In elderly patients with severe aortic valve stenosis considered for transcatheter aortic valve implantation (TAVR), the anticipated short- and long-term clinical benefits play a central role in decision making. The long-term outcome of TAVR critically depends on the myocardial damage that has evolved before intervention. \(^1\) \(^4\) Pressure overload resulting in high wall stress may cause myocardial cell injury and apoptosis. \(^5\) \(^7\) Chronic elevation of the serum concentration of cardiac troponins without symptoms of ischemia is the clinical hallmark of such myocardial injury. \(^8\) In patients with severe aortic valve stenosis, chronic elevation of cardiac troponin T (TnT) as assessed by high-sensitive assays is associated with poor short term and midterm survival. \(^9\) There is, however, only limited data on long-term survival \(^10\) and the impact of elevated TnT on the need for subsequent rehospitalization after TAVR has not been studied, so far.

The putative impact on outcome of myocardial injury as assessed by TnT may be particularly large in patients with low-gradient severe aortic valve stenosis (LGSAS) characterized by impairment of LV function. \(^11\) \(^12\) Specifically, in this setting, elevated TnT may indicate reduced potential for LV recovery. This issue has not been studied so far. Likewise, the interaction of coronary artery disease (CAD) with the impact of TnT on outcome has not been studied. In addition to pressure overload, CAD may accentuate subendocardial ischemia below the threshold for myocardial infarction. \(^7\)

To clarify these issues, we interrogated our database for patients undergoing TAVR between June, 2008 until November, 2018. We sought to investigate the impact of pre-TAVR TnT on death and rehospitalization during long-term follow-up, with a special reference to the role of LGSAS and CAD.

2 | METHODS

2.1 | Study population and transcatheter aortic valve implantation procedure

We investigated patients undergoing transfemoral TAVR at our heart center from June, 2008 to November, 2018.

All patients who were potential candidates for TAVR were assessed by our multidisciplinary institutional heart team for eligibility, procedure feasibility, access route, valve type, and size. Indications for TAVR followed contemporary European guidelines. \(^13\) \(^15\) The pre-TAVR work-up consisted of transthoracic and, if needed, transoesophageal echocardiography as well as computed tomography angiography (CTA). Systolic annular dimensions were obtained from CTA by planimetric area measurement with subsequent calculation of an effective annulus diameter as previously described. \(^16\) In patients with coronary artery disease scheduled for TAVR, coronary stenoses that were considered clinically relevant were treated by PCI before or during the TAVR procedure. We did not perform TAVR in patients with acute or subacute myocardial infarction.

TAVR was performed as described previously, \(^17\) using general anesthesia and transoesophageal echocardiographic guidance in the majority of patients. The default postinterventional antithrombotic treatment consisted of dual-antiplatelet therapy with acetyl salicylic acid (100 mg/day) plus clopidogrel (75 mg/day) for 6 months followed by lifelong acetyl salicylic acid 100 mg/day. In patients with an indication for oral anticoagulation, we usually did not recommend concomitant antiplatelet therapy.

2.2 | Follow-up, endpoints and definitions

In our clinical routine, troponin T is assessed by the high-sensitivity assay (Elecsys® Troponin T-high sensitive, Roche Diagnostics, Suisse) on every hospital admission. In patients with symptoms suggestive of myocardial ischemia as well as in those with elevated TnT, a second sample is obtained. TAVR was postponed in patients with acute or subacute myocardial infarction. For the purpose of this study, we evaluated the serum concentrations of TnT on admission to the hospital for TAVR or before PCI, if PCI had been performed less than 4 weeks prior to TAVR.

As part of our routine quality assurance program, all patients with TAVR were monitored with contacts by questionnaire or telephone call at 30 days, 6 months, and 1 year after the procedure and from then on annually for 5 years. For patients reporting events or not responding, the referring cardiologists and/or general practitioners were contacted for further information. If needed, we obtained additional information on circumstances of death from relatives or caregivers. End-of-follow-up (EoF) was December 31, 2019, patients with incomplete follow-up were censored at the time of the last contact.

Our primary endpoint was the composite of all-cause death and rehospitalization for any cause. As secondary endpoints, we assessed the two components of the primary endpoint, as well as death and rehospitalization.

CAD was defined as ≥50% diameter stenosis of an epicardial vessel by visual estimation. For the purpose of this study, we assume LGSAS in patients undergoing TAVR for an aortic valve stenosis with a valve area <1 cm², but a mean gradient <40 mmHg. We did not indicate TAVR in patients with LGSAS, unless associated with reduced left ventricular ejection fraction (<50%) or reduced stroke volume index (<35 mL/m²) or with compelling symptoms not explained otherwise.

2.3 | Statistical analysis

The cohort was stratified by tertiles of preinterventional TnT. All analyses were performed according to these strata. The Kaplan–Meier method was used to calculate and visualize cumulative outcomes. To account for competing risk, we fitted a regression model for competing risk assay (Elecsys® Troponin T-high sensitive, Roche Diagnostics, Suisse) on every hospital admission. In patients with symptoms suggestive of myocardial ischemia as well as in those with elevated TnT, a second sample is obtained. TAVR was postponed in patients with acute or subacute myocardial infarction. For the purpose of this study, we evaluated the serum concentrations of TnT on admission to the hospital for TAVR or before PCI, if PCI had been performed less than 4 weeks prior to TAVR.

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The cohort was stratified by tertiles of preinterventional TnT. All analyses were performed according to these strata. The Kaplan–Meier method was used to calculate and visualize cumulative outcomes. To account for competing risk, we fitted a regression model for competing risk, as previously described by Fine and Gray. \(^16\) Cumulative incidence functions were calculated for all endpoints and compared by log rank test. We fitted univariate and multivariate Cox proportional regression models until EoF to test differences in outcome and estimate crude and adjusted hazard ratios (HR) with 95%-confidence
intervals (CI). The primary multivariate Cox models comprised the logistic EuroScore plus variables of Tables 1 and 2 that were not included in the logistic EuroScore and showed a significant difference between TnT strata. Additional models also included CAD and the interaction term of CAD*TnT strata, or the interaction term of LGSAS*TnT strata.

Continuous variables are reported as mean ± SD, ordinal variables as median (interquartile range), and categorical data as number (percentage). For comparison between groups, continuous variables were tested using the unpaired Student’s t-test or the Mann–Whitney U-test, as appropriate. Differences in categorical

TABLE 1  Baseline characteristics

|                        | All patients (n = 2,129) | Trop < 21 ng/L (n = 671) | Trop 21 – 42 ng/L (n = 736) | Trop > 43 ng/L (n = 722) | p-value |
|------------------------|--------------------------|--------------------------|-----------------------------|--------------------------|---------|
| Age (years)            | 82.6 ± 5.6               | 81.9 ± 5.5               | 82.9 ± 5.2                  | 83.0 ± 6.1               | <0.001  |
| Sex (female)           | 1,217 (57.2)             | 488 (72.7)               | 385 (52.3)                  | 344 (47.6)               | <0.001  |
| Logistic EuroSCORE (%) | 20.5 ± 15.8              | 14.5 ± 9.7               | 18.9 ± 13.4                 | 27.7 ± 19.5              | <0.001  |
| Mean aortic gradient (mm Hg) | 45.4 ± 14.4           | 45.9 ± 13.2              | 46.1 ± 15.4                 | 45.4 ± 14.4              | 0.025   |
| LVEF (%)               | 52.4 ± 12.0              | 57.3 ± 8.0               | 52.4 ± 11.6                 | 47.8 ± 13.6              | <0.001  |
| Low gradient severe AS | 687 (32.3)               | 198 (29.5)               | 241 (32.7)                  | 248 (34.3)               | 0.146   |
| Arterial hypertension  | 1,886 (88.6)             | 578 (86.1)               | 669 (90.9)                  | 639 (88.5)               | 0.020   |
| Cholesterol (mg/dl)    | 178.3 ± 76.8             | 188.0 ± 48.0             | 175.3 ± 44.5                | 172.1 ± 46               | <0.001  |
| Diabetes mellitus      | 645 (30.3)               | 175 (26.1)               | 224 (30.4)                  | 246 (34.1)               | 0.005   |
| GFR (ml/min)           | 49.0 ± 20.8              | 56.4 ± 19.5              | 50.1 ± 20.4                 | 41.1 ± 19.4              | <0.001  |
| Coronary artery disease| 1,355 (63.6)             | 369 (55.0)               | 470 (63.9)                  | 516 (71.5)               | <0.001  |
| Periphery artery disease| 269 (12.6)              | 63 (9.4)                 | 80 (10.9)                   | 126 (17.5)               | <0.001  |
| Cerebrovascular disease| 432 (20.3)               | 132 (19.7)               | 151 (20.5)                  | 149 (20.6)               | 0.889   |
| Pulmonary hypertension | 1,118 (52.5)             | 277 (41.3)               | 402 (54.6)                  | 439 (60.8)               | <0.001  |
| Previous MI            | 334 (15.7)               | 61 (9.1)                 | 123 (16.7)                  | 150 (20.8)               | <0.001  |
| Previous CABG          | 192 (9.0)                | 51 (7.6)                 | 65 (8.8)                    | 76 (10.6)                | 0.159   |

Note: Values are mean ± or n.
Abbreviations: AS, aortic valve stenosis; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; Euro SCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

TABLE 2  Procedural characteristics

|                        | All patients (n = 2,129) | Trop < 21 ng/L (n = 671) | Trop 21 – 42 ng/L (n = 736) | Trop > 43 ng/L (n = 722) | p-value |
|------------------------|--------------------------|--------------------------|-----------------------------|--------------------------|---------|
| Dilatation             |                          |                          |                             |                          |         |
| Predilation            | 459 (21.6)               | 132 (19.7)               | 162 (22.0)                  | 165 (22.9)               | 0.330   |
| Postdilatation         | 435 (20.4)               | 139 (20.7)               | 141 (19.2)                  | 155 (21.5)               | 0.537   |
| Valve-in-valve         | 48 (2.3)                 | 8 (1.2)                  | 13 (1.8)                    | 27 (3.7)                 | 0.003   |
| Valve type             |                          |                          |                             |                          | 0.398   |
| Sapien XT             | 386 (18.1)               | 118 (17.6)               | 137 (18.6)                  | 131 (18.1)               |         |
| Sapien 3              | 1,091 (51.2)             | 338 (50.4)               | 374 (50.8)                  | 379 (52.5)               |         |
| CoreValve             | 217 (10.2)               | 67 (10.0)                | 69 (9.4)                    | 81 (11.2)                |         |
| Evolut R              | 300 (14.1)               | 97 (14.5)                | 110 (14.9)                  | 93 (12.9)                |         |
| Evolut pro            | 14 (0.7)                 | 5 (0.7)                  | 6 (0.8)                     | 3 (0.4)                  |         |
| Symetis               | 67 (3.1)                 | 25 (3.7)                 | 21 (2.9)                    | 21 (2.9)                 |         |
| Portico               | 10 (0.5)                 | 3 (0.4)                  | 7 (1.0)                     | -                        |         |
| Allegra               | 5 (0.2)                  | 1 (0.1)                  | 3 (0.4)                     | 1 (0.1)                  |         |
| Lotus                 | 39 (1.8)                 | 17 (2.5)                 | 9 (1.2)                     | 13 (1.8)                 |         |

Note: Values are n (%).
variables were tested by the Pearson \( \chi^2 \)-test. In the 2-sided test, a p-value <0.05 was regarded as significant. All statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL, United States).

3 | RESULTS

3.1 | Study cohort

Our study includes 2129 patients with severe aortic valve stenosis who underwent TAVR at our institution. The preinterventional serum concentration of TnT was above the upper limit of normal (<14 ng/L) in 1776 patients (83.4%). Boundaries for tertiles of TnT were <21 ng/L and >42 ng/L.

The baseline demographic and clinical characteristics are shown in Table 1 for the entire cohort and for the strata defined by tertiles of TnT. The mean age was 82.6 years, 912 patients (42.8%) were male and the logistic EuroSCORE was 20.5 ± 15.8. The strata defined by tertiles of TnT differed significantly in the majority of baseline characteristics, indicating more adverse risk profiles with increasing TnT. Of note, with increasing tertile of TnT age and logistic EuroSCORE increased and left ventricular ejection decreased. Likewise, the proportion of patients with diabetes mellitus and CAD increased with tertiles of TnT concentration and glomerular filtration rate deteriorated.

As shown in Table 2, we did not find any major differences in procedural characteristics between the TnT strata except for the proportion of valve-in-valve procedures. We implanted balloon-expandable valves in 1477 patients (69.3%) and self-expanding valves in 613 patients (28.8%). Only a minority of the TAVRs were valve-in-valve procedures (48 [2.3%]).

3.2 | Primary outcome

Follow-up until EoF was complete in 1804 (84.4%) patients. The median follow-up until EoF or time of censoring was 1105 days. Our primary endpoint all-cause death and any rehospitalization were reached in 1479 patients. As shown in Figure 1, event rates for the composite of all-cause death and any hospitalization differed significantly between TnT strata with increasing separation of the time-to-event curves over time (p < .001). Three-year incidences for the primary endpoint were 70.9% in the low tertile, 76.6% in the middle tertile and 81.7% in the high tertile. With the first tertile as reference, the crude hazard ratio of the primary endpoint was 1.23 (95% CI 1.08–1.40, p < .001) for the second tertile and 1.50 (95% CI 1.32–1.70, p < .001) for the third tertile. In the multivariate analysis (Table 3), TnT strata prevailed as independent predictors of the primary endpoint with similar hazard ratios as in the crude analysis (Figure 2). Other significant predictors for the primary endpoint were logistic EuroSCORE and the presence of LGSAS.

3.3 | Secondary outcomes

During the entire follow-up 671 patients died. As shown in Figure 3, all-cause mortality differed significantly between strata of TnT with increasing separation of the curves. Three-year all-cause mortality was 23.3% in the low tertile, 33.3% in the middle tertile, and 47.1% in the high tertile of TnT (p < .001). In the crude analysis, this resulted in a HR for all-cause death of 1.56 (95% CI 1.25–1.95, p < .001) for the second TnT tertile and of 2.55 (95% CI 2.07–3.14, p < .001) for the third TnT tertile, as compared with the first tertile. Similar hazard ratios were obtained in the multivariate analysis, which also identified logistic EuroSCORE and LGSAS as independent predictors of all-cause mortality (Table 4).

During the study period, rehospitalization for any cause was needed in 1176 patients (78.5%). The time to event curves shown in Figure 4 demonstrates a difference in the rate of rehospitalization between TnT strata that did not reach statistical significance (p = 0.15).

3.4 | Subgroups

As shown in Figure 2, the HRs for the primary endpoint of the middle and high troponin tertile compared with the low tertile were similar in patients with or without LGSAS. Neither in the bivariate nor in the full Cox model, did we find a significant interaction of LGSAS with the association between TnT tertiles and the primary endpoint (p = 0.9 and p = 0.99, respectively). Likewise, in the subsets defined by the presence or absence of CAD, the HR for the primary endpoint were...
TABLE 3  Cox regression analysis, primary endpoint (all-cause mortality and rehospitalization of any cause)

|                          |                    | HR (95% CI) | p-value |               | HR (95% CI) | p-value |
|--------------------------|--------------------|-------------|---------|---------------|-------------|---------|
|                          | Univariate         |             |         |               |             |         |
|                          |                     |             |         | Multivariate  |             |         |
| Troponin (tertile)       |                    |             |         |               |             |         |
| ≤21 ng/L                 | Reference           | Reference   |         |               | Reference   |         |
|                          | ≥22 – 42 ng/L       | 1.233 (1.084 – 1.402) | 0.001   | ≥43 ng/L       | 1.186 (1.040 – 1.352) | 0.011   |
|                          | ≥43 ng/L            | 1.497 (1.318 – 1.699) | <0.001  |               | 1.379 (1.201 – 1.584) | <0.001  |
| Age (years)              | 1.000 (0.991 – 1.008) | 0.985     |         |               |             |         |
| Sex (female)             | 0.867 (0.783 – 0.961) | 0.007     |         |               |             |         |
| Logistic EuroSCORE (%)   | 2.409 (1.778 – 3.264) | <0.001    |         |               | 1.510 (1.050 – 2.172) | 0.026   |
| Mean aortic gradient (mm Hg) | 0.990 (0.986 – 0.993) | <0.001    |         |               |             |         |
| LVEF (%)                 | 0.993 (0.989 – 0.997) | 0.001     |         |               |             |         |
| LGSAS                    | 1.287 (1.156 – 1.432) | <0.001    |         |               | 1.217 (1.089 – 1.361) | 0.001   |
| Arterial hypertension    | 1.213 (1.028 – 1.432) | 0.022     |         |               | 1.186 (1.002 – 1.404) | 0.048   |
| Cholesterol (mg/dl)      | 0.998 (0.997 – 0.999) | <0.001    |         |               | 0.999 (0.998 – 1.000) | 0.055   |
| Diabetes mellitus        | 1.165 (1.044 – 1.300) | 0.006     |         |               |             |         |
| GFR (ml/min)             | 0.993 (0.990 – 0.996) | <0.001    |         |               |             |         |
| Coronary artery disease  | 1.151 (1.034 – 1.281) | 0.010     |         |               |             |         |
| Periphery artery disease | 1.346 (1.165 – 1.557) | <0.001    |         |               |             |         |
| Cerebrovascular disease  | 1.131 (0.998 – 1.281) | 0.053     |         |               | 1.022 (0.894 – 1.167) | 0.754   |
| Pulmonary hypertension   | 1.342 (1.211 – 1.487) | <0.001    |         |               |             |         |
| Previous MI              | 1.086 (0.946 – 1.247) | 0.242     |         |               |             |         |
| Previous CABG            | 0.968 (0.812–1.154) | 0.718     |         |               |             |         |
| Valve-in-valve           | 1.186 (0.844 – 1.667) | 0.247     |         |               |             |         |

Abbreviations: AS, aortic valve stenosis; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LGSAS, low gradient severe aortic valve stenosis; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

FIGURE 2  Hazard ratios with 95%-confidence intervals for primary endpoint in the entire cohort and in subgroups defined low-gradient severe aortic valve stenosis (LGSAS) and coronary artery disease (CAD). Hazard ratios for primary endpoint

FIGURE 3  Kaplan-Meier-curves with cumulative incidences of death from any cause in strata of preprocedural troponin T (p < .001). Cumulative incidences for death from any cause versus time after procedure. TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]
also similar (Figure 2) and the p-values for interaction were insignificant in both, the bivariate and the full Cox model (p = 0.98 and p = 0.99, respectively).

### TABLE 4 Cox regression analysis, all-cause-mortality

| Troponin (tertile) | Univariate |          |          | Multivariate |          |          |
|-------------------|------------|----------|----------|--------------|----------|----------|
|                   | HR (95% CI)| p-value  | HR (95% CI)| p-value      |          |          |
| ≤21 ng/L          | Reference  |          | Reference |              |          |          |
| 22 – 42 ng/L      | 1.564 (1.254 – 1.951) | <0.001 | 1.459 (1.166 – 1.825) | <0.001 |          |          |
| ≥43 ng/L          | 2.550 (2.072 – 3.139) | <0.001 | 2.219 (1.777 – 2.771) | <0.001 |          |          |
| Age (years)       | 1.017 (1.002 – 1.032) | 0.028 |          |              |          |          |
| Sex (female)      | 0.805 (0.688 – 0.942) | 0.007 |          |              |          |          |
| Logistic EuroSCORE (%) | 5.222 (3.410 – 7.995) | <0.001 | 2.163 (1.294 – 3.613) | 0.003 |          |          |
| Mean aortic gradient (mm Hg) | 0.987 (0.981 – 0.993) | <0.001 |          |              |          |          |
| LVEF (%)          | 0.987 (0.981 – 0.994) | <0.001 |          |              |          |          |
| LGSAS             | 1.441 (1.229 – 1.692) | <0.001 | 1.309 (1.105 – 1.550) | 0.002 |          |          |
| Arterial hypertension | 0.912 (0.722 – 1.154) | 0.444 |          |              |          |          |
| Cholesterol (mg/dl) | 0.997 (0.996 – 0.999) | 0.003 | 0.999 (0.997 – 1.001) | 0.422 |          |          |
| Diabetes mellitus | 1.139 (0.963 – 1.348) | 0.128 |          |              |          |          |
| GFR (ml/min)      | 0.982 (0.977 – 0.986) | <0.001 |          |              |          |          |
| Coronary artery disease | 1.056 (0.896 – 1.244) | 0.514 |          |              |          |          |
| Periphery artery disease | 1.405 (1.135 – 1.738) | 0.002 |          |              |          |          |
| Cerebrovascular disease | 1.227 (1.019 – 1.478) | 0.030 | 1.073 (0.879 – 1.311) | 0.488 |          |          |
| Pulmonary hypertension | 1.286 (1.098 – 1.506) | 0.002 |          |              |          |          |
| Previous MI       | 1.062 (0.859 – 1.313) | 0.577 |          |              |          |          |
| Previous CABG     | 1.107 (0.853 – 1.436) | 0.444 |          |              |          |          |
| Valve-in-valve    | 1.105 (0.651 – 1.877) | 0.712 |          |              |          |          |

Abbreviations: AS, aortic valve stenosis; CABG, coronary artery bypass graft; GRF, glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LGSAS, low gradient severe aortic valve stenosis; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

**FIGURE 4** Cumulative incidence curves related mortality and rehospitalization as competing risk events after regression model of Fine and Gray for troponin tertiles (death as outcome, rehospitalization as competing risk). Fine and Gray regression model for competing risk. TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]

**DISCUSSION**

To the best of our knowledge, our study is the largest to evaluate the impact of preprocedural TnT on the long-term outcome of TAVR. Our main findings are: Baseline TnT before TAVR is strongly associated with the composite risk of all-cause death and rehospitalization during long-term follow-up. This association is driven by both components but mainly by deaths. The association of baseline TnT with death and rehospitalization was independent of the presence or absence of CAD or LGSAS.

The fourth Universal Definition of Myocardial Infarction stresses the concept of myocardial injury that was the objective of the current study. It is defined by the chronic constant elevation of cardiac troponin without symptoms of ischemia. It has been suggested that in this setting elevated cardiac troponins values may reflect exocytosis of the early releasable cytosolic troponin pool by stressed...
myocardial cells. Experimental studies have also shown that wall stretch can induce apoptosis and autophagy of myocardial cells. Moreover, left ventricular hypertrophy in conjunction with elevated preload may result in subclinical subendocardial ischemia causing troponin release. These mechanisms will result in adverse remodeling with increased myocardial fibrosis that is known to be linked to poor prognosis. Consistent with these concepts, elevated cardiac troponins have been associated with left ventricular hypertrophy, myocardial fibrosis, and poor recovery of LV function in previous studies on patients undergoing aortic valve replacement. In this study, we demonstrate that these mechanisms have an impact on outcomes well beyond the subacute phase and into long-term follow-up.

Even though we did not perform TAVR in patients with acute and subacute myocardial infarction, we found a shift toward higher tertiles of TnT in patients with CAD. Obstructive CAD may predispose to subclinical subendocardial ischemia as one of the potential mechanisms of TnT release in severe aortic valve stenosis. Nevertheless, CAD did not interact with the association of TnT with outcome suggesting that myocardial injury exerts similar adverse effects irrespective of its underlying mechanism. Overall, the impact of CAD on prognosis was low in our study, which at least in part may be attributed to our policy to fix relevant coronary artery stenoses before or during TAVR. The residual influence of CAD on prognosis might have been negligible as compared with the myocardial sequelae of the pre-existing aortic valve stenosis.

We speculated that myocardial injury might play a prominent role in LGSAS. LGSAS variable degrees of left ventricular dysfunction ranging from subtle changes such as reduction in stroke volume to severely reduced ejection fraction play a prominent role. More extensive myocardial injury before TAVR may limit the potential for subsequent recovery of LV function. Nevertheless, LGSAS did not interfere with the association between baseline TnT and outcome. Thus, the degree of myocardial injury appears to be relevant irrespective of its impact on the actual gradient.

We chose the composite of all-cause death and all-cause rehospitalization as our primary endpoint, because this endpoint is not biased by interpretation. Although a large proportion of the endpoint was driven by cardiac death and rehospitalization due to cardiac causes, there also was conspicuous association of TnT tertiles with deaths and rehospitalizations not primarily attributable to the cardiac condition. It has to be kept in mind, however, that the timing of death from other causes such as cancer or infection will be modified by the cardiac condition. Likewise, the threshold of sending a patient to the hospital for treatment of noncardiac disease will be strongly influenced by the concomitant cardiac status. Thus, cardiac and noncardiac causes for death and rehospitalization are almost always intertwined. This justifies our choice of primary endpoint and explains the association of TnT tertiles with deaths and rehospitalizations not primarily attributable to the cardiac causes.

In previous studies on patients undergoing TAVR, elevated baseline levels of cardiac troponins were associated with early (<30 days) complications as defined by VARC-2 and impaired improvement of left ventricular function. Likewise, a recent meta-analysis reported decreased survival during short-term and mid-term follow-up with elevated baseline levels of cardiac troponins. In this meta-analysis, 8 studies (3018 patients) on baseline levels of cardiac troponins focussed on 1-year follow-up or median follow-up of 434 days, one study reported 2-year survival (192 patients) and 3-year survival. The study on 3-year survival by Akodad et al. was the largest in this meta-analysis and comprised 1390 patients. In this study, 3-year survival after TAVR was significantly reduced in the middle and the high tertile of baseline TnT, which is consistent with our study. Contrary to our study, however, the middle tertile comprised a broad spectrum of TnT values ranging from 24 to 1800 ng/L. Our study substantially expands these findings by showing that baseline TnT levels as low as 21 to 41 ng/L are already associated with decreased survival. Also to the best of our knowledge—we show for first an association of baseline TnT with the risk for rehospitalization. Similar to our study, CAD did not affect survival in the study by Akodad and coworkers. Yet, this study neither addressed the interaction of CAD with the association between TnT and survival, nor the role of LGSAS.

### 4.1 Limitations

The retrospective nature of our study needs to be considered as limitation of our study. Although we adjusted our observations for differences in co-variables between tertiles of TnT, we cannot exclude the influence of unknown confounders.

Many of the elderly and often frail patients did not return to in-house follow-up visits. Therefore, we needed to rely on questionnaires and telephone interviews for follow-up. For this reason, we focussed on hospital readmissions as one of the key events related to clinical outcomes. Although we always asked for discharge letters, the cause of readmission could not always be assessed with certainty. For the same reason, we did not obtain reliable data on events below the threshold for readmission or on long-term echocardiographic outcomes.

### 5 Conclusion

When discussing treatment options in patients considered for TAVR, the heart team should be aware of a reduced long-term benefit of the intervention in patients with baseline elevations in TnT irrespective of the presence or absence of CAD. In patients at higher risk for adverse outcomes, such as those with LGSAS, the absolute impact of elevated baseline TnT may be even larger than in those without. Although the impact of elevated baseline TnT on outcome does not appear strong enough to serve as a unique criterion for withholding intervention, it may serve as one element in decision making and may prompt intensified surveillance after TAVR. Our findings may also assist in counseling patients and relatives on the anticipated benefits of TAVR.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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