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ORIGINAL RESEARCH

Postprocedural Troponin Elevation and Mortality After Transcatheter Aortic Valve Implantation

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BACKGROUND: This study sought to investigate the role of postprocedural troponin elevations in mortality prediction after transcatheter aortic valve implantation and to define the threshold at which clinically relevant postprocedure myocardial injury determines mortality.

METHODS AND RESULTS: A total of 1333 consecutive patients with transcatheter aortic valve implantation with available postprocedural high-sensitivity cardiac troponin T measurements were included in the analysis. The threshold at which postprocedure myocardial injury determines long-term mortality was identified using restricted cubic spline analysis. A >18.3-fold increase of troponin above the upper reference limit was identified as threshold for relevant postprocedure myocardial injury. Associations remained significant in a landmark analysis between 30 days and 2 years (hazard ratio [HR], 1.61, [95% CI, 1.13–2.28]; *P*=0.01), after adjusting for known confounders (adjusted HR, 1.90 [95% CI, 1.40–2.57]; *P*<0001), and in subgroups of patients with coronary artery disease (adjusted HR, 2.17 [95% CI, 1.44–3.29]; *P*<0.001), renal dysfunction (adjusted HR, 1.88 [95% CI, 1.35–2.62]; *P*<0.001), and intermediate/high surgical risk (adjusted HR, 2.70 [95% CI, 1.40–5.22]; *P*=0.003).

CONCLUSIONS: This study determined a troponin threshold for the identification of patients at increased mortality risk after transcatheter aortic valve implantation. The proposed definition of postprocedure myocardial injury advances risk stratification in patients with transcatheter aortic valve implantation and may assist in postprocedural patient management.

Key Words: aortic stenosis ■ myocardial infarction ■ risk stratification ■ transcatheter aortic valve implantation

Aortic stenosis is the most common acquired valvular heart disease in the Western world, and the prevalence is projected to rise further given the aging of the population.[1–4] Once symptoms of aortic stenosis occur after a long-lasting asymptomatic phase of disease progression, aortic stenosis is associated with considerable morbidity, mortality, and healthcare costs.[1,5,6] Aortic valve replacement either by surgery or as a transcatheter procedure represents the standard therapy after a comprehensive evaluation of the individual surgical risk and comorbid burden.[7] The success of transcatheter aortic valve implantation (TAVI) over the past years has prompted the expansion of TAVI from initially inoperable and high-risk patients to a younger and low-risk patient population.[8–11]

Postprocedural myocardial injury or infarction has been observed after TAVI and is associated with worse outcomes. While certain degrees of cardiac biomarker elevations after TAVI are considered to occur in almost all patients,[12–14] postprocedural myocardial injury has been observed in up to two thirds of patients,[15,16] depending on patients' baseline risk and the endpoint definition applied. Postprocedural myocardial injury has been related with excess mortality and adverse left

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CLINICAL PERSPECTIVE

What Is New?

- This study determined a troponin threshold for the identification of patients at increased mortality risk after transcatheter aortic valve implantation.

What Are the Clinical Implications?

- The proposed definition of clinically relevant postprocedure myocardial injury advances risk stratification in patients undergoing transcatheter aortic valve implantation and may assist in postprocedural patient management.

Nonstandard Abbreviations and Acronyms

EuroSCORE II	European System for Cardiac Operative Risk Evaluation II score
hs-cTnT	high-sensitivity cardiac troponin T
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI	transcatheter aortic valve implantation
URL	upper reference limit

ventricular remodeling in most studies,[12,14,16–18] although some failed to confirm this association.[19–21] In particular, the clinical relevance of only slight cardiac biomarker elevations following TAVI remains a matter of ongoing debate,[20,22] and threshold values of high-sensitivity cardiac troponin indicating clinically relevant postprocedural myocardial injury have not yet been investigated.

This study therefore sought to determine the association between postprocedural myocardial injury and long-term clinical outcomes after TAVI using data from the prospective Zurich SwissTAVI Registry. In particular, we determine a threshold for the association of postprocedural troponin elevation and mortality after TAVI.

METHODS

Data are available from corresponding author upon reasonable request.

Study Population

The study is based on data from the prospective Zurich SwissTAVI Registry. All patients who underwent TAVI at the University Hospital Zurich, Switzerland, between April 2012 and December 2019 were entered into a dedicated database (Zurich SwissTAVI Registry). As previously described,[23–26] the SwissTAVI Registry is a national, multicenter cohort study, initiated by the Swiss Working Group of Interventional Cardiology and the Swiss Society of Cardiac and Thoracic Vascular Surgery in 2011 and registered at ClinicalTrials.gov (NCT01368250). An independent Clinical Trials Unit is responsible for central data monitoring and verification of data completeness and accuracy. All patients are evaluated for TAVI by a multidisciplinary board of interventional cardiologists, cardiac surgeons, cardiac anesthesiologists, and imaging specialists (ie, the Heart Team). In all patients, demographic, clinical, and procedural characteristics are systematically collected using a web-based database with standardized case report forms. Electrocardiogram, transthoracic echocardiography, coronary angiography, and cardiac computed tomography were routinely performed before the procedure. Transcatheter aortic valve implantation was performed according to current guidelines and recommendations and using standard techniques in the cardiac catheterization laboratory or the hybrid operating room.[7] Routine laboratory analyses were performed according to the laboratory's standard operating procedures, and values at baseline and follow-up were collected in the database. Follow-up was performed in-hospital, at 30 days, and yearly thereafter by means of standardized clinical visits or phone calls.

Of 1400 consecutive patients, 1333 (95.2%) had postprocedural measurements of high-sensitivity cardiac troponin T (hs-cTnT) levels available and were included in the analysis. The study was approved by the Ethics Committee (Cantonal Ethics Committee Zurich), conducted in full conformance with the Declaration of Helsinki, and all patients provided written informed consent for prospective follow-up.

Measurement of Cardiac Troponin

Peak hs-cTnT levels during the index hospitalization for the TAVI procedure were used to define postprocedural myocardial injury. Cardiac troponin was measured using the high-sensitivity Elecsys cTnT assay (Roche Diagnostics, Mannheim, Germany). Based on the 99th percentile in a healthy population and the requirement of a ≤10% coefficient of variation, the upper reference limit (URL) for hs-cTnT levels was 14 ng/L.

Definitions

Based on prior studies,[12,16,27] the primary endpoint was mortality at 2 years. Secondary endpoints included mortality at 30 days, as well as cardiovascular death, cerebrovascular events (stroke or transient ischemic attack), and myocardial infarction at both 30 days and 2 years. Renal dysfunction was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

Coronary artery disease was defined as the presence of 1 or more coronary lesions with ≥50% diameter stenosis by visual estimation on the coronary angiogram in vessels ≥1.5 mm in diameter. Patients were dichotomized according to the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) Score into a low-risk (STS-PROM Score <4%) and an intermediate/high-risk group (STS-PROM Score ≥4%). In the SwissTAVI Registry, endpoint definitions are based on the updated standardized endpoint definitions for TAVI of the Valve Academic Research Consortium-2 and clinical events were reviewed and adjudicated by a dedicated clinical event committee.[28]

Statistical Analysis

Continuous variables are presented as mean and SD, and categorical variables as numbers and percentages, respectively. Baseline and procedural characteristics were compared using χ^2 tests for proportions and unpaired *t* tests for means. The association of postprocedural peak hs-cTnT levels with mortality was first assessed using univariable Cox regression models. Second, nonparametric restricted cubic splines were used to model the association of the fold increase of postprocedural peak hs-cTnT levels above the URL with mortality at 2 years. We compared models with different numbers of knots (3, 4, and 5 knots). Because the model with 4 knots showed the best performance based on the Akaike information criterion, a model with 4 flexible knots was compared with a model where the knots were placed at quartiles of the variable. The final model with 4 flexible knots was again determined using the Akaike information criterion. The lower 95% CI was used to determine the ideal cutoff value. In addition, sensitivity analyses were performed to assess the robustness of the retrieved cutoff value. The cohort was then divided based on the above determined cutoff value of postprocedural peak hs-cTnT levels above the URL, and baseline characteristics compared among groups (above versus below the cutoff value). Kaplan–Meier analysis and univariable and multivariable Cox regression analyses were used to assess the discriminative power of the identified cutoff value, with time zero defined as the date of the TAVI procedure. Subjects who died during the procedure were included in the analysis and survival time was set to 1 day. All variables with $P<0.1$ in univariable analysis were included in the multivariable model (age, sex, chronic obstructive pulmonary disease, atrial

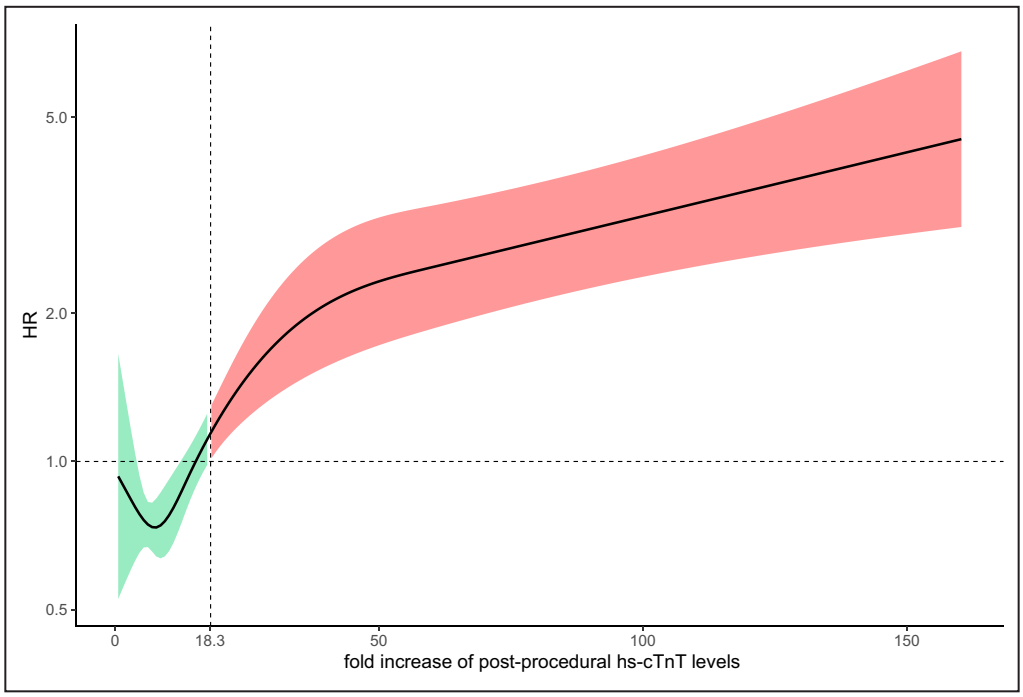

Figure 1. Restricted cubic spline analysis to determine the threshold at which postprocedural myocardial injury determines mortality.
Green and red areas represent the 95% CI. Univariable Cox proportional hazard regression with restricted cubic splines was used to flexibly model the association of peak hs-cTnT levels above URL with mortality at 2 years after transcatheter aortic valve implantation. The minimal threshold at which hs-cTnT is significantly associated with mortality at 2 years was identified at 18.3-fold increase above URL. HR indicates hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; and URL, upper reference limit.

fibrillation, renal failure, peripheral artery disease, and STS-PROM Score as a continuous variable). The independent association of the cutoff value was also tested for secondary endpoints. Furthermore, interactions of postprocedural peak hs-cTnT levels above the URL with sex as well as all variables included in the multivariable model were tested by including interaction terms in the corresponding Cox regression models. We used the cox.zph command which is part of the survival package (version 3.2-7) in the statistical software R to test for the proportional hazard assumption. We also used Poisson regression with robust SEs to calculate rate ratios for in-hospital events. In an explorative analysis, we determined factors associated with postprocedural myocardial injury using univariable and multivariable logistic regression models. Findings were considered statistically significant at the 0.05 level. All analyses were performed with R software for statistical computing (Version 4.0.2).

RESULTS

Threshold Definition for Postprocedural Myocardial Injury After TAVI

Out of 1333 patients, 187 (14.0%) patients died during the 2-year follow-up. A significant association between postprocedural peak hs-cTnT levels and mortality at 2 years was observed in univariable Cox regression analysis (hazard ratio [HR], 1.01 [95% CI, 1.01–1.01]; $P<0.001$). Restricted cubic splines with 4 knots placed at flexible locations were then used to model the relation of postprocedural peak hs-cTnT levels above the URL with mortality at 2 years (Figure 1). At an 18.3-fold increase of postprocedural peak hs-cTnT levels above the URL, the lower end of the CI crossed a relative risk for all-cause mortality of 1. A ≥18.3-fold increase of postprocedural peak hs-cTnT levels above the URL was therefore defined as postprocedural myocardial injury.

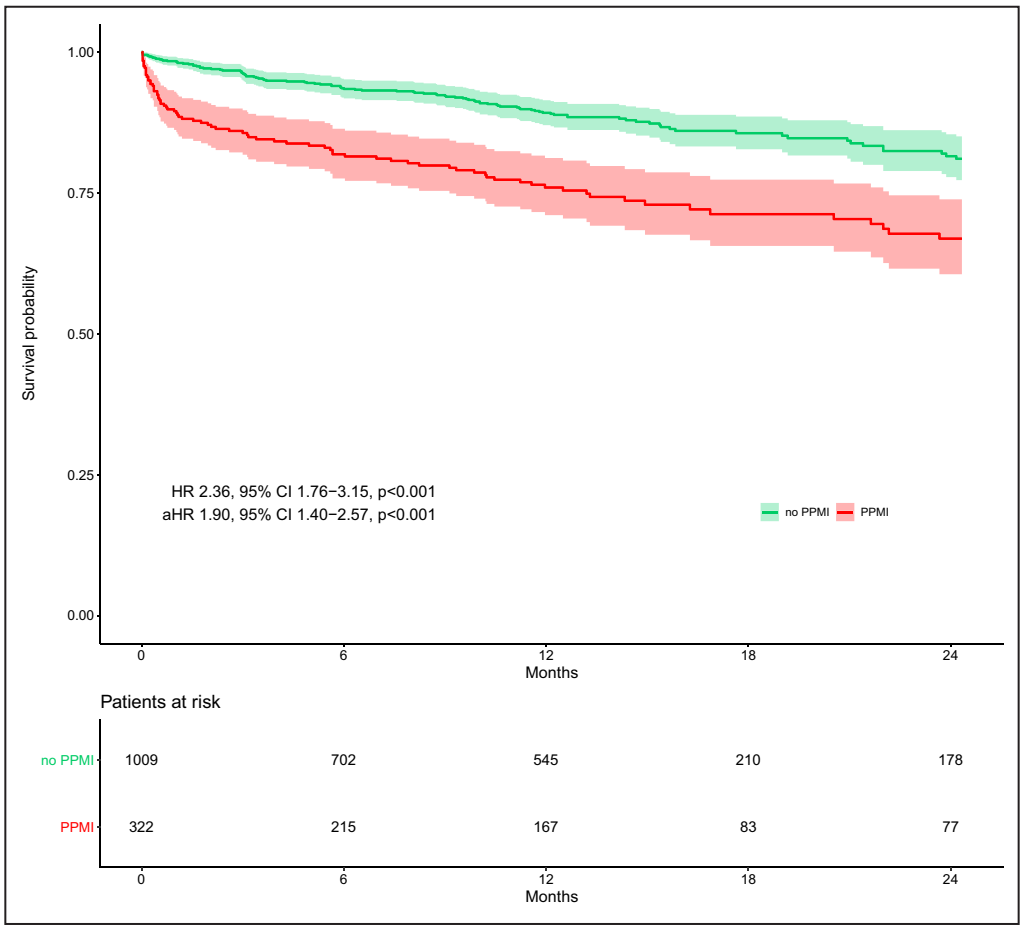

Figure 2. Kaplan–Meier estimates of survival according to the presence/absence of postprocedural myocardial injury.
The HR was adjusted for age, sex, chronic obstructive pulmonary disease, atrial fibrillation, peripheral artery disease, and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) Score. aHR indicates adjusted hazard ratio; HR, hazard ratio; and PPMI, postprocedural myocardial injury.

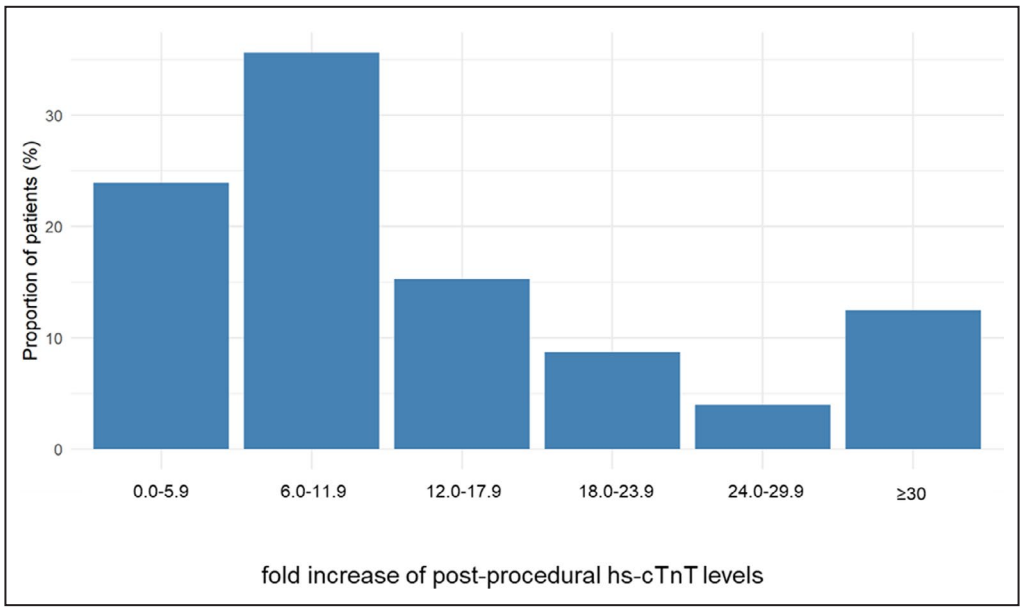

Figure 3. Increases of high-sensitivity cardiac troponin T levels following transcatheter aortic valve implantation.
Proportion of patients across categories of postprocedural increases of hs-cTnT above the URL. hs-cTnT indicates high-sensitivity cardiac troponin T; and URL, upper reference limit.

Kaplan–Meier analyses showed that mortality at 2 years was significantly higher in patients with postprocedural peak hs-cTnT levels ≥18.3-fold above the URL than in those with values below (*P*<0.001, Figure 2). No significant interaction between postprocedural peak hs-cTnT levels and sex was observed.

Baseline and Procedural Characteristics

Postprocedural myocardial injury as defined by a ≥18.3-fold increase of postprocedural peak hs-cTnT levels occurred in 322 (24.2%) patients (Figure 3). Baseline characteristics according to the presence/absence of postprocedural myocardial injury are given in Table 1. Mean postprocedural peak hs-cTnT level was 253.8 (±411.3) ng/L and mean postprocedural hs-cTnT increase above the URL was 18.1 (±29.4)-fold. Patients with postprocedural myocardial injury were older, had a higher STS-PROM Score, and a higher European System for Cardiac Operative Risk Evaluation II Score (EuroSCORE II). They more often had prior percutaneous coronary intervention, known coronary artery disease and renal dysfunction, and more often presented with severe dyspnea, high-grade mitral regurgitation, and pulmonary hypertension. Procedural characteristics according to the presence/absence of postprocedural myocardial injury are given in Table 2. Patients with postprocedural myocardial injury had a longer procedure time and more frequently underwent concomitant coronary revascularization during the TAVI procedure. Postprocedural myocardial injury was observed in 26 out of 31 (83.9%) patients with transapical TAVI.

Postprocedural Myocardial Injury After TAVI and Outcomes

In-hospital outcomes of patients with and without postprocedural myocardial injury are given in Table S1. Postprocedural myocardial injury was significantly associated with an excess risk of mortality at 2 years (HR, 2.36 [95% CI, 1.76–3.15]; *P*<0.001, Table 3 and Table S2). The association of postprocedural myocardial injury with 2-year mortality remained significant irrespective of the presence (adjusted HR, 2.17 [95% CI, 1.44–3.29]; *P*<0.001) or absence (adjusted HR, 2.67 [95% CI, 1.20–5.93]; *P*=0.03) of coronary artery disease (Figure 4A), as well as the presence (adjusted HR, 1.88 [95% CI, 1.35–2.62]; *P*<0.001) or absence (adjusted HR, 2.21 [95% CI, 1.09–4.50]; *P*=0.03) of renal dysfunction (Figure 4B). Furthermore, the association of postprocedural myocardial injury with 2-year mortality was significant both in patients with low (adjusted HR, 1.76 [95% CI, 1.13–2.75]; *P*=0.015) and intermediate/high surgical risk (adjusted HR, 2.70 [95% CI, 1.40–5.22]; *P*<0.001, Figure 4C). This association remained significant in a univariable landmark analysis between 30 days and 2 years (HR, 1.61 [95% CI, 1.13–2.28]; *P*=0.01, Figure 5), while in multivariable landmark analysis, the association was not significant (adjusted HR, 1.22 [95% CI, 0.84–1.76]; *P*=0.32).

Table 1. Baseline Characteristics According to the Presence of Postprocedural Myocardial Injury Defined as an 18.3-Fold Increase of Postprocedural Troponin Levels Above the Upper Reference Limit

	No PPMI (N=1011)	PPMI (N=322)	Total (N=1333)	*P* value
Age				0.006
No.	1011	322	1333	
Mean (SD)	80.2 (7.6)	81.5 (7.6)	80.5 (7.7)	
Sex				0.51
Male	549 (54.3%)	168 (52.2%)	717 (53.8%)	
Female	462 (45.7%)	154 (47.8%)	616 (46.2%)	
BMI				0.17
No.	1011	321	1332	
Mean (SD)	27.1 (5.1)	26.7 (4.8)	27.0 (5.1)	
Diabetes				0.32
Yes	270 (26.7%)	77 (23.9%)	347 (26.0%)	
No	741 (73.3%)	245 (76.1%)	986 (74.0%)	
Hypertension				0.96
Yes	780 (77.2%)	248 (77.0%)	1028 (77.1%)	
No	231 (22.8%)	74 (23.0%)	305 (22.9%)	
Dyslipidemia				0.97
Yes	498 (49.3%)	159 (49.4%)	657 (49.3%)	
No	513 (50.7%)	163 (50.6%)	676 (50.7%)	
Coronary artery disease				0.005
Yes	474 (46.9%)	180 (55.9%)	654 (49.1%)	
No	537 (53.1%)	142 (44.1%)	679 (50.9%)	
Myocardial infarction				0.77
Yes	95 (9.4%)	32 (9.9%)	127 (9.5%)	
No	916 (90.6%)	290 (90.1%)	1206 (90.5%)	
PCI				0.03
Yes	225 (22.3%)	91 (28.3%)	316 (23.7%)	
No	786 (77.7%)	231 (71.7%)	1017 (76.3%)	
Pacemaker implantation				0.92
Yes	77 (7.6%)	24 (7.5%)	101 (7.6%)	
No	934 (92.4%)	298 (92.5%)	1232 (92.4%)	
Atrial fibrillation				0.27
Yes	196 (19.5%)	58 (18.2%)	254 (19.0%)	
No	813 (80.5%)	263 (81.8)	1076 (81.0)	
Pulmonary hypertension				0.01
Yes	34 (3.4%)	21 (6.8%)	55 (4.2%)	
No	956 (96.6%)	286 (93.2%)	1242 (95.8%)	
COPD				0.22
Yes	121 (12.0%)	47 (14.6%)	168 (12.6%)	
No	890 (88.0%)	275 (85.4%)	1165 (87.4%)	
Cerebrovascular event				0.48
Yes	114 (11.3%)	41 (12.7%)	155 (11.6%)	
No	897 (88.7%)	281 (87.3%)	1178 (88.4%)	
Renal failure				<0.001
Yes	643 (63.7%)	252 (78.5%)	895 (67.2%)	
No	367 (36.3%)	69 (21.5%)	436 (32.8%)	
Dyspnea				0.03
NYHA I	175 (17.3%)	45 (14.0%)	220 (16.5%)	

(*Continued*)

Table 1. (Continued)

	No PPMI (N=1011)	PPMI (N=322)	Total (N=1333)	*P* value
NYHA II	346 (34.2%)	92 (28.6%)	438 (32.9%)	
NYHA III	421 (41.6%)	153 (47.5%)	574 (43.1%)	
NYHA IV	69 (6.8%)	32 (9.9%)	101 (7.6%)	
EuroSCORE II				<0.001
No.	955	294	1249	
Mean (SD)	4.3 (4.0)	5.8 (6.3)	4.7 (4.7)	
STS-PROM Score				<0.001
No.	1009	321	1330	
Mean (SD)	4.3 (3.2)	5.7 (4.7)	4.7 (3.7)	
Troponin at baseline (ng/L)				<0.001
No.	773	257	1030	
Median (IQR)	23.0 (15.0–40.0)	42.0 (21.0–88.0)	26.0 (16.0–49.0)	
Postprocedural peak troponin (ng/L)				<0.001
No.	1011	322	1333	
Median (IQR)	112.0 (74.0–159.0)	433.5 (311.8–746.5)	139.0 (86.0–252.0)	
Postprocedural peak CK (U/L)				<0.001
No.	992	319	1311	
Mean (SD)	151.3 (300.0)	776.1 (3569.4)	303.3 (1798.0)	
LVEF (%)				0.921
No.	1002	317	1319	
Mean (SD)	53.9 (13.7)	53.8 (14.0)	53.9 (13.8)	
Transaortic mean pressure gradient (mm Hg)				0.29
No.	986	306	1292	
Mean (SD)	40.6 (16.1)	41.7 (17.7)	40.8 (16.5)	
Aortic valve area (cm^2)				0.89
No.	911	284	1195	
Mean (SD)	0.7 (0.2)	0.7 (0.3)	0.7 (0.2)	
Aortic regurgitation grade				0.54
None/mild	859 (87.0%)	271 (86.3%)	1130 (86.9%)	
Moderate	80 (8.1%)	23 (7.3%)	103 (7.9%)	
Severe	48 (4.9%)	20 (6.4%)	68 (5.2%)	
Mitral regurgitation grade				0.02
None/mild	760 (77.2%)	214 (69.3%)	974 (75.3%)	
Moderate	178 (18.1%)	75 (24.3%)	253 (19.6%)	
Severe	46 (4.7%)	20 (6.5%)	66 (5.1%)	
Tricuspid regurgitation grade				0.58
None/mild	866 (88.7%)	271 (87.1%)	1137 (88.3%)	
Moderate	79 (8.1%)	31 (10.0%)	110 (8.5%)	
Severe	31 (3.2%)	9 (2.9%)	40 (3.1%)	
Aspirin				0.27
Yes	561 (55.5%)	190 (59.0%)	751 (56.3%)	
No	450 (44.5%)	132 (41.0%)	582 (43.7%)	
Statin				0.49
Yes	581 (57.5%)	192 (59.6%)	773 (58.0%)	
No	430 (42.5%)	130 (40.4%)	560 (42.0%)	
β-Blocker				0.90
Yes	492 (48.7%)	158 (49.1%)	650 (48.8%)	

(*Continued*)

Table 1. (Continued)

	No PPMI (N=1011)	PPMI (N=322)	Total (N=1333)	*P* value
No	519 (51.3%)	164 (50.9%)	683 (51.2%)	
ACE inhibitor				0.65
Yes	312 (30.9%)	95 (29.5%)	407 (30.5%)	
No	699 (69.1%)	227 (70.5%)	926 (69.5%)	
Diuretics				0.004
Yes	557 (55.1%)	207 (64.3%)	764 (57.3%)	
No	454 (44.9%)	115 (35.7%)	569 (42.7%)	

Values are given as mean and SD or numbers and percentages. Renal failure was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. ACE indicates angiotensin-converting enzyme; BMI, body mass index; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PPMI, postprocedural myocardial injury; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Postprocedural myocardial injury was also significantly associated with secondary endpoints including cardiovascular death (adjusted HR, 2.58 [95% CI, 1.58–4.23]; *P*=0.008), myocardial infarction (adjusted HR, 3.41 [95% CI, 1.24–9.38]; *P*<0.001), and acute kidney failure (adjusted HR, 2.91 [95% CI, 1.88–4.52]; *P*<0.001) at both 30 days and 2 years (Table 3).

Table 2. Procedural Characteristics According to the Presence of Postprocedural Myocardial Injury Defined as an 18.3-Fold Increase of Postprocedural Troponin Levels Above the Upper Reference Limit

	No PPMI (N=1011)	PPMI (N=322)	Total (N=1333)	*P* value
Access site				<0.001
No.	1010	322	1332	
Femoral	983 (97.3%)	288 (89.4%)	1271 (95.4%)	
Transapical	5 (0.5%)	26 (8.1%)	31 (2.3%)	
Subclavian	20 (2.0%)	8 (2.5%)	28 (2.1%)	
Aortic	2 (0.2%)	0 (0.0%)	2 (0.2%)	
Prosthesis type				0.005
Edwards Sapien 3	289 (28.6%)	86 (26.9%)	375 (28.2%)	
SJM Portico	232 (23.0%)	58 (18.1%)	290 (21.8%)	
Medtronic Evolut R	161 (15.9%)	42 (13.1%)	203 (15.3%)	
Medtronic CoreValve	106 (10.5%)	47 (14.7%)	153 (11.5%)	
Edwards Sapien XT	66 (6.5%)	38 (11.9%)	104 (7.8%)	
Concomitant PCI				0.006
Yes	47 (4.7%)	28 (8.7%)	75 (5.6%)	
No	963 (95.3%)	294 (91.3%)	1257 (94.4%)	
Procedure time (min)				0.003
No.	366	166	532	
Mean (SD)	55.7 (42.6)	67.4 (41.7)	59.4 (42.6)	
Postprocedure mean trans-prosthetic pressure gradient (mm Hg)				0.10
No.	975	286	1261	
Mean (SD)	8.1 (4.6)	8.6 (5.3)	8.2 (4.8)	
Postprocedure mean trans-prosthetic pressure gradient (mm Hg) binary				0.75
<20 mm Hg	951 (97.5%)	278 (97.2%)	1229 (97.5%)	
≥20 mm Hg	24 (2.5%)	8 (2.8%)	32 (2.5%)	
Device success				0.28
Device failure (VARC-2)	140 (15.3%)	49 (18.0%)	189 (15.9%)	
Device success (VARC-2)	775 (84.7%)	223 (82.0%)	998 (84.1%)	

Values are given as mean and SD or numbers and percentages. PCI indicates percutaneous coronary intervention; PPMI, postprocedural myocardial injury; and VARC-2, Valve Academic Research Consortium-2.

Table 3. Outcomes According to Presence of Postprocedural Myocardial Injury as Defined by an 18.3-Fold Increase Above the Upper Reference Limit

Outcome	No PPMI	PPMI	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
30 d						
All-cause mortality	16 (1.6%)	33 (10.2%)	6.74 (3.71–12.20)	<0.001	6.09 (3.30–11.20)	<0.001
Cardiovascular death	9 (0.9%)	14 (4.3%)	5.16 (2.23–11.90)	<0.001	4.48 (1.90–10.60)	<0.001
Cerebrovascular events	20 (2.0%)	12 (3.7%)	2.03 (0.99–4.15)	0.06	1.76 (0.85–3.68)	0.14
Myocardial infarction	2 (0.2%)	5 (1.6%)	8.39 (1.63–43.30)	0.007	9.92 (1.85–53.10)	0.007
Acute kidney failure	25 (2.5%)	35 (10.9%)	4.80 (2.87–8.03)	<0.001	3.95 (2.33–6.71)	<0.001
2 y						
All-cause mortality*	107 (10.6%)	80 (24.8%)	2.36 (1.76–3.15)	<0.001	1.90 (1.40–2.57)	<0.001
Cardiovascular death	34 (3.4%)	34 (10.6%)	3.31 (2.06–5.33)	<0.001	2.58 (1.58–4.23)	0.008
Cerebrovascular events	28 (2.8%)	13 (4.0%)	1.58 (0.82–3.05)	0.32	1.34 (0.68–2.62)	0.40
Myocardial infarction	8 (0.8%)	8 (2.5%)	3.35 (1.26–8.93)	0.02	3.41 (1.24–9.38)	<0.001
Acute kidney failure	42 (4.2%)	43 (13.4%)	3.50 (2.29–5.36)	<0.001	2.91 (1.88–4.52)	<0.001

Reported are numbers of first events (%), HRs with corresponding 95% CI from Cox regression models. Multivariable Cox regression models were adjusted for age, sex, chronic obstructive pulmonary disease, peripheral artery disease, renal dysfunction, and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) Score. HR indicates hazard ratio; and PPMI, periprocedural myocardial injury.

*The proportional hazards assumption for this variable was violated at 2 years.

Sensitivity Analyses

Sensitivity analyses testing the robustness of the results are given in Table S3. The estimated threshold remained unchanged when restricting the univariable analysis follow-up time to 30 days and 5 years. Similarly, the threshold remained unchanged when adjusting the restricted cubic spline analysis for age, sex, chronic obstructive pulmonary disease, renal dysfunction, peripheral artery disease, and the STS-PROM Score. Changes in inclusion criteria only modestly affected the estimated threshold. When excluding patients with baseline hs-cTnT levels >70-fold increase above the URL, the lower bound of the 95% CI crossed the HR of 1 at a 22.7-fold increase of postprocedural peak hs-cTnT levels above the URL.

DISCUSSION

This observational study for the first time determined a threshold for the association of postprocedural troponin elevation and long-term mortality after TAVI. Using spline curve analysis, an 18-fold hs-cTnT increase after TAVI was identified as minimum value being significantly associated with mortality at 2 years. The proposed definition of clinically relevant postprocedural myocardial injury advances patient risk stratification after TAVI and assists in postprocedural clinical care.

Postprocedural Myocardial Injury in Patients With TAVI

Although postprocedural myocardial injury is among the most frequent complications occurring after TAVI, the clinical relevance of biomarker elevations remains controversial.[12,13,15,16] While biomarker increases after coronary revascularization have been extensively studied,[29–31] there is a paucity of data on the impact of biomarker increases on prognosis in patients undergoing TAVI, and most studies are limited by their rather small sample size and short-term follow-up. Pathophysiological mechanisms underlying the occurrence of postprocedural myocardial injury in patients with TAVI are multifaceted, but only poorly understood. Coronary artery occlusion by the transcatheter heart valve in most severe cases, mechanical compression of the left ventricular outflow tract, distal microembolization of calcium particles during valve manipulation, and myocardial ischemia related to transient hypotension during rapid ventricular pacing are considered to be principally involved, along with direct left ventricular trauma in transapical procedures (Figure 6).[13,15,16,29,32] An embolic cause is further supported by cardiac magnetic resonance findings of multifocal small-sized new myocardial late enhancements after TAVI of subendocardial or intramural localization as well as by in vitro models of aortic valvuloplasty.[32,33] Concomitant coronary artery disease further aggravates myocardial oxygen supply–demand mismatch that may occur during procedural phases of hypotension. In this study, patients with myocardial injury after TAVI were older, had higher surgical risk scores, more often presented with coronary artery disease and renal dysfunction, and more frequently had high-grade mitral regurgitation. The association between known coronary artery disease as well as renal dysfunction and an increased occurrence of myocardial injury after

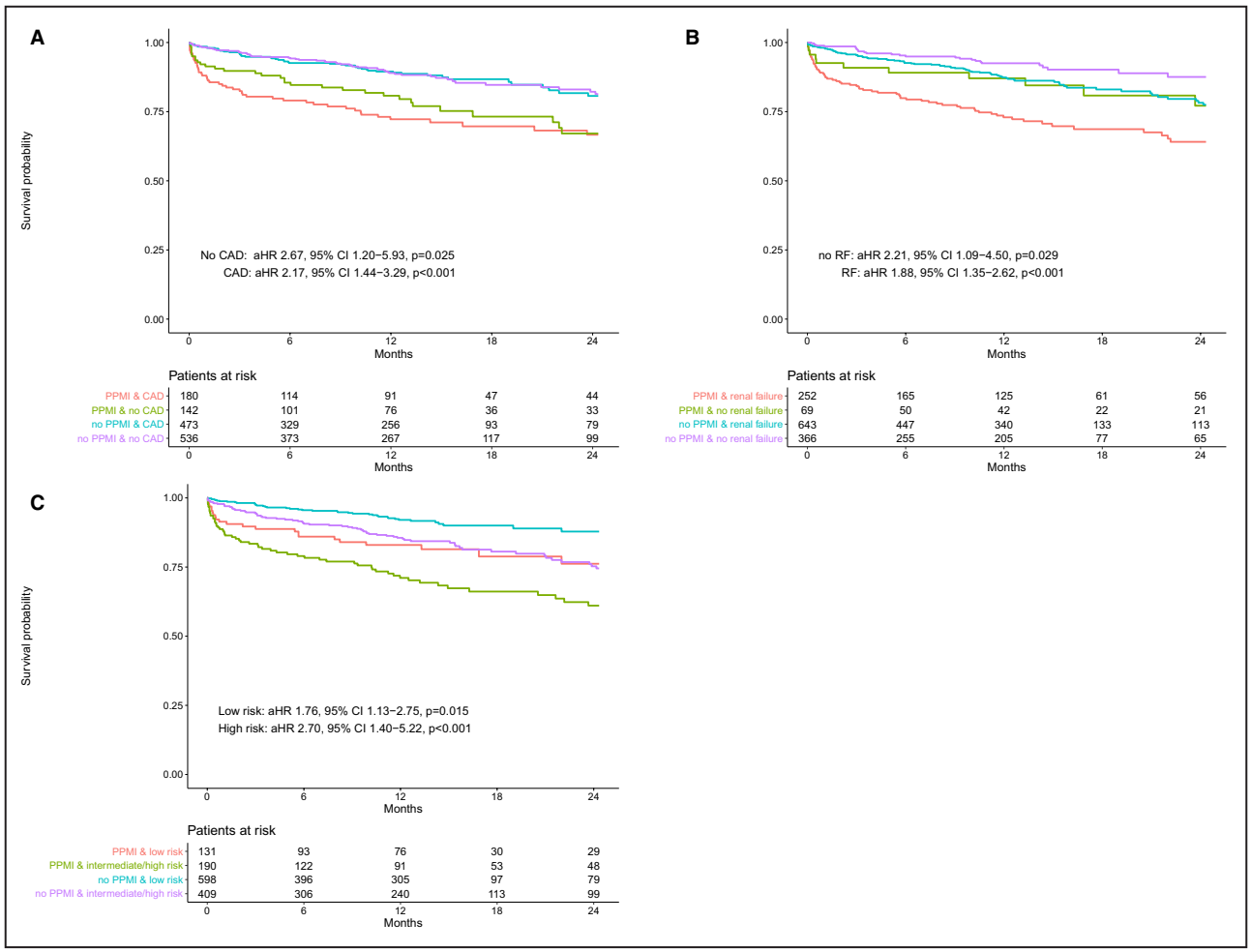

Figure 4. Kaplan–Meier estimates of survival according to the presence/absence of postprocedural myocardial injury stratified for coronary artery disease, renal dysfunction, and surgical risk.
A, Kaplan–Meier estimates of survival in patients with and without PPMI stratified according to the presence/absence of coronary artery disease. **B**, Kaplan–Meier estimates of survival in patients with and without PPMI stratified according to the presence/absence of renal dysfunction. **C**, Kaplan–Meier estimates of survival in patients with and without PPMI stratified according to low or intermediate/high surgical risk. The hazard ratio in (**A** through **C**) was adjusted for age, sex, chronic obstructive pulmonary disease, atrial fibrillation, peripheral artery disease, and Society of Thoracic Surgeons Predicted Risk of Mortality score. aHR indicates adjusted hazard ratio; CAD, coronary artery disease; PPMI, postprocedural myocardial injury; and RF, renal failure.

TAVI has previously been reported.[12,13,16] In these susceptible patients, preventive measures to reduce the amount of myocardial injury may improve prognosis after TAVI.

Postprocedural Myocardial Injury and Outcomes in Patients With TAVI

Myocardial injury after TAVI has been related to worse prognosis in most studies.[12,14,16] To date, thresholds for the definition of postprocedural myocardial injury after TAVI are ambiguous, not well established, and may vary among studies. Given the lack of scientific evidence in the field, the Valve Academic Research Consortium-2 consensus definition of myocardial infarction after TAVI arbitrarily included a 15-fold increase in cardiac troponin levels.[28] In this study, spline curve analysis identified a threshold of 18 as optimal cutoff value of postprocedural hs-cTnT elevations for long-term mortality prediction, with proven robustness in multiple subgroup, multivariable, and landmark analyses. Relations of postprocedural hs-cTnT elevations with mortality proved to be significant also in high-risk patient subsets including those with coronary artery disease, renal dysfunction, and increased surgical risk. Hence, the proposed definition of clinically relevant myocardial injury after TAVI is based on a large contemporary cohort of patients and sound statistical methodology.

Incorporating elevated postprocedural troponin levels complements postprocedural risk assessment and therefore guides further management of patients

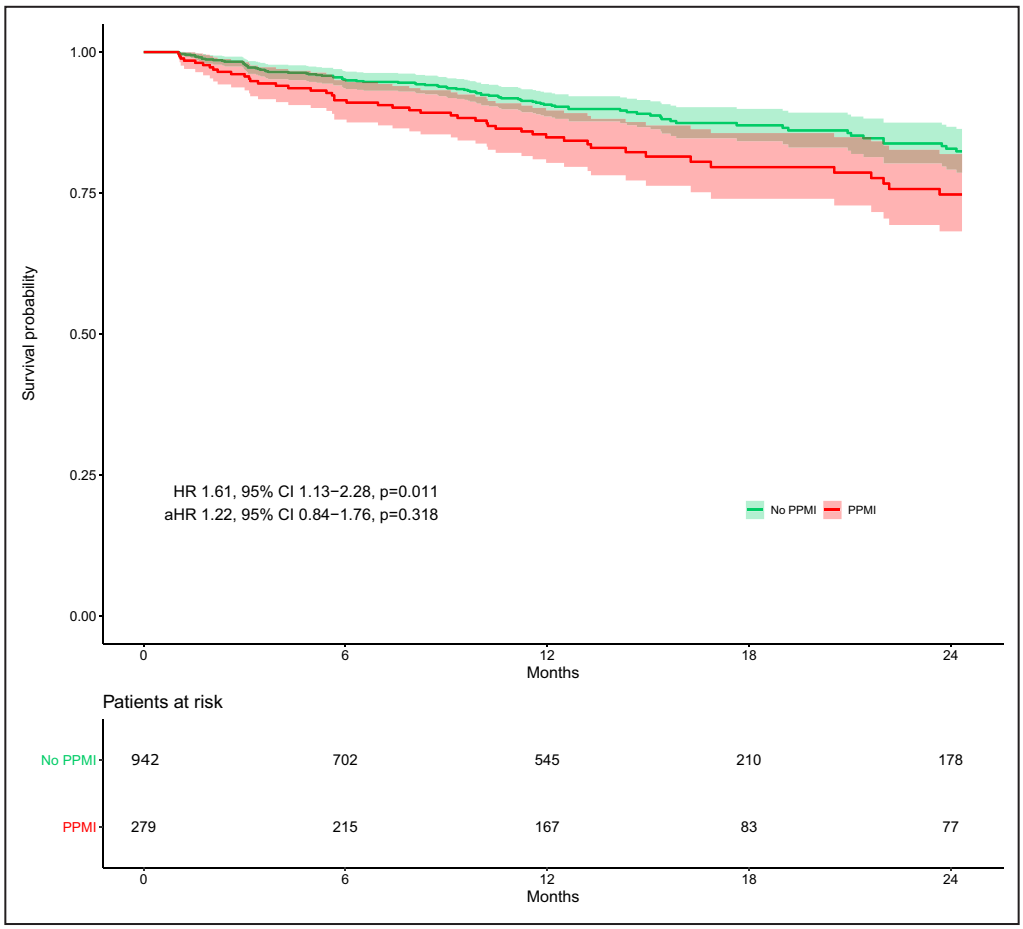

Figure 5. Landmark analysis of survival between 30 days and 2 years according to the presence/absence of postprocedural myocardial injury.
CI = confidence interval, HR, hazard ratio; PPMI, post-procedural myocardial infarction.

undergoing TAVI. A comprehensive risk stratification in patients with recent TAVI allows for the identification of patients in need of intense postprocedural care, closer monitoring, and prompt follow-up. Furthermore, the use of a standardized and appropriate definition of clinically relevant myocardial injury after TAVI would provide uniformity for the comparability of clinical and healthcare studies as well as the assessment of patient outcomes and quality initiatives. Although the need for sex-related definitions of reference values is widely recognized, no sex-related differences in the relation of postprocedural peak hs-cTnT levels and mortality were observed.

Whether myocardial ischemia as reflected by increased hs-cTnT levels directly drives mortality after TAVI, or whether elevated hs-cTnT levels represent a surrogate of a highly comorbid patient population at increased risk, remains to be determined. Furthermore, whether a causal relationship between increased rates of in-hospital complications including vascular complications, renal failure, and repeated unplanned interventions and the occurrence of postprocedural hs-cTnT elevations exists needs to be further elucidated.

Limitations

Some limitations merit consideration. The prospective observational study enrolled a large contemporary cohort of patients undergoing TAVR and included comprehensive clinical, procedural, and outcome data, along with systematically measured postprocedural hs-cTnT levels. The study is, however, inherently subject to the limitation of a single-center design. Furthermore, although established risk factors were incorporated into the multivariable models, we cannot exclude that unmeasured or unknown confounding factors may have affected the observed associations of postprocedural peak hs-cTnT levels with outcomes after TAVI.

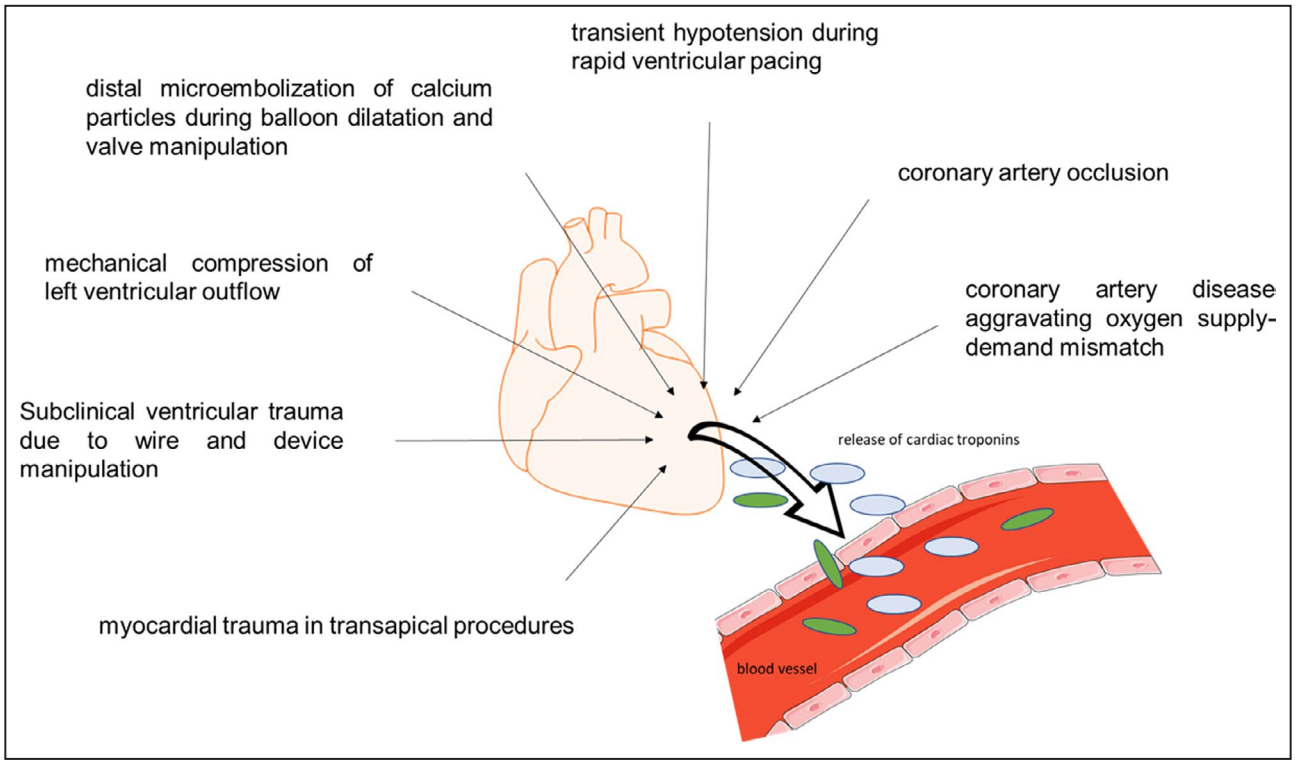

Figure 6. Schematic illustration of pathophysiological mechanisms contributing to increases of cardiac troponin levels in patients undergoing transcatheter aortic valve implantation.

CONCLUSIONS

This contemporary study for the first time established a hs-cTnT threshold for the definition of postprocedural myocardial injury after TAVI. An elevation of hs-cTnT ≥18-fold the URL was recognized as most appropriate for the identification of patients with TAVI at increased risk of long-term mortality. Hence, clinically relevant postprocedural myocardial injury should be incorporated into patient stratification after TAVI to further improve postprocedural patient care, management, and outcomes.

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Disclosures

The authors have nothing to disclose regarding the content of the paper.

Supplementary Material

Tables S1–S3

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
2. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol*. 2012;60:1854–1863. doi: 10.1016/j.jacc.2012.02.093
3. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol*. 1993;21:1220–1225. doi: 10.1016/0735-1097(93)90249-Z
4. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392. doi: 10.1016/j.echo.2017.02.009
5. Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. *J Am Coll Cardiol*. 2015;66:561–577. doi: 10.1016/j.jacc.2015.05.066
6. Goldsweig AM, Tak HJ, Chen LW, Aronow HD, Shah B, Kolte D, Desai NR, Szerlip M, Velagapudi P, Abbott JD. Relative costs of surgical and transcatheter aortic valve replacement and medical therapy. *Circ Cardiovasc Interv*. 2020;13:e008681. doi: 10.1161/CIRCINTERVENTIONS.119.008681
7. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Munoz DR, et al; ESC Scientific Document Group. ESC/EACTS Guidelines for the management of valvular heart disease: the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association

for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2017;2017:2739–2791. doi: 10.1093/eurheartj/ehx391
8. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607. doi: 10.1056/NEJMoa1008232
9. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052
10. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798. doi: 10.1056/NEJMoa1400590
11. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–1715. doi: 10.1056/NEJMoa1816885
12. Rodes-Cabau J, Gutierrez M, Bagur R, De Larochelliere R, Doyle D, Cote M, Villeneuve J, Bertrand OF, Larose E & Manazzoni J, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2011;57:1988–1999. doi: 10.1016/j.jacc.2010.11.060
13. Barbash IM, Dvir D, Ben-Dor I, Badr S, Okubagzi P, Torguson R, Corso PJ, Xue Z, Satler LF, Pichard AD, et al. Prevalence and effect of myocardial injury after transcatheter aortic valve replacement. *Am J Cardiol*. 2013;111:1337–1343. doi: 10.1016/j.amjcard.2012.12.059
14. Yong ZY, Wiegerinck EMA, Boerlage-van Dijk K, Koch KT, Vis MM, Bouma BJ, Henriques JPS, Cocchieri R, Piek JJ, de Mol BAJM, et al. Predictors and prognostic value of myocardial injury during transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2012;5:415–423. doi: 10.1161/CIRCINTERVENTIONS.111.964882
15. Sato T, Aizawa Y, Yuasa S, Taya Y, Fujita S, Ikeda Y, Kitazawa H, Takahashi M, Okabe M. The determinants and outcomes of myocardial injury after transcatheter aortic-valve implantation: SAPIEN 3 study. *Cardiovasc Revasc Med*. 2020;21:973–979. doi: 10.1016/j.carrev.2019.12.028
16. Koskinas KC, Stortecky S, Franzone A, O'Sullivan CJ, Praz F, Zuk K, Räber L, Pilgrim T, Moschovitis A, Fiedler GM, et al. Post-procedural troponin elevation and clinical outcomes following transcatheter aortic valve implantation. *J Am Heart Assoc*. 2016;5:3002430. doi: 10.1161/JAHA.115.002430
17. Akodad M, Spaziano M, Chevalier B, Garot P, Benamer H, Dinan-Zannier A, Troussier X, Unterseeh T, Champagne S, Hovasse T, et al. Prognostic impact of pre-transcatheter and post-transcatheter aortic valve intervention troponin: a large cohort study. *J Am Heart Assoc*. 2019;8:e011111. doi: 10.1161/JAHA.118.011111
18. Michail M, Cameron JN, Nerlekar N, Ihdayhid AR, McCormick LM, Gooley R, Niccoli G, Crea F, Montone RA, Brown AJ. Periprocedural myocardial injury predicts short- and long-term mortality in patients undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2018;11:e007106. doi: 10.1161/CIRCINTERVENTIONS.118.007106
19. Sinning J-M, Hammerstingl C, Schueler R, Neugebauer A, Keul S, Ghanem A, Mellert F, Schiller W, Müller C, Vasa-Nicotera M, et al. The prognostic value of acute and chronic troponin elevation after transcatheter aortic valve implantation. *EuroIntervention*. 2016;11:1522–1529. doi: 10.4244/EIJY15M02_02
20. Carrabba N, Valenti R, Migliorini A, Vergara R, Parodi G, Antoniucci D. Prognostic value of myocardial injury following transcatheter aortic valve implantation. *Am J Cardiol*. 2013;111:1475–1481. doi: 10.1016/j.amjcard.2013.01.301
21. Stundl A, Schulte R, Lucht H, Weber M, Sedaghat A, Shamekhi J, Zur B, Grube E, Mellert F, Welz A, et al. Periprocedural myocardial injury depends on transcatheter heart valve type but does not predict mortality in patients after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:1550–1560. doi: 10.1016/j.jcin.2017.05.029
22. Kohler WM, Freitag-Wolf S, Lambers M, Lutz M, Niemann PM, Petzina R, Lutter G, Bramlage P, Frey N, Frank D. Preprocedural but not periprocedural high-sensitive Troponin T levels predict outcome in patients undergoing transcatheter aortic valve implantation. *Cardiovasc Ther*. 2016;34:385–396. doi: 10.1111/1755-5922.12208
23. Stortecky S, Heg D, Tueller D, Pilgrim T, Muller O, Noble S, Jeger R, Toggweiler S, Ferrari E, Taramasso M, et al. Infective endocarditis after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;75:3020–3030. doi: 10.1016/j.jacc.2020.04.044
24. Muller O, Fournier S, Pilgrim T, Heg D, Noble S, Jeger R, Toggweiler S, Taramasso M, Windecker S, Stortecky S, et al. Local versus general anesthesia for transcatheter aortic valve replacement: a SwissTAVI registry analysis. *JACC Cardiovasc Interv*. 2019;12:1874–1876. doi: 10.1016/j.jcin.2019.05.047
25. Stähli BE, Tasnady H, Lüscher TF, Gebhard C, Mikulicic F, Erhart L, Bühler I, Landmesser U, Altwegg L, Wischnewsky MB, et al. Early and late mortality in patients undergoing transcatheter aortic valve implantation: comparison of the novel EuroScore II with established risk scores. *Cardiology*. 2013;126:15–23. doi: 10.1159/000351438
26. Stahli BE, Gebhard C, Saleh L, Falk V, Landmesser U, Nietlispach F, Maisano F, Luscher TF, Maier W, Binder RK. N-terminal pro-B-type natriuretic peptide-ratio predicts mortality after transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2015;85:1240–1247. doi: 10.1002/ccd.25788
27. Goliasch G, Winter M-P, Ayoub M, Bartko PE, Gebhard C, Mashayekhi K, Ferenc M, Buettner HJ, Hengstenberg C, Neumann F-J, et al. A contemporary definition of periprocedural myocardial injury after percutaneous coronary intervention of chronic total occlusions. *JACC Cardiovasc Interv*. 2019;12:1915–1923. doi: 10.1016/j.jcin.2019.06.053
28. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es G-A, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33:2403–2418. doi: 10.1093/eurheartj/ehs255
29. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med*. 2011;364:453–464. doi: 10.1056/NEJMra0912134
30. Toma A, Stahli BE, Gebhard C, Gick M, Minners J, Mashayekhi K, Avran A, Ferenc M, Buettner HJ, Neumann FJ. Clinical implications of periprocedural myocardial injury in patients undergoing percutaneous coronary intervention for chronic total occlusion: role of antegrade and retrograde crossing techniques. *EuroIntervention*. 2018;13:2051–2059. doi: 10.4244/EIJ-D-17-00338
31. Kong TQ, Davidson CJ, Meyers SN, Tauke JT, Parker MA, Bonow RO. Prognostic implication of creatine kinase elevation following elective coronary artery interventions. *JAMA*. 1997;277:461–466. doi: 10.1001/jama.277.6.461
32. Kim W-K, Rolf A, Liebetrau C, Van Linden A, Blumenstein J, Kempfert J, Bachmann G, Nef H, Hamm C, Walther T, et al. Detection of myocardial injury by CMR after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2014;64:349–357. doi: 10.1016/j.jacc.2014.03.052
33. Haberthur D, Lutter G, Appel M, Attmann T, Schramm R, Schmitz C, Quaden RB. Percutaneous aortic valve replacement: valvuloplasty studies in vitro. *Eur J Cardiothorac Surg*. 2011;39:631–634. doi: 10.1016/j.ejcts.2010.07.045