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Predictors and Impact of Myocardial Injury After Transcatheter Aortic Valve Replacement

A Multicenter Registry

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ABSTRACT

BACKGROUND Cardiac biomarker release signifying myocardial injury post-transcatheter aortic valve replacement (TAVR) is common, yet its clinical impact within a large TAVR cohort receiving differing types of valve and procedural approaches is unknown.

OBJECTIVES This study sought to determine the incidence, clinical impact, and factors associated with cardiac biomarker elevation post TAVR.

METHODS This multicenter study included 1,131 consecutive patients undergoing TAVR with balloon-expandable (58%) or self-expandable (42%) valves. Transfemoral and transapical (TA) approaches were selected in 73.1% and 20.3% of patients, respectively. Creatine kinase-myocardial band (CK-MB) measurements were obtained at baseline and at several time points within the initial 72 h post TAVR. Echocardiography was performed at baseline and at 6- to 12-month follow-up.

RESULTS Overall, 66% of the TAVR population demonstrated some degree of myocardial injury as determined by a rise in CK-MB levels (peak value: 1.6-fold [interquartile range (IQR): 0.9 to 2.8-fold]). A TA approach and major procedural complications were independently associated with higher peak of CK-MB levels ($p < 0.01$ for all), which translated into impaired systolic left ventricular function at 6 to 12 months post TAVR ($p < 0.01$). A greater rise in CK-MB levels independently associated with an increased 30-day, late (median of 21 [IQR: 8 to 36] months) overall and cardiovascular mortality ($p < 0.001$ for all). Any increase in CK-MB levels was associated with poorer clinical outcomes, and there was a stepwise rise in late mortality according to the various degrees of CK-MB increase after TAVR ($p < 0.001$).

CONCLUSIONS Some degree of myocardial injury was detected in two-thirds of patients post TAVR, especially in those undergoing TA-TAVR or presenting with major procedural complications. A greater rise in CK-MB levels associated with greater acute and late mortality, imparting a negative impact on left ventricular function.
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ABBREVIATIONS AND ACRONYMS

CK-MB = creatinine kinase-myocardial band

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

TA = transapical

TAVR = transcatheter aortic valve replacement

TF = transfemoral

VARC = Valve Academic Research Consortium

Transcatheter aortic valve replacement (TAVR) has emerged as a therapeutic alternative to surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis (AS) at high or prohibitive perioperative risk (1). Compared with conventional open-heart surgery, TAVR procedures are less invasive due to the avoidance of aortic cross-clamping and cardioplegia. However, TAVR systematically associates with some degree of myocardial injury, defined biochemically by variable increases in cardiac biomarkers (2–4). A negative clinical impact associated with a higher degree of myocardial injury post TAVR has also been suggested (2,5), and the recent Valve Academic Research Consortium (VARC-2) consensus on TAVR has established specific biomarkers cut-off values for defining clinically significant myocardial infarction post TAVR (2,6). However, a validation of these VARC definitions upon clinically relevant myocardial infarction post TAVR is still lacking.

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Prior studies evaluating myocardial injury post TAVR included limited numbers of patients and duration of follow-up, with a paucity of cardiovascular outcomes data (2–4). Also, a single transcatheter valve system (balloon- or self-expandable) and/or delivery approach were used in most previous studies (2–4). Thus, a comprehensive understanding of the factors associated with myocardial injury post TAVR in a real-world all-comers population, incorporating the true clinical impact of varying degrees of myocardial injury detected biochemically, is currently lacking. Finally, most previous studies had focused on troponin levels as a biomarker of myocardial injury, yet there are limited data regarding the impact of creatinine kinase-myocardial band (CK-MB) levels, which has undergone a more robust validation for defining periprocedural myocardial infarction in the cardiac surgery and percutaneous coronary intervention fields (7). The objectives of the present study were to evaluate the incidence, prognostic significance and factors associated with myocardial injury as determined by CK-MB elevation (including validation of the VARC-2 proposed cut-off for myocardial infarction) in a large multicenter cohort of patients undergoing TAVR with differing valve types and approaches.

METHODS

STUDY POPULATION. This was a multicenter study including 1,172 patients who underwent TAVR from March 2007 until December 2014, in different centers across North America, South America, and Europe. A total of 41 patients were excluded due to procedural death (within the first 24 h after the procedure), precluding the collection of at least one blood sample for cardiac biomarker measurements post procedure. Therefore, the final study population consisted of 1,131 patients, 486 patients (43.0%) from 3 centers in North America, 123 patients (10.9%) from 4 centers in South America and 522 patients (46.1%) from 6 centers in Europe. A balloon-expandable valve was used in 658 patients, being an Edwards-Sapien (Edwards Lifesciences Inc., Irvine, California) in 261 (23.1%), Sapien XT (Edwards Lifesciences Inc.) in 380 (33.6%), Sapien 3 (Edwards Lifesciences Inc.) in 14 (1.2%), and Inovare (Braile Biomedical, São Paulo, Brazil) in 2 patients (0.2%). Also, a self-expandable valve was used in 473 patients, being a CoreValve (Medtronic, Minneapolis, Minnesota) in 458 (40.5%), Portico (St. Jude Medical, Minneapolis, Minnesota) in 13 (1.1%), and Lotus (Boston Scientific SciMed Inc., Maple Grove, Minnesota) in 1 (0.1%). Indications for TAVR, device type and approach were based on the assessment recommendation of the heart team at each center. Data were prospectively collected in a dedicated database at each center. The first one-half of patients treated at each center were considered as early TAVR experience. Clinical outcomes for the

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purpose of this study were defined according to the Valve Academic Research Consortium (VARC)-2 criteria (6). Clinical follow-up was carried out by clinical visits and/or through phone contact at 1 month, 6-months to 12-months post TAVR, and yearly thereafter in all participating centers. Complete clinical follow-up was available in all but 6 patients, lost to follow-up (0.5%).

MEASUREMENTS OF SERUM MARKERS SIGNIFYING MYOCARDIAL INJURY. Blood samples were collected at baseline, and at 6 to 12, 24, 48, and 72 h post TAVR, with CK-MB levels being measured at each time point. The upper normal limits for CK-MB were established at each participating institution based on the 99th percentile values in a healthy population. Myocardial injury was defined as an increase in CK-MB above this upper limit at any time point (up to 72 h) post TAVR. The degree of CK-MB elevation was calculated by dividing the CK-MB level by the upper limit level, and this was expressed as n-fold increase. In those patients with elevated baseline CK-MB levels, myocardial injury was defined as any increase >20% post procedure (8).

DOPPLER-ECHOCARDIOGRAPHIC MEASUREMENTS. A Doppler echocardiographic examination was performed at baseline, pre-TAVR, upon hospital discharge and at 6 months to 1 year post TAVR. Echocardiographic data at follow-up was available in 532 patients (62.7% of the study population at risk). The following measurements were obtained in all patients: aortic annulus diameter, left ventricular ejection fraction (LVEF) (calculated by the biplane Simpson method), mean transvalvular gradient (calculated with the Bernoulli formula), and the valve effective orifice area (AVA; calculated by the continuity equation). The presence and severity of aortic regurgitation was recorded in all patients. Severity of aortic regurgitation was classified according to the VARC-2 classification as follows: none/trace, mild, moderate, and severe (6).

STATISTICAL ANALYSIS. Categorical variables are reported as n (%). Continuous variables are expressed as mean ± SD or median (25th to 75th interquartile range [IQR]), depending upon variable distribution. Group comparisons were performed using the Student *t* test or Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. For CK-MB analysis the values after the procedure were evaluated in relation to the upper limit as determined at each center. Two experimental factors (subjects classified as random factor and time period as a fixed factor) were defined to analyze the changes in repeated CK-MB measurements over time

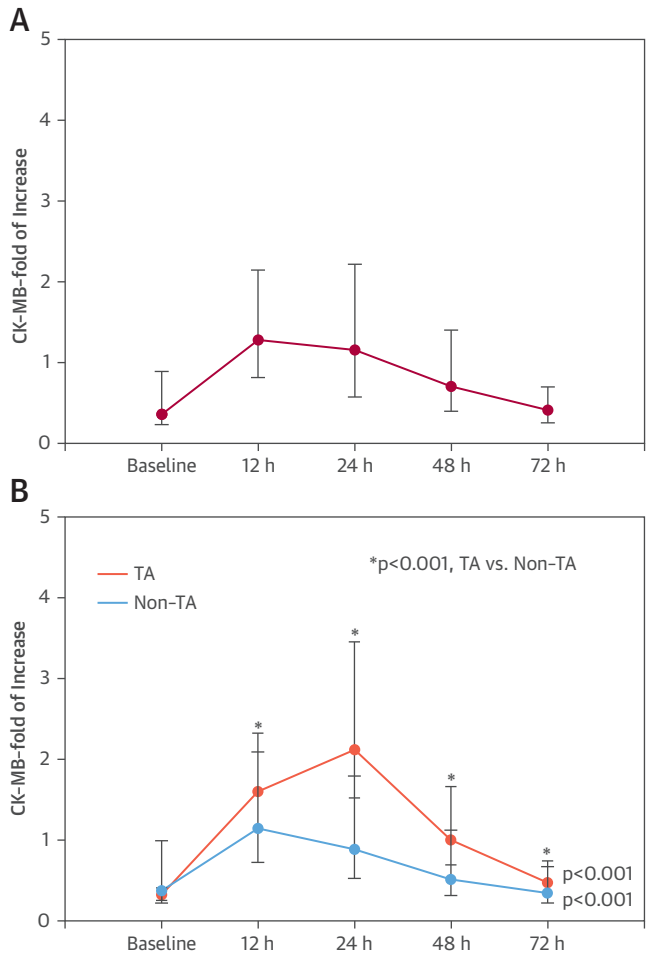
TABLE 1 Clinical, Echocardiographic, and Procedural Characteristics of the Study Population (N = 1,131)

Clinical variables	
Age, yrs	80 ± 7
Male	572/1,131 (50.6)
NYHA functional class	
I-II	266/1,123 (23.7)
III-IV	857/1,123 (76.3)
Coronary artery disease	608/1,131 (53.8)
Prior PCI	346/1,130 (30.6)
Prior CABG	253/1,131 (22.4)
History of atrial fibrillation	307/1,080 (28.4)
Cerebrovascular disease	142/880 (16.1)
Peripheral vascular disease	264/1,131 (23.3)
COPD	304/1,131 (26.9)
Porcelain aorta	153/1,131 (13.5)
eGFR, ml/min/1.73 m^2	60.7 ± 25.5
CKD	608/1,130 (53.8)
STS-PROM, %	8.2 ± 6.8
Echocardiographic variables	
LVEF, %	56 ± 15
Mean aortic gradient, mm Hg	45.6 ± 16.8
Aortic valve area, cm^2	0.64 ± 0.22
Moderate/severe mitral regurgitation	212/924 (22.9)
Procedural variables	
Success*	879/1,116 (78.8)
Approach	
Transfemoral	827/1,131 (73.1)
Transapical	230/1,131 (20.3)
Transaortic	48/1,131 (4.3)
Subclavian	26/1,131 (2.3)
Prosthesis type	
Balloon-expandable	658/1,131 (58.2)
Self-expandable	473/1,131 (41.8)
Prosthesis size, mm	
≤26	830/1,122 (74.0)
>26	292/1,122 (26.0)
Valve-in-valve	61/1,131 (5.4)
Time of procedure "skin to skin," min	70 (60-88)
30-day outcomes	
Major vascular complications	136/1,130 (12.0)
Major or life-threatening bleeding	140/1,129 (12.4)
Valve embolization/need for a second valve	57/1,131 (5.0)
Pacemaker	173/1,130 (15.3)
Coronary obstruction	6/1,131 (0.5)
Stroke	40/1,131 (3.5)
Death	65/1,131 (5.7)
Hospitalization length, days	7 (5-12)
Echocardiographic post procedure	
LVEF, %	57 ± 14
Mean aortic gradient, mm Hg	10.8 ± 6.0
Aortic valve area, cm^2	1.56 ± 0.50
Moderate/severe mitral regurgitation	111/744 (14.9)
Moderate/severe aortic regurgitation	132/1,101 (12.0)

Values are mean ± SD, n/N (%), or median (interquartile range). *Following Valve Academic Research Consortium-2 criteria (6).

CABG = coronary artery bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality.

FIGURE 1 Changes in Serum Markers of Myocardial Injury After TAVR



Changes in CK-MB levels within 72 h after TAVR in the entire study population **(A)** and grouped according to the approach (TA vs. non-TA) **(B)**. Values are expressed as median (25th to 75th interquartile range). CK-MB = creatine kinase-myocardial band; TA = transapical; TAVR = transcatheter aortic valve replacement.

(baseline, 6 to 12, 24, 48, and 72 h). Considering the presence of some missing CK-MB measurements in 11% of patients, the CK-MB levels over time were analyzed as a repeated-measures factor with the use of an unstructured covariance matrix to obtain unbiased estimates. Ulterior comparisons were performed using the Tukey method. The normality assumption was verified with the Shapiro-Wilk tests on the error distribution from the Cholesky factorization of the statistical model. The Brown and Forsythe variation of Levene's test statistic was used to verify the homogeneity of variances. CK-MB elevation values were log transformed to stabilize variances. Reported p-values were based on this transformation. The predictors of higher rise in CK-MB values were determined using a linear regression analyses normalized by baseline values. Univariate and multivariate logistic regression analyses were used to determine the predictors of 30-day mortality. Continuous variables were checked for the assumption of linearity using quartiles of the distribution and fractional polynomials before building the model in order to obtain the correct relationships. The graphic representations suggested linear relationships with the logit for all continuous variables. Univariate and multivariate Cox proportional hazard models were used to determine the predictors of cumulative late overall and cardiac mortality. Variables with a probability value <0.10 were candidates for the multivariate regression model building. Coronary artery disease was also added into the multivariate models. The final statistical model was built using 2 statistical approaches: a forward approach, Akaike and Schwarz' Bayesian criteria. For the Cox models, the martingales residuals were used to examine the functional form of the continuous variables. Measurements of CK-MB elevation were log-transformed. After model building, the adequacy of the proportional hazards assumption was checked. To check the proportionality assumption, we first used the graphical representation of the logarithm cumulative hazard rates versus time to assess parallelism and the constant separation among the different values of nominal variables, whereas the continuous variables were stratified into 4 strata. Second, an artificially time-dependent covariate was added to the model to test the proportionality assumption. For all variables in the final models, the proportional hazards assumptions were not rejected as local tests linked to the time-dependent covariates were not significant and scatter plots were roughly constant over time. All analyses were performed using a hierarchical method in order to account for between-center variability. Mortality rates were presented using Kaplan-Meier estimates and comparisons between groups were performed using the log-rank test. The correlation between LVEF and CK-MB increase were evaluated with the Pearson's correlation. All results were considered significant with p values <0.05. Analyses were conducted using the statistical packages SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina) and Statistical Package for Social Sciences, version 20 (SPSS Inc., IBM, Armonk, New York).

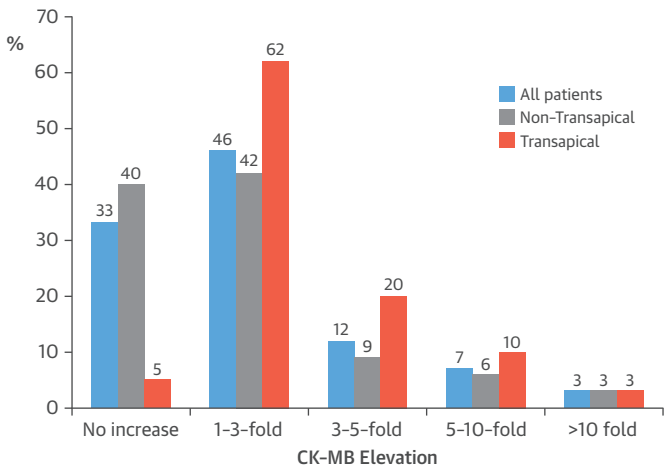
RESULTS

The clinical, echocardiographic, procedural characteristics and 30-day outcomes of the study population are shown in Table 1. Also, the clinical,

echocardiographic, and procedural characteristics and 30-day outcomes of the study population according to valve type are shown in Online Table 1.

SERUM MARKERS OF MYOCARDIAL INJURY POST-TAVR. The median peak values of CK-MB at each time point within the initial 72 h post TAVR, overall and stratified according to the approach (TA vs. non-TA) are shown in **Figure 1**. CK-MB levels were within normal limits in 92.0% of the patients at baseline and rose above the upper normal limit in 65.6% of patients, with a median increase of 1.6-fold (IQR: 0.9- to 2.8-fold) at 12 to 24 h post TAVR, and returned to baseline values at 72 h post TAVR. In the TA cohort, CK-MB levels rose above the upper normal values in 97.3% of patients compared with 54.4% of patients in the non-TA (TF, transaortic and trans-subclavian) cohort ($p < 0.001$), with median peak values of 2.2-fold (IQR: 1.6- to 3.3-fold) and 1.2-fold (IQR: 0.7- to 2.4-fold), respectively ($p < 0.001$). The percent of patients with increased CK-MB levels grouped according to the degree of rise in CK-MB post TAVR in the entire study population and to the approach are shown in **Figure 2**.

FIGURE 2 Degree of Increase in CK-MB Levels After TAVR



Percent of patients with increased CK-MB values according to the degree of CK-MB elevation in all patients and according to the approach (TA vs. non-TA). Abbreviations as in **Figure 1**.

PREDICTORS OF MYOCARDIAL INJURY POST-TAVR. The degree of myocardial injury according to baseline and procedural characteristics of the entire study population is shown in **Table 2**. Factors associated with a greater degree of myocardial injury in the multivariate analysis were a TA approach (R^2: 0.070; $p < 0.001$), an early TAVR experience (R^2: 0.013; $p < 0.001$) and procedural complications such as valve embolization/need for a second valve (R^2: 0.019; $p < 0.001$), major/life-threatening bleeding (R^2: 0.007; $p = 0.001$), and conversion to open-heart surgery (R^2: 0.013; $p < 0.001$). The degree of myocardial injury according to baseline and procedural characteristics for the non-TA cohort is shown in **Table 3**. Factors associated with a greater degree of myocardial injury in the multivariate analysis (non-TA cohort) were the use of a self-expandable valve (R^2: 0.039; $p < 0.001$), valve embolization/need for a second valve (R^2: 0.007; $p = 0.009$), major/life-threatening bleeding (R^2: 0.009; $p = 0.003$), conversion to open-heart surgery (R^2: 0.022; $p < 0.001$) and early TAVR experience (R^2: 0.011; $p = 0.001$). The results were similar when only the CoreValve system was evaluated in the self-expandable valve group (Online Table 2).

In an additional analysis, the factors associated with an increase in CK-MB levels >5-fold were also evaluated. The baseline and procedural characteristics of patients according to a CK-MB increase >5-fold are shown in Online Table 3. The results of the univariate and multivariate analyses for determining the predictors of a CK-MB rise >5-fold in the entire study population and the non-TA cohort are shown in Online Table 4. The TA approach, valve embolization/need for a second valve and conversion to open-heart surgery were the independent predictors of a rise in CK-MB >5-fold post TAVI ($p < 0.05$ for all).

CLINICAL IMPACT OF MYOCARDIAL INJURY. A total of 65 patients (5.7%) had died at 30 days post TAVR, and a further 328 patients died (29.0%) at a median follow-up of 21 (8 to 36) months post TAVR. A total of 191 patients died from cardiac causes (16.9%, 58.2% of the deaths). The variables associated with a higher risk of 30-day mortality, cumulative late overall and cardiac mortality are shown in **Table 4**. A greater increase in CK-MB levels was associated with increased 30-day mortality (OR: 2.26 for each increase of 1-fold above upper limit values; 95% CI: 1.76 to 2.90; $p < 0.001$), and remained independently associated with greater 30-day mortality in the multivariate analysis (OR: 1.71; 95% CI: 1.25 to 2.35; $p < 0.001$). Greater increments in CK-MB levels post TAVR were also independently associated with late cumulative mortality (HR: 1.32 for each increase of 1-fold increase above the upper limit values; 95% CI: 1.12 to 1.54; $p < 0.001$) and late cardiac mortality (HR: 1.39; 95% CI: 1.12 to 1.74; $p = 0.003$). In a subanalysis of the TF and TA cohorts, a greater increase in CK-MB levels remained as an independent predictor of 30-day and late mortality in the TF cohort ($p < 0.001$ for both) (Online Table 5), but not in the TA cohort (Online Table 6).

TABLE 2 Overall Degree of CK-MB Increase After TAVR According to Baseline and Procedural Variables (N = 1,131)

	CK-MB Fold	p Value
Baseline variables		
Age, yrs		
≥ Median (82 yrs)	1.58 (0.85–2.71)	0.242
< Median (82 yrs)	1.44 (0.81–2.60)	
Sex		
Male	1.51 (0.85–2.64)	0.783
Female	1.50 (0.80–2.73)	
History of atrial fibrillation/flutter		
Yes	1.36 (0.72–2.36)	0.371
No	1.50 (0.85–2.65)	
Coronary artery disease		
Yes	1.52 (0.86–2.69)	0.549
No	1.47 (0.80–2.66)	
Prior CABG		
Yes	1.58 (0.89–2.47)	0.599
No	1.47 (0.82–2.69)	
Prior PCI		
Yes	1.52 (0.87–2.68)	0.583
No	1.50 (0.82–2.66)	
Cerebrovascular disease		
Yes	1.60 (0.85–2.95)	0.246
No	1.53 (0.83–2.70)	
Peripheral vascular disease		
Yes	1.75 (1.11–2.78)	<0.001
No	1.39 (0.79–2.67)	
COPD		
Yes	1.50 (0.88–2.61)	0.701
No	1.50 (0.82–2.69)	
eGFR, ml/min/1.73 m^2		
≥ Median (60 ml/min)	1.49 (0.82–2.67)	0.471
< Median (60ml/min)	1.51 (0.84–2.67)	
STS-PROM		
≥ Median (6%)	1.53 (0.88–2.51)	0.105
< Median (6%)	1.47 (0.82–2.78)	
Porcelain aorta		
Yes	1.74 (1.08–2.82)	0.027
No	1.44 (0.80–2.64)	
Procedural variables		
Prosthesis type		
Balloon-expandable	1.53 (0.80–2.65)	0.015
Self-expandable	1.44 (0.87–2.69)	
Approach		
Transfemoral/transaortic/ trans-subclavian	1.20 (0.73–2.35)	<0.001
Transapical	2.20 (1.63–3.34)	
Device success		
Yes	1.50 (0.83–2.63)	0.029
No	1.52 (0.89–2.85)	
Life-threatening/major bleeding		
Yes	2.27 (1.16–3.83)	<0.001
No	1.41 (0.79–2.44)	
Major vascular complications		
Yes	1.82 (0.95–3.24)	0.001
No	1.46 (0.81–2.60)	
Valve embolization/need for a second valve		
Yes	2.39 (1.19–6.44)	<0.001
No	1.48 (0.82–2.60)	
Conversion to surgery		
Yes	4.65 (1.64–7.76)	<0.001
No	1.48 (0.82–2.64)	
Coronary obstruction		
Yes	7.46 (3.27–9.02)	<0.001
No	1.50 (0.83–2.64)	
TAVR experience		
Early	1.81 (0.98–3.19)	<0.001
Late	1.19 (0.72–2.16)	

CK-MB = creatinine kinase-myocardial band; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

Kaplan-Meier overall and cardiac survival curves according to differing degrees of CK-MB increments (<1-, 1- to 3-, 3- to 5-, and >5-fold) are shown in Figures 3 and 4, for the overall and non-TA cohorts, respectively. Any increase in CK-MB levels (<1-fold vs. >1-fold) was associated with a higher mortality ($p < 0.001$), and there was a stepwise increase in late mortality according to the various degrees of CK-MB elevation after TAVR ($p < 0.001$). In those patients with increased CK-MB levels, a >5-fold increase was associated with a higher overall (33.6% vs. 22.9% at 2 years; $p < 0.001$), and cardiac mortality (25.8% vs. 14.1%; $p < 0.001$). In the non-TA cohort, a >5-fold increase in CK-MB levels was also associated with increased overall (30.6% vs. 20.1%; $p < 0.001$) and cardiac mortality (24.6% vs. 12.1%; $p < 0.001$).

The correlation between the increase in CK-MB levels and the changes in LVEF between baseline and follow-up (Δ) for the entire population are shown in Figure 5. The increase in CK-MB levels after the procedure demonstrated a weak, but significant negative impact in changes of LVEF between baseline and follow-up ($r = -0.17$; $p < 0.001$). Also, the patients presenting with either unchanged or reduced LVEF 6-12 months post TAVR compared to baseline exhibited greater CK-MB levels as compared with those patients whose LVEF significantly improved after TAVR ($p = 0.004$; Figure 6).

DISCUSSION

The present large-scale real-world study demonstrates that some degree of myocardial injury, as determined by a post-procedural rise in CK-MB levels, is common after TAVR. The use of the TA

TABLE 3 Overall Degree of CK-MB Increase After TAVR in the Nontransapical Cohort (Transfemoral, Transaortic, and Trans-Subclavian) According to the Baseline and Procedural Variables

	CK-MB Fold	p Value
Baseline variables		
Age, yrs		
≥ Median (82 yrs)	1.21 (0.73–2.36)	0.713
< Median (82 yrs)	1.19 (0.73–2.35)	
Sex		
Male	1.19 (0.73–2.40)	0.607
Female	1.22 (0.73–2.27)	
History of atrial fibrillation/flutter		
Yes	1.04 (0.64–1.94)	0.113
No	1.25 (0.75–2.29)	
Coronary artery disease		
Yes	1.17 (0.72–2.37)	0.978
No	1.27 (0.75–2.34)	
Prior CABG		
Yes	1.11 (0.67–2.29)	0.923
No	1.25 (0.75–2.36)	
Prior PCI		
Yes	1.19 (0.72–2.27)	0.540
No	1.22 (0.73–2.37)	
Cerebrovascular disease		
Yes	1.19 (0.70–2.29)	0.819
No	1.13 (0.70–2.36)	
Peripheral vascular disease		
Yes	1.28 (0.73–2.27)	0.215
No	1.19 (0.73–2.36)	
COPD		
Yes	1.16 (0.72–2.09)	0.265
No	1.24 (0.73–2.39)	
eGFR, ml/min/1.73 m^2		
≥ Median (60 ml/min)	1.17 (0.75–2.37)	0.635
< Median (60ml/min)	1.25 (0.69–2.34)	
STS-PROM		
≥ Median (6%)	1.15 (0.69–2.11)	0.051
< Median (6%)	1.25 (0.75–2.45)	
Porcelain aorta		
Yes	1.19 (0.75–1.94)	0.363
No	1.20 (0.73–2.37)	
Procedural variables		
Prosthesis type		
Balloon-expandable	0.99 (0.65–1.97)	<0.001
Self-expandable	1.42 (0.86–2.69)	
Device success		
Yes	1.19 (0.73–2.29)	0.039
No	1.33 (0.74–2.66)	
Life-threatening/major bleeding		
Yes	2.00 (0.94–3.60)	<0.001
No	1.17 (0.70–2.20)	
Major vascular complications		
Yes	1.68 (0.90–2.98)	<0.001
No	1.17 (0.70–2.25)	
Valve embolization/need for a second valve		
Yes	1.62 (1.04–6.45)	<0.001
No	1.19 (0.72–2.28)	
Conversion to surgery		
Yes	4.41 (1.53–7.28)	<0.001
No	1.19 (0.73–2.29)	
Coronary obstruction		
Yes	5.37 (3.09–28.6)	<0.001
No	1.19 (0.73–2.32)	
TAVR experience		
Early	1.39 (0.81–2.86)	<0.001
Late	1.10 (0.68–1.98)	

Abbreviations as in Tables 1 and 2.

approach and major procedural complications such as valve embolization/need for a second valve, major/life-threatening bleeding and conversion to open-heart surgery were the most important factors associated with a larger increase in CK-MB levels. Greater degree of myocardial injury was independently associated with poorer outcomes as determined by an increase in 30-day and late mortality, as well as impaired LVEF at 6- to 12-month follow-up. Any increase in CK-MB levels after TAVR was associated with poorer clinical outcomes, with a stepwise increase in mortality according to the various degrees of CK-MB elevation (**Central Illustration**).

INCIDENCE AND DEGREE OF MYOCARDIAL INJURY POST TAVR. Most patients undergoing SAVR experience some degree of myocardial injury, reflected by rise in CK-MB levels, and a >5-fold increase in the upper normal limits occurs in nearly 20% of these patients (9,10). While avoiding the need for cardiopulmonary bypass translates into a lesser degree of myocardial injury during TAVR, up to two-thirds of patients undergoing TAVR had significant elevation in CK-MB levels post procedure, and the frequency of >3-fold and ≥5-fold increases in CK-MB upper normal limits occurred in 21.0% and 9.6% of cases, respectively. These findings appear similar to those observed during percutaneous coronary intervention (11).

In accordance with previous smaller studies, a TA approach was found to be one of the most important factors in determining a higher degree of myocardial injury post TAVR in the present study (2,4). TA-TAVR involves puncturing and introducing a large bore catheter through the LV apex, and this has been postulated as the primary reason for biomarker elevations in such instances (2,12). Additionally, this has been related to new myocardial necrosis as evaluated by cardiac magnetic resonance, involving ~5% of the

TABLE 4 Univariate and Multivariate Analyses of the Predictor of Poorer Outcomes Post-TAVR

	Univariate		Multivariate Model	
Outcome	**OR/HR (95% CI)**	**p Value**	**OR/HR (95% CI)**	**p Value**
30-day mortality (n = 65)				
Coronary artery disease	0.75 (0.45–1.25)	0.275	–	–
Peripheral vascular disease	1.84 (1.04–3.26)	0.035	–	–
LVEF	0.98 (0.97–0.99)	0.041	0.98 (0.96–0.99)	0.026
Early experience	1.99 (1.17–3.38)	0.011	–	–
Major or life-threatening bleeding	5.83 (3.38–10.04)	<0.001	3.07 (1.57–5.99)	0.001
Stroke	3.97 (1.64–9.60)	0.002	–	–
Acute kidney injury	10.01 (5.66–17.7)	<0.001	6.11 (3.32–11.22)	<0.001
CK-MB elevation*	2.26 (1.76–2.90)	<0.001	1.71 (1.25–2.35)	<0.001
Cumulative mortality (n = 328)				
Male	1.27 (1.02–1.60)	0.036	–	–
NYHA functional class III-IV	1.92 (1.40–2.64)	<0.001	1.85 (1.29–2.66)	<0.001
History of atrial fibrillation	1.82 (1.44–2.30)	<0.001	1.69 (1.30–2.20)	<0.001
Coronary artery disease	1.18 (0.94–1.48)	0.157	–	–
Cerebrovascular disease	1.36 (1.02–1.82)	0.035	–	–
Peripheral vascular disease	1.46 (1.13–1.90)	0.004	–	–
COPD	1.52 (1.20–1.93)	<0.001	1.42 (1.08–1.87)	0.01
TA approach	1.57 (1.15–2.15)	0.005	–	–
Early experience	1.29 (0.98–1.69)	0.060	–	–
Life-threatening/major bleeding	2.01 (1.54–2.64)	<0.001	–	–
Stroke	2.05 (1.30–3.23)	0.002	–	–
Acute kidney injury	2.67 (2.09–3.42)	<0.001	2.12 (1.60–2.80)	<0.001
CK-MB elevation*	1.42 (1.26–1.62)	<0.001	1.32 (1.12–1.54)	<0.001
Cumulative cardiac mortality (n = 191)				
Male	1.36 (1.01–1.83)	0.042	–	–
NYHA functional class III-IV	1.73 (1.16–2.60)	0.008	–	–
History of atrial fibrillation	1.62 (1.18–2.21)	0.003	–	–
Coronary artery disease	0.99 (0.74–1.33)	0.959	–	–
Peripheral vascular disease	1.55 (1.11–2.15)	0.009	–	–
COPD	1.54 (1.13–2.09)	0.006	1.68 (1.15–2.45)	0.007
LVEF	0.99 (0.98–0.99)	0.022	0.99 (0.98–0.99)	0.039
Moderate/Severe mitral regurgitation	1.56 (1.07–2.27)	0.022	–	–
TA approach	1.81 (1.20–2.71)	0.004	–	–
Early experience	1.48 (1.05–2.08)	0.024		
Life-threatening/major bleeding	2.29 (1.62–3.22)	<0.001	1.75 (1.14–2.69)	0.010
Stroke	2.79 (1.64–4.75)	<0.001	–	–
Acute kidney injury	3.73 (2.74–5.07)	<0.001	3.06 (2.07–4.52)	<0.001
CK-MB elevation*	1.60 (1.37–1.87)	<0.001	1.39 (1.12–1.74)	0.003

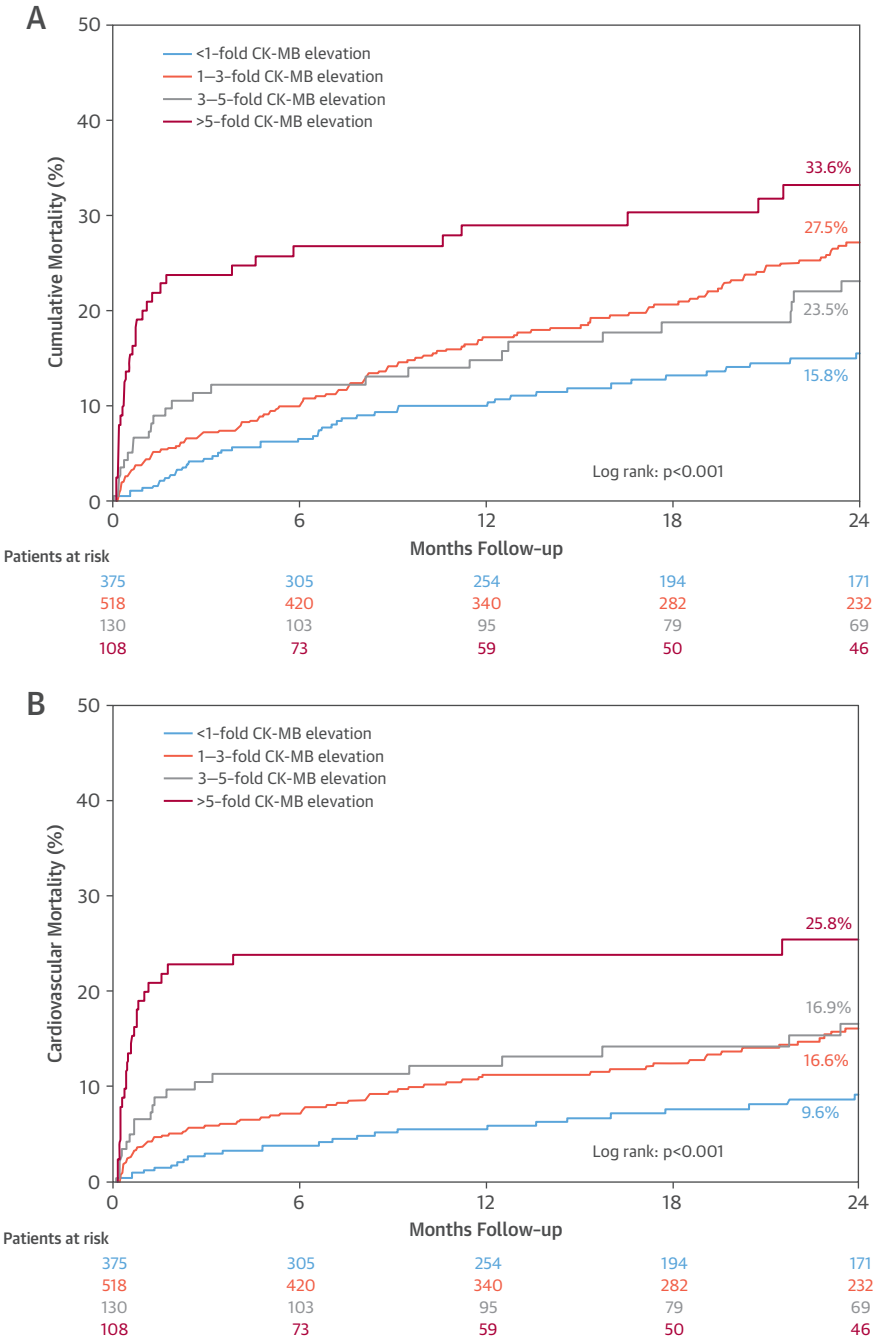
*For every 1-fold increase of CK-MB level in relation to the upper limit.

CI = confidence interval; HR = hazard ratio; OR = odds ratio; TA = transapical; other abbreviations as in Tables 1 and 2.

myocardium at the apex (12), leading to apical wall abnormalities (5,12,13). Several studies have found the TA approach to be independently associated with mortality (14,15), and a recent study identified that this approach correlates with late mortality secondary to advanced heart failure (16). The results of this study highlight the importance of myocardial injury as the potential pathophysiological link between TA approach and increased mortality, outlining the importance of minimizing myocardial damage in such cases (i.e., reducing sheath size or avoiding myocardial tears).

Major periprocedural complications such as major/life-threatening bleeding, valve embolization/need for a second valve and conversion to open-heart surgery were also associated with a greater increase in CK-MB levels. Previous studies have shown the negative clinical impact of these complications after TAVR (17,18). The present study suggests that an association with a higher degree of myocardial injury may further contribute to poorer outcomes in such patients. While the link between open-heart surgery and myocardial injury is obvious, one may hypothesize that periods of severe hypotension, longer

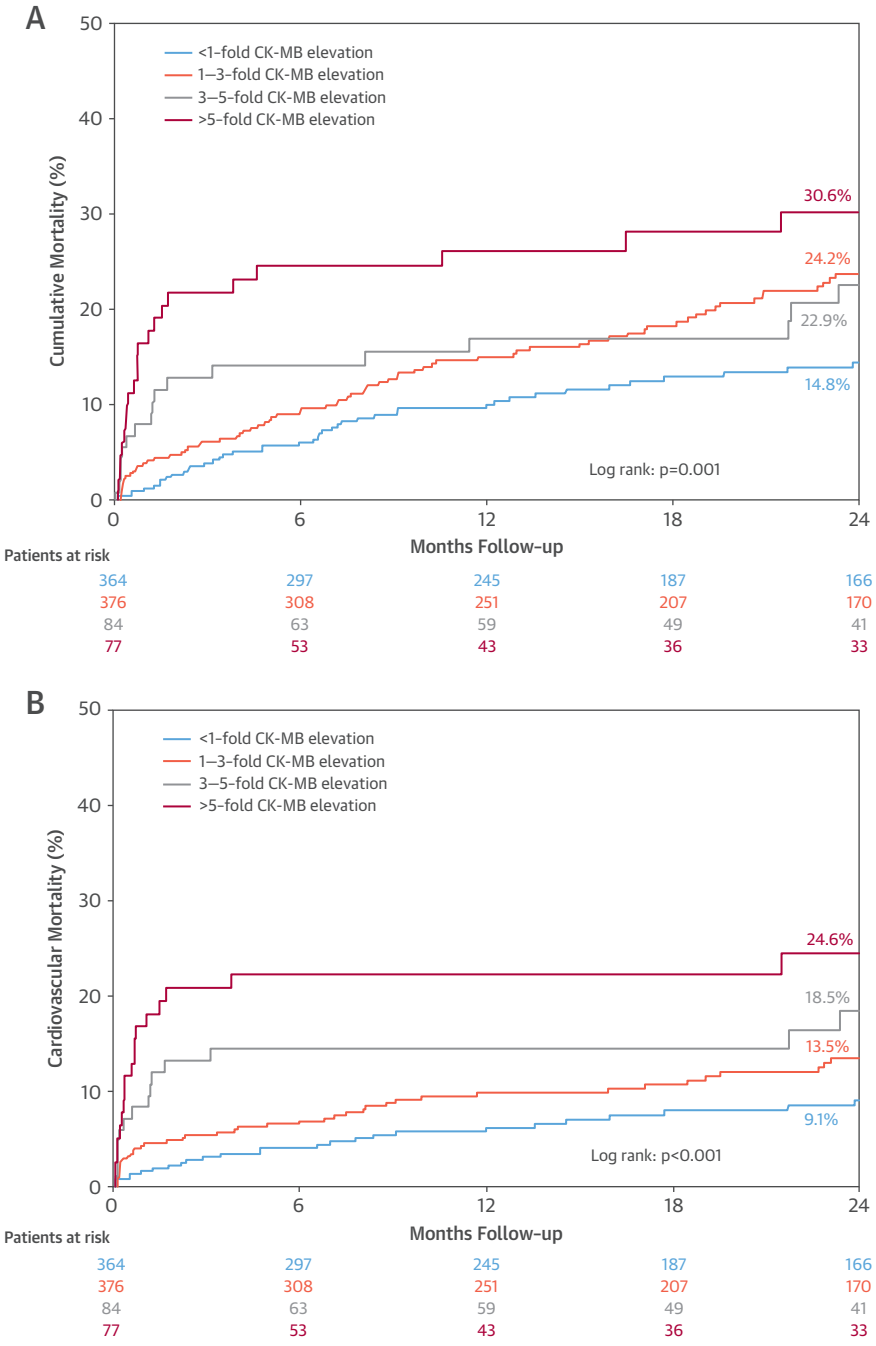
FIGURE 3 Kaplan-Meier Mortality Curves in All Patients



Kaplan-Meier mortality curves for cumulative overall death **(A)** and for cardiovascular death **(B)** according to the percentiles of CK-MB peak of increase after TAVR. For group comparisons in **(A)** group <1 versus groups 1 to 3, 3 to 5, and >5 ($p < 0.05$); in **(B)** group 1 versus groups 1 to 3, 3 to 5, and >5 ($p < 0.01$). Abbreviations as in Figure 1.

procedures with increased ischemic times and increased device manipulation may have contributed to the increased levels of CK-MB levels in patients suffering from major bleeding or device malpositioning/embolization. An early stage in the TAVR experience was also associated with a greater CK-MB increase, suggesting both the roles of the learning curve and the advancements in the TAVR

FIGURE 4 Kaplan-Meier Survival Curves in Non-TA Patients



Kaplan-Meier mortality curves for cumulative overall death **(A)** and for cardiovascular death **(B)**, according to the percentiles of CK-MB peak of increase after TAVR. For group comparisons in **(A)** group <1 versus groups 1 to 3, 3 to 5, and >5 ($p < 0.05$); in **(B)** group 1 versus groups 3 to 5 and >5 ($p < 0.01$). Abbreviations as in Figure 1.

technology on the degree of myocardial injury post TAVR.

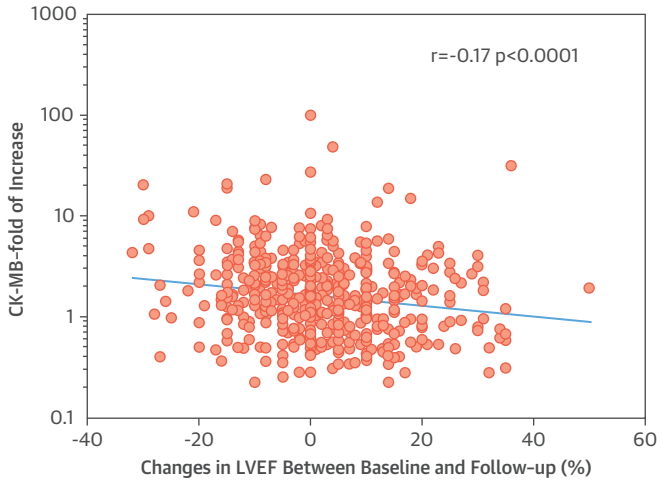
Apart from major periprocedural complications, the use of a self-expandable valve was also associated with a mild but significant higher rise in CK-MB levels in the non-TA cohort. Similar to the results reported in the CHOICE (Comparison of Balloon-Expandable vs Self-expandable Valves in Patients Undergoing

Transcatheter Aortic Valve Replacement) trial (19), patients receiving a self-expandable valve exhibited longer procedural times, received a higher volume of contrast agent and had an increased incidence of valve embolization/need for a second valve compared to the balloon-expandable group. This may partially explain the differences in myocardial injury between valve types, but given the non-randomized nature of the study, future studies are warranted to confirm and better understand the mechanisms associated with these results. Importantly, no differences between valve types were observed in those patients with the highest (>5-fold) increase in CK-MB levels.

CLINICAL IMPACT OF PERI-PROCEDURAL TAVR-RELATED MYOCARDIAL INJURY. The occurrence and degree of myocardial injury after cardiac surgery and percutaneous coronary intervention have been associated with poorer short and mid-term clinical outcomes (7,20). Importantly, the degree of CK-MB increase and the associated worse outcomes formed the basis for defining the occurrence of clinically relevant myocardial infarction after such procedures (7). This is of major clinical relevance considering the changes in the acute and late management of such patients, compared with those without periprocedural myocardial infarction.

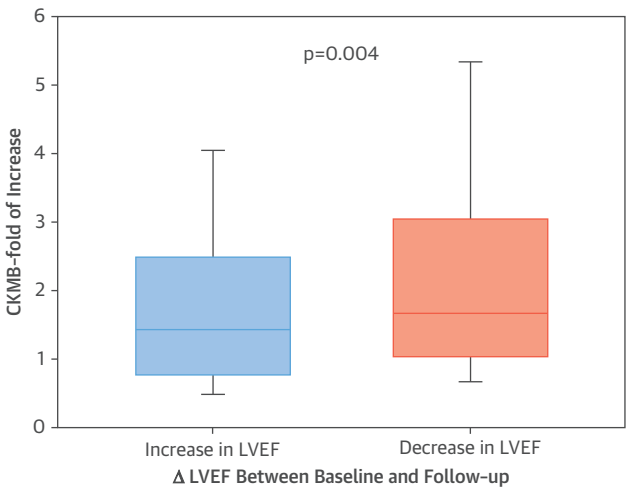
Following a similar theme, previous studies in the TAVR field have demonstrated increased short- and mid-term mortality to be associated with greater rise in biomarkers of myocardial injury after the procedure (2,4,6,21,22). However the limited number of patients/events in most studies precluded a formal validation of a threshold of biomarker elevation representing a "clinically relevant" myocardial infarction after TAVR. Our study confirms the major impact of myocardial injury as determined by CK-MB rise post TAVR on 30-day and 1-year overall mortality and extends previous observations by showing an increased risk of late (>1-year) overall and cardiac mortality in relationship to higher degrees of myocardial injury. In accordance with previous studies (22), any increase in CK-MB values associated with poorer outcomes, with an apparent stepwise increase in late mortality according to the various degrees of CK-MB elevation after TAVR. Interestingly, according to the VARC-2 criteria for defining clinically relevant myocardial infarction (6), a >5-fold increase in CK-MB threshold was associated with a higher mortality rate. This suggests that patients with greater degrees of myocardial injury could potentially benefit from both a closer clinical follow-up as well as medications for preventing adverse LV remodeling in such cases (i.e., angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, or spironolactone). However, this needs further prospective evaluation in future studies. Interestingly, the correlation between a greater increase in CK-MB levels and mortality post TAVR was apparent in the TF but not in the TA approach cohort, although the relatively low number of patients in the TA group may partially explain such results.

FIGURE 5 Myocardial Injury and LVEF Changes After TAVR



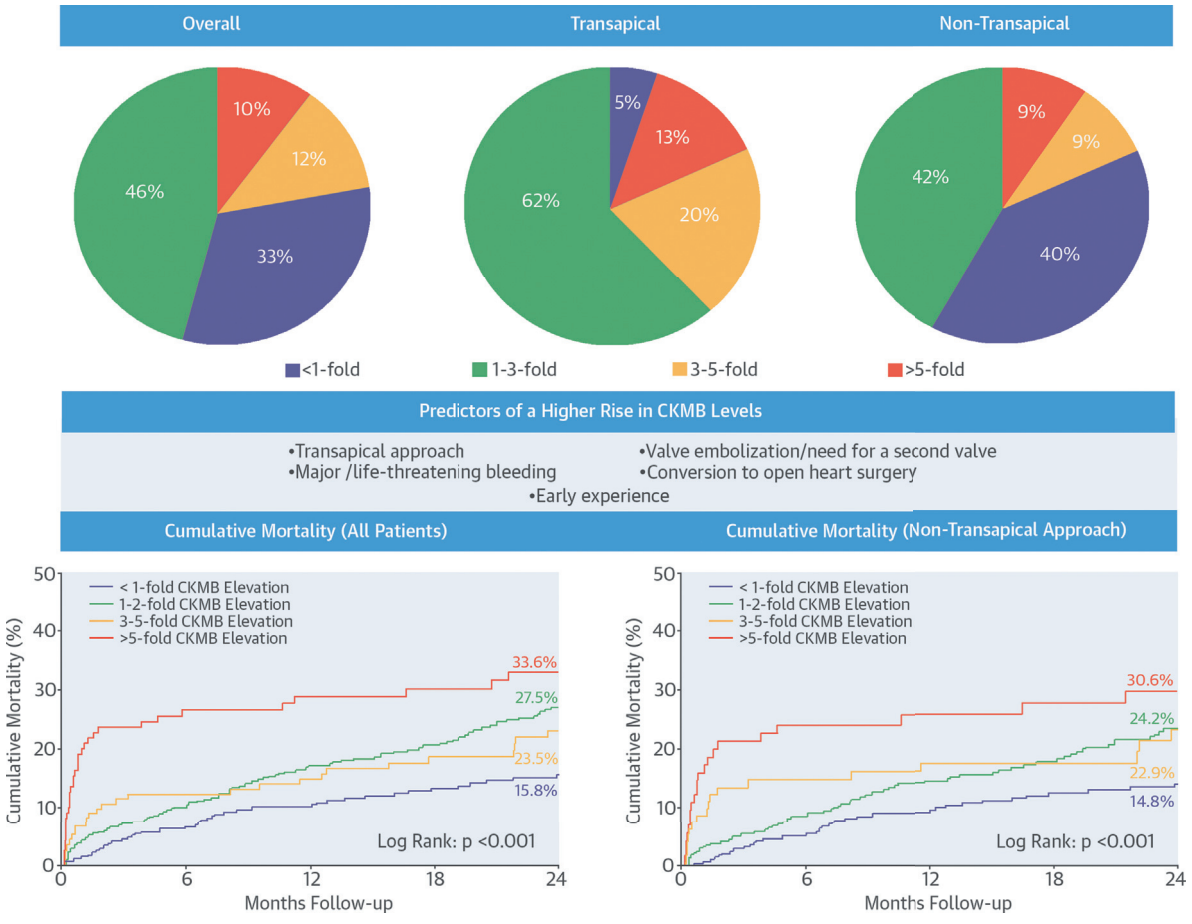
Relationship between the maximal increase in CK-MB levels and the changes in LVEF after TAVR. LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

FIGURE 6 Absolute Change (Δ) in LVEF According to the CK-MB Peak After TAVR



Median levels of peak in CK-MB after TAVR according to the increase or decrease in LVEF between the baseline and 6- to 12-month echocardiography. Values are medians (25th to 75th interquartile range). Abbreviations as in Figures 1 and 5.

CENTRAL ILLUSTRATION **Incidence, Predictors, and Cumulative Mortality According to Various Degrees of Increase in CK-MB Levels After TAVR**



Ribeiro, H.B. et al. J Am Coll Cardiol. 2015; 66(19):2075–88.

Percent of patients with each fold of increase in creatinine kinase-myocardial band (CK-MB) levels, for the overall population and according to approach, including its independent predictors and the ensuing cumulative mortality for the entire population and the nontransapical approach group.
TAVR = transcatheter aortic valve replacement.

Greater elevations in CK-MB levels were also correlated with impaired LV function at mid-term follow-up, which is consistent with previous studies (2,12,13). Therefore, it is important to keep in mind that strategies for reducing the ensuing myocardial injury in TAVR patients, especially in those patients with impaired baseline LVEF pre-TAVR, are of utmost importance (13,23). Accordingly, it has been suggested that in those patients with low LVEF deemed unsuitable for TF-TAVR, other alternative approaches such as transaortic, subclavian, or transcarotid approaches would be preferable to the TA approach. Improvements in the design of the TA delivery systems for minimizing apical trauma should also be encouraged (13,15). Additionally, future enhancements to the TF delivery system with more easily used transcatheter valves, may facilitate deployment with shorter rapid-pacing runs and lower ischemic times (24).

STUDY LIMITATIONS. Although the present analysis includes a large cohort of TAVR patients with systematic cardiac biomarker evaluation, the patients were however not randomized according to approach and valve type. Consequently, the multivariate analysis may not have accounted for the unmeasured between-group confounders unduly influencing study conclusions. The participating centers used different assays for measuring CK-MB levels and this

intercenter variability may have influenced the results. This was partially offset by the use of a relative increase in CK-MB levels with respect to the upper normal limits (fold or increase) as recommended by VARC-2 (6). Also, a hierarchical analysis was performed to account for between-center/country variance. Echocardiographic data were based on each site report, and no central echocardiographic core laboratory analysis was available. All centers were encouraged to calculate LVEF by using the Simpson method in order to improve accuracy and reduce variability (25). Although data on previous coronary artery disease and need for revascularization was complete, no data were available on the completeness of coronary revascularization before TAVR. The influence of this factor on myocardial injury post TAVR will need to be determined in future studies. Additionally, one might argue that cardiac troponins should be the preferred biomarkers for the diagnosis of myocardial injury because of their higher sensitivity and specificity than CK-MB levels (8,26,27). Nonetheless, acute and chronic comorbidities frequently lead to small elevations in troponin levels at baseline, that together with the recently developed ultra and highly-sensitive assays, along with its diverse analytical sensitivity (28), will likely lead to a myriad of challenges to define a precise cutoff of myocardial injury in such patients according to troponin (26). Finally, the early mortality rate observed in our study was relatively high compared to more recent TAVR series. Future studies in the context of TAVR, with the systematic measurement of CK-MB and troponin, are necessary to further evaluate its prognostic significance and confirm the most appropriate cut-off to predict worse clinical outcomes, also with valve types other than the balloon-expandable and self-expandable systems, including the latest generation of transcatheter valves.

CONCLUSIONS

Myocardial injury as determined by CK-MB rise is frequent among TAVR patients, especially with TA-TAVR, and in those patients suffering from major procedural complications. These results support the use of alternative approaches to TA, particularly in some patients at risk, like those with impaired LVEF. Also, reducing the size of transfemoral sheaths and increasing heart team experience and the retrievability/repositionability properties of most of the more recent generation transcatheter valves should be associated with a significant reduction in bleeding and malpositioning/embolization complications, which may translate into a reduction in the degree of myocardial injury post TAVR. This, however, will need to be determined in future studies. A higher degree of myocardial injury was associated with poorer acute and late outcomes. Although any increase in CK-MB levels associates with poorer clinical outcomes, there is a stepwise increase in late mortality according to the various degrees of CK-MB elevation. In line with the VARC-2 definition for clinically relevant myocardial infarction post TAVR, a CK-MB rise >5-fold the upper normal limits related with incremental mortality rates, although the best cutoff for predicting mortality should be confirmed in future studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Evidence of myocardial injury emerges commonly in patients after TAVR. Predictors of injury include a transapical approach, operator/center early experience, procedural complications such as major bleeding, device embolism, and need for a second prosthesis or surgery. More severe myocardial injury (particularly CK-MB >5 times the upper limit or normal) is associated with late LV dysfunction and increased acute and late mortality.

TRANSLATIONAL OUTLOOK: Future studies are needed to identify patients before TAVR who are at greatest risk of periprocedural myocardial injury and to develop management strategies to minimize its adverse impact on clinical outcomes.

REFERENCES

1. Rodes-Cabau J. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2012;9:15–29.

2. Rodes-Cabau J, Gutierrez M, Bagur R, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J Am Coll Cardiol 2011;57:1988–99.

3. 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;111:1475–81.

4. Barbash IM, Dvir D, Ben-Dor I, et al. Prevalence and effect of myocardial injury after transcatheter aortic valve replacement. Am J Cardiol 2013;111:1337–43.

5. Barbash IM, Dvir D, Ben-Dor I, et al. Impact of transapical aortic valve replacement on apical wall motion. J Am Soc Echocardiogr 2013;26:255–60.

6. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

7. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563–70.

8. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.

9. Vikenes K, Andersen KS, Melberg T, Farstad M, Nordrehaug JE. Long-term prognostic value of cardiac troponin I and T versus creatine kinase-MB mass after cardiac surgery in low-risk patients with stable symptoms. Am J Cardiol 2010;106:780–6.

10. Januzzi JL, Lewandrowski K, MacGillivray TE, et al. A comparison of cardiac troponin T and creatine kinase-MB for patient evaluation after cardiac surgery. J Am Coll Cardiol 2002;39:1518–23.

11. Brener SJ, Lytle BW, Schneider JP, Ellis SG, Topol EJ. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. J Am Coll Cardiol 2002;40:1961–7.

12. Ribeiro HB, Larose E, de la Paz Ricapito M, et al. Myocardial injury following transcatheter aortic valve implantation: insights from delayed-enhancement cardiovascular magnetic resonance. EuroIntervention 2015;11:205–13.

13. Ribeiro HB, Dahou A, Urena M, et al. Myocardial injury after transaortic versus transapical transcatheter aortic valve replacement. Ann Thorac Surg 2015;99:2001–9.

14. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705–15.

15. Blackstone EH, Suri RM, Rajeswaran J, et al. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral TAVR: a PARTNER-I trial substudy. Circulation 2015;131:1989–2000.

16. Urena M, Webb JG, Eltchaninoff H, et al. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol 2015;65:437–48.

17. Rodes-Cabau J, Dauerman HL, Cohen MG, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. J Am Coll Cardiol 2013;62:2349–59.

18. Makkar RR, Jilaihawi H, Chakravarty T, et al. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the US PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). J Am Coll Cardiol 2013;62:418–30.

19. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311:1503–14.

20. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

21. Yong ZY, Wiegerinck EM, Boerlage-van Dijk K, et al. Predictors and prognostic value of myocardial injury during transcatheter aortic valve implantation. Circ Cardiovasc Interv 2012;5:415–23.

22. Paradis J-M, Maniar HS, Lasala JM, et al. Clinical and functional outcomes associated with myocardial injury after transfemoral and transapical transcatheter aortic valve replacement: a subanalysis from the PARTNER Trial (Placement of Aortic Transcatheter Valves). J Am Coll Cardiol Intv 2015;8:1468–79.

23. Clavel MA, Webb JG, Rodes-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. Circulation 2010;122:1928–36.

24. Selle A, Figulla HR, Ferrari M, et al. Impact of rapid ventricular pacing during TAVI on microvascular tissue perfusion. Clin Res Cardiol 2014;103:902–11.

25. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

26. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. JAMA 2013;309:2262–9.

27. Herrmann J, Lennon RJ, Jaffe AS, Holmes DR Jr., Rihal CS, Prasad A. Defining the optimal cardiac troponin T threshold for predicting death caused by periprocedural myocardial infarction after percutaneous coronary intervention. Circ Cardiovasc Interv 2014;7:533–42.

28. Panteghini M. A critical appraisal of experimental factors influencing the definition of the 99th percentile limit for cardiac troponins. Clin Chem Lab Med 2009;47:1179–82.

KEY WORDS aortic stenosis, cardiac biomarkers, creatine kinase-MB, transapical, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this article.