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)

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Journal Title: JACC: Cardiovascular Interventions
Volume: Volume 8, Number 11
Publisher: Elsevier | 2015-09-01, Pages 1468-1479
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.jcin.2015.06.018
Permanent URL: https://pid.emory.edu/ark:/25593/rrm18

Final published version: http://dx.doi.org/10.1016/j.jcin.2015.06.018

HHS Public Access

Author manuscript

JACC Cardiovasc Interv. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

JACC Cardiovasc Interv. 2015 September ; 8(11): 1468–1479. doi:10.1016/j.jcin.2015.06.018.

Clinical and Functional Outcomes Associated with Myocardial Injury after Transfemoral and Transapical TAVR: A Sub-analysis from the PARTNER Trial

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Abstract

Objective—This study sought to clarify the clinical and echocardiographic prognostic implication of myocardial injury after TAVR.

Methods—Patients treated with TAVR in the PARTNER trial were divided into tertiles (T1, T2, T3) based on the difference between the post-procedure day 1 and the baseline values of 2 cardiac biomarkers (ΔcTnI (Troponin I) and ΔCKMB). Patients were stratified according to their access route (Transfemoral (TF) (N=1840) or Transapical (TA) (N=1173)).

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Relationships with Industry

Dr. Susheel Kodali has received consulting fees from Edwards Lifesciences and is a member of the Scientific Advisory Board for Thubrikar Aortic Valve; Dr Martin B. Leon is a nonpaid member of the PARTNER Trial Executive Committee; Dr. Raj Makkar has received grant support from Edwards Lifesciences and St. Jude Medical, is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical; Dr. Lars Svensson has is an unpaid member of the PARTNER Trial Executive Committee, holds equity in Cardiosolutions and ValvXchange, and has Intellectual Property Rights/Royalties from Posthorax; Dr. Vinod Thourani is a member of the PARTNER Trial Steering Committee and a consultant for Edwards Lifesciences, Sorin Medical, St. Jude Medical, and DirectFlow; Dr Mathew Williams has received consulting fees from Edwards Lifesciences; Dr Alan Zajarias has received consulting fees from Edwards Lifesciences. The other authors have no disclosures.

Results—At 30 days after TF-TAVR, patients in the highest tertile (T3) of cardiac biomarker elevation had a higher rate of all cause mortality (ΔcTnI: T3: 5.4% vs T1: 0.5%, p=0.006; ΔCKMB: T3: 5.7% vs T1: 0.9%, p=0.006) and cardiovascular mortality (ΔcTnI: T3: 4.9% vs T1: 0.5 %, p=0.01; ΔCKMB: T3: 3.9% vs T1: 0.5%, p=0.02). At 1 year, only patients in the highest CKMB tertile had higher all cause (25.4% vs 16.8%, p=0.02) and cardiovascular (10.3% vs 5.0%) mortality. Multivariable analysis demonstrated that greater release of cardiac biomarkers was independently associated with increased mortality in the TF population. After TA-TAVR, being in the highest tertile of cardiac biomarker elevation had no influence on clinical and echocardiographic outcomes at 30 days and 1 year.

Conclusions—After TF-TAVR, a greater degree of myocardial injury was associated with higher 30 day all-cause and cardiovascular mortality. At 1 year, being in the highest tertile of ΔCKMB was correlated with a higher rate of all-cause and cardiac mortality. Finally, the level of myocardial injury after TA-TAVR had no impact on clinical and echocardiographic outcomes.

Keywords

TAVR; Transcatheter Aortic Valve Replacement; Troponin; CKMB; myocardial injury

Introduction

Transcatheter aortic valve replacement (TAVR) has become the standard treatment option for inoperable patients with severe symptomatic aortic stenosis (1, 2) and has been shown to be non-inferior to surgical aortic valve replacement in terms of survival among selected high-risk patients (3, 4). Recent studies have shown that a transapical (TA) approach to TAVR is associated with some degree of myocardial injury, which is exacerbated by renal dysfunction. (5–7)

Myocardial injury after TAVR could be influenced by procedural or patient specific factors. Myocardial damage following cardiac surgery or percutaneous coronary intervention has been strongly associated with cardiovascular morbidity and mortality (8–10), however, the clinical significance of cardiac biomarker elevation after TAVR remains uncertain. Accordingly, we sought to better characterize the clinical and echocardiographic impact of myocardial damage after transfemoral (TF) and TA TAVR using data from the multicenter Placement of Aortic Transcatheter Valves (PARTNER) trial.

Methods

Study Population

The design and results of the PARTNER trial (cohorts A and B) have been previously published (1–4). Briefly, the randomized portion of the trial enrolled patients with severe symptomatic aortic stenosis who were either high risk for surgical AVR (cohort A) or deemed inoperable (cohort B). In cohort A, after assessment of vascular anatomy, patients were allocated to a TF or TA placement cohort and randomized to TAVR with the Edwards SAPIEN heart valve system (Edwards Lifesciences, Irvine, California) or surgical valve replacement. In cohort B, patients were randomized to standard therapy or TAVR via a TF approach if vascular access was adequate. After completion of the randomized trial, a non-

randomized continued access (NRCA) registry allowed treatment of both cohort A and cohort B patients with TAVR. Inclusion and exclusion criteria, data collection, and monitoring were the same in both the randomized trial and the NRCA registry. All patients were presented and adjudicated as appropriate candidates during conference calls with the executive committee and other investigators.

For the current analysis, we included only patients who were randomized to and treated with TAVR in the randomized trial and those treated with TAVR in the NRCA registry (as-treated population) who had cardiac biomarkers (cardiac Troponin I (cTnI) and creatinine kinase MB fraction (CK-MB)) measured at baseline and on the first day after the procedure. Many centers used several different immunoassays for measurements of troponin and CK-MB. In order to have the largest study group possible, but to limit variability and to allow each patient to become his/her own control, we elected to exclude patients with troponin T measurements (because a minority of centers were using this specific immunoassay). The PARTNER study was approved by the institutional review board at each participating site, and all patients provided written informed consent.

Cardiac Biomarkers

Patients were stratified according to their access route (TF or TA). Cardiac biomarkers were measured at baseline and on post-procedure day 1. As biomarker measurements were not performed in a central laboratory, in order to control for the potential differences in reference values, patients in each group were divided into tertiles (T1, T2, T3) based on the difference between the post-procedure day 1 value and the baseline values of each cardiac marker (ΔcTnI and ΔCKMB).

Study endpoints

Study end points were reported according to Valve Academic Research Consortium (VARC) definitions(11) or according to the definitions established in the PARTNER 1 protocol. All adverse events were adjudicated by an independent clinical events committee. Independent core laboratory analysis was performed on all echocardiograms and electrocardiograms. All data were sent for analysis to an independent academic biostatistics group.

Periprocedural myocardial infarction (MI) was defined according to a modified version of the VARC criteria (12) as described in the PARTNER trial protocol (1–4). Any of the following criteria met the definition of MI: 1) acute MI demonstrated by autopsy; 2) emergent percutaneous coronary intervention performed for acute ST-elevation myocardial infarction; 3) administration of thrombolytics for acute myocardial infarction; 4) clinical periprocedural MI (up through 7 complete days post index procedure) defined as:

a. periprocedural Q-wave MI: development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK-MB or CK (in absence of CK-MB data). New Q waves in the absence of symptoms or elevated markers was not considered an MI;

b. periprocedural non-Q-wave MI: documented signs or symptoms of ischemia and/or new ischemic changes on ECG and CK-MB elevation > 10x the upper limit of normal (ULN). In the absence of CK-MB data, CK was used with the same > 10 X ULN criteria.

Statistical Analysis

Continuous variables were analyzed via mean +/− standard deviation or medians and quartiles, as appropriate, and were compared using Student's t test. If data were not normally distributed, the Mann-Whitney U test was used instead. Categorical variables were analyzed with the chi-square test or Fisher's exact test where asymptotic validity was not met. For each access route (TF vs TA), clinical and echocardiographic outcomes were compared across tertiles, and between the highest and lowest tertiles (T3 and T1). Kaplan-Meier estimates were used to construct survival curves for time-to-event variables, which were compared using the log-rank test. Statistical significance was defined as a p value < 0.05. Univariable analysis and multivariable logistic regression were performed to identify independent predictors of 30-day and 1-year all-cause mortality and cardiovascular mortality, respectively. To avoid overfitting, variables included in the multivariable model were selected only if they were of clinical interest and/or fulfilled the entry criterion of $p<0.1$ in the univariable analysis. We also used cubic spline plots to display the estimated cubic spline function relating ΔTnI and ΔCKMB to the 30-day and 1-year all-cause mortality for a Cox model (supplementary appendix). Data are based on an extract date of March 11, 2014. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Funding Source

The PARTNER trial was funded by Edwards Lifesciences and designed collaboratively by the steering committee and the sponsor. The present analysis was carried out mainly by investigators at the Cardiovascular Research Foundation, Columbia University Medical Center and Washington University School of Medicine. The authors had unrestricted access to the study data, drafted the manuscript, made the decision to submit for publication, and guarantee the completeness and accuracy of its content.

Results

Patients and baseline characteristics

Among the 3013 patients enrolled in the as-treated population of the PARTNER trial, 1840 were treated with TAVR via the TF approach and 1173 by a TA approach. In the TF population, 557 patients had cTnI measurements at the 2 specified time points. Among these patients, the ΔcTnI had the following distribution: T1 [n=187, −82.81 to 0.30 ng/mL]; T2 [n=184, 0.31 to 0.88 ng/mL]; and T3 [n=186, 0.89 to 402.38 ng/mL]. ΔCKMB data was available in 632 patients with the following distribution: T1 [n=211, −80.00 to 0.80 U/L]; T2 [n=212, 0.90 to 2.90 U/L]; and T3 [n=209, 3.00 to 85.90 U/L]. In the TA population, ΔcTnI was available in 340 patients: T1 [n=113, −5.62 to 4.41 ng/mL]; T2 [n=114, 4.42 to 8.09 ng/mL]; and T3 [n=113; 8.10 to 348.87 ng/mL], Also among the TA population, 416 were included in the ΔCKMB analysis with the following distribution: T1 [n=138, −27.00 to

9.40 U/L]; T2 [n=139, 9.41 to 21.60 U/L]; and T3 [n=139, 21.61 to 4027.00 U/L]. Baseline and periprocedural characteristics of patients stratified by approach and further divided by tertiles for each cardiac biomarker are shown in Tables 1 A and B. Patients in the highest tertiles of both biomarkers were more commonly women and had a lower prevalence of prior CABG irrespective of approach. The hemodynamic and echocardiographic data are summarized in Table 2A and B.

Clinical and echocardiographic outcomes

Transfemoral approach

Mortality: When compared to the lowest tertile (T1), patients in the highest tertile (T3) of cardiac biomarker elevation who underwent a TF approach had a higher rate of all cause mortality (ΔcTnI: T3: 5.4% vs T1: 0.5%, p=0.006; ΔCKMB: T3: 5.7% vs T1: 0.9%, p=0.006) and cardiovascular mortality (ΔcTnI: T3: 4.9% vs T1: 0.5 %, p=0.01; ΔCKMB: T3: 3.9% vs T1: 0.5%, p=0.02) at 30 days (Figure 1A). At 1 year, there was still a significant difference in all cause mortality (25.4% vs 16.8%, p=0.02) and in cardiovascular mortality (10.3% vs 5.0%) between the highest and the lowest CKMB tertiles (Figure 1 B). However, there was no longer a significant association between a larger periprocedural cTnI release and higher 1-year all cause (ΔcTnI: T3: 23.2% vs T1: 18.9%, p=0.22) and cardiovascular (ΔcTnI: T3: 13.0% vs T1: 7.8%, p=0.09) mortality. The rates of MI were very low and were similar across tertiles for both markers (ΔcTnI: p=0.60, ΔCKMB: p=0.37) (Table 3).

Functional Assessment and Echocardiography: At 1 year, the proportion of patients with >1 improved NYHA class was similar across the tertiles for both cTnI and CKMB (ΔcTnI: T3: 67.4% vs T1: 61.1%, p=0.28; ΔCKMB: T3: 57.4% vs T1: 65.2%, p=0.16). Additionally, no significant differences were noted across the tertiles in the 6 minute walk performed at 1 year (ΔcTnI: T3: 216.9 m vs T1: 224.5 m, p=0.64; ΔCKMB: T3: 218.1 m vs T1: 236.2 m p=0.30).

In paired analyses of baseline and 1 year LVEF measurements, there was a significant improvement in the LVEF at 1 year in T1 and T2 ΔcTnI tertiles (ΔcTnI: T1: 3.10%, p=0.002; T2: 2.72%, p=0.006; T3:1.78, p*=0.17) and in each ΔCKMB tertile (ΔCKMB: T1:4.41%, p=0.0001; T2:2.58%, p=0.01; T3:2.35%, p=0.02). The degree of cTnI or CKMB elevation was not associated with LVEF change (ΔcTnI: T3:1.78% vs T1:3.10%, p=0.31, ΔCKMB: T3: 2.35% vs T1: 4.41%, p=0.15).

Transapical approach

Mortality: There was no significant difference in all-cause or cardiovascular mortality at 30 days or 1 year when comparing patients in the lowest and highest tertiles (Figure 2A and B). The incidence of MI at 30 days was similar between the highest and lowest tertiles of both biomarkers (ΔcTnI: T3: 1.8% vs T1: 0.9%, p=0.56; ΔCKMB: T3: 1.5% vs T1: 0.7%, p=0.56) (Table 3).

Functional Assessment and Echocardiography: At 1 year, the fraction of individuals with improvement of the New York Heart Association (NYHA) functional classification by more

than one class was similar between tertiles of both cardiac biomarkers (ΔcTnI: T3: 79.5% vs T1: 71.4%, p=0.25; ΔCKMB: T3: 72.7% vs T1: 79.8% p=0.26). The 6-minute walk distance at 1 year was also similar between T3 and T1 for both biomarkers (ΔcTnI: T3: 214.6 m vs T1: 245.5 m, p=0.15; ΔCKMB: T3: 187.7 m vs T1: 201.1 m p=0.49).

In paired analyses, there was no significant change in LVEF from baseline to 1 year in any tertile of either cardiac biomarker (ΔcTnI: T1:2.28%, p=0.06; T2:1.32%, p=0.18; T3: −0.37%, p=0.41; ΔCKMB: T1:2.27%, p=0.09; T2:1.74%, p=0.23; T3: −0.03%, p=0.90) after TA-TAVR at 1 year. The degree of myocardial injury across tertiles (T3 vs T1) did not influence the change in LVEF 1 year after a TA procedure (ΔcTnI: p=0.09, ΔCKMB: p= 0.18).

Multivariable analysis—Multivariable analyses were performed to evaluate the association between a greater release of cardiac biomarkers and increased mortality in the TF population. After adjusting for significant confounders (Table 4), the highest tertile of ΔTnI and of ΔCKMB remained independent predictors of 30-day all-cause and cardiovascular mortality mortality. At 1 year, a higher CKMB elevation (T3 vs T1) was an independent predictor of all cause death and of cardiac death. In the multivariable analysis, renal disease requiring dialysis was identified as a predictor of 1 year all cause mortality while the incidence of major vascular complication was linked to a higher rate of cardiovascular mortality at 12 months.

Discussion

In patients with elevated surgical risk treated with TAVR in the PARTNER trial and NRCA registry, post-operative cardiac biomarker elevation was common after the procedure. Higher differences between pre and post-procedural CKMB values resulted in an increase in short term all cause and cardiac mortality rates in patients undergoing transfemoral TAVR. Also, in the multivariable analysis, the highest tertile of CKMB persisted as an independent predictor of 1 year all cause and cardiac mortality. The degree of myocardial injury did not influence the improvement of NYHA class, the performance at the 6-minute walk test, or the change in LVEF at 1 year. There was no association of myocardial injury with 30 or 1-year mortality in patients undergoing TA-TAVR as measured by changes in the cardiac biomarkers.

Larger cardiac biomarker elevation is seen after TA-TAVR due to instrumentation of the left ventricular apex and the surgical repair of the ventriculotomy. A certain degree of myocardial injury is expected during this procedure resulting in higher CKMB and TnI elevation, perhaps masking its prognostic value. Our findings are similar to those reported by Barbash et al. who showed that an increase of cTnI or CKMB had no prognostic accuracy to predict 30-day mortality among TA patients(7). In addition, there were no statistically significant differences between tertiles for NYHA functional class improvement, 6-minute walk test distance, or LVEF recovery at 1 year after TA-TAVR, minimizing the importance of these laboratory findings. In the TF subset, cardiac biomarker elevation appears to play a role in predicting mortality. Elevation of TnI or CKMB after TAVR may be associated to patient or procedural characteristics. Patients with higher degree of cardiac enzymes

elevation were older, more frequently females, had lower BMI and lower rates of CAD, COPD, diabetes mellitus and prior CABG. Periprocedural biomarker elevation may be due to the presence of lower capillary density, and larger degree of left ventricular hypertrophy in previously unscarred ventricles. Procedural characteristics, such as procedural time, episodes of hypotension, duration of rapid ventricular pacing, injury by the guidewire or delivery system, coronary obstruction, or abnormal coronary perfusion due to elevated left ventricular end diastolic pressure, pre-existing unrevascularized coronary disease and procedural hypotension are associated with episodes of ventricular ischemia. Yong et al.(13) identified procedural duration as an independent predictor of myocardial injury after TAVR with the Medtronic Corevalve device. In our analysis with the Edwards SAPIEN transcatheter heart valve, procedural time was longer in the highest tertiles of ΔcTnI and ΔCKMB after TF cases only. Longer cases are also associated with procedural complications which may further predispose to myocardial ischemia. Depth of implant has also been identified as a risk factor for periprocedural myocardial damage in patients undergoing self-expanding TAVR, but this finding may apply to patients undergoing TAVR with a balloon expanding prosthesis.

Numerous studies have demonstrated that the occurrence of myocardial injury after a cardiac procedure such as cardiac surgery or percutaneous coronary intervention is correlated with worse future cardiovascular outcomes(14, 15). Nevertheless, there is a paucity of data on the impact of myocardial injury following TAVR. Following a TF procedure, Buellesfeld et al(16) and Grube et al(17) have reported an incidence of 1.5% to 1.8% of CKMB elevation greater than 2 times the upper limit of normal. Using the definition of spontaneous myocardial infarction, Svensson et al(18) demonstrated that periprocedural myocardial infarctions occurred in 17% of patients who underwent a TA procedure. The study by Rodes-Cabau et al (5) showed that uncomplicated TAVR was associated with some degree of troponin elevation in 99% of patients. In our study, the presence of biomarker elevation was associated with mortality in the TF patients even in levels that were not considered diagnostic for a myocardial infarction. In these high risk patients the extent of comorbidities may suggest a lower threshold of injury required to be considered pathologic. Furthermore, it is possible that the degree of coronary reserve is lower in these patients, which may predispose to procedural myocardial damage.

In another study (5), the TA approach and baseline renal insufficiency were the main predictors of a greater increase in cardiac biomarkers levels. Indeed, cardiac mortality at 9 month follow-up was higher in patients with a larger rise in cardiac troponin level. A greater degree of myocardial injury was linked with a reduced improvement of LVEF. In our study, patients in the highest CKMB tertile had a significantly higher cardiovascular mortality at 12 months and only patients in the highest tertile of delta troponin did not significantly improve their LVEF after TF-TAVR. On the contrary, all the patients who underwent a TA procedure had no significant modification of their LVEF at 1 year, regardless of the degree of cardiac biomarker elevation.

Renal dysfunction can be interrelated with higher levels of cardiac troponin even in the absence of clinically suspected myocardial ischemia(19). In the study by Carrabba et al(6), TAVR was systematically associated with myocardial injury, occurring at a greater level in

individuals who developed acute kidney injury. However, in our analysis, all tertiles of cTnI, after both TF and TA procedures, were associated with similar rates of 30-day need for dialysis. Nonetheless, in the multivariable analysis, post procedural renal failure requiring dialysis was still identified as an independent predictor of 1 year all-cause mortality.

Study limitations

Several limitations of the present analysis should be considered. The PARTNER trial was performed using first-generation devices (22 and 24 F sheath introducer diameter for the TF approach and 29 F for the TA route) with operators and sites at the beginning of their learning curve. The evolution toward lower profile TAVR devices might affect the level of myocardial damage after TAVR, especially for TA cases. Moreover, different reference values of biomarkers measured created the need to analyze the data in tertiles utilizing each patient as his/her own control. Furthermore, to decrease the variability associated with the use of multiple troponin assays, only patients with available troponin I measurements have been included in our analysis. Consequently, the number of patients included was reduced, therefore affecting the power to detect significant differences between tertiles. Also, the delta was calculated only with the 24h post-procedural value. Since troponin is known to peak around 48h post TAVR(5), the calculation used in our analysis might have underestimated the maximal delta in a certain number of patients. To establish the exact location and the precise amount of myocardial injury, cardiac magnetic resonance imaging after TAVR could have been a useful imaging modality. In addition, the small number of clinical adverse events allowed the adjustment for very few covariates, subsequently limiting the multivariable analysis. Finally, other potential unmeasured confounders may still be present and this post-hoc secondary analysis of data collected as part of a randomized trial should be considered hypothesis-generating and not definitive.

Conclusion

Our study, which is the largest published to date on the topic of cardiac biomarker elevation after TAVR, demonstrates that after TF-TAVR a higher elevation of cTnI is associated with higher frequencies of 30 day all-cause and cardiovascular mortality. A greater rise of CKMB after TF-TAVR is correlated with increased rates of 30-day and 1 year all-cause and cardiovascular mortality. The degree of myocardial injury after TA-TAVR had no influence on short and long term survival. Further studies are needed to elucidate the patient and procedural factors that contribute to greater myocardial injury during TAVR so that steps can be taken to address those that are modifiable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

The PARTNER trial was funded by Edwards Lifesciences and designed collaboratively by the steering committee and the sponsor. Dr. Brian Lindman was supported by K23 HL116660 from the NIH.

Abbreviations list

AVR	Aortic valve replacement
CKMB	Creatine kinase MB fraction
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NYHA	New-York Heart Association
TA	Trans-apical
TF	Trans-femoral
TAVR	Transcatheter aortic valve replacement
TnI	Troponin I
VARC	Valve Academic Research Consortium

References

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010; 363:1597–1607. [PubMed: 20961243]
2. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012; 366:1696–1704. [PubMed: 22443478]
3. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011; 364:2187–2198. [PubMed: 21639811]
4. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012; 366:1686–1695. [PubMed: 22443479]
5. Rodés-Cabau J, Gutiérrez 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; 57:1988–1999. [PubMed: 21565636]
6. 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. [PubMed: 23465097]
7. Barbash IM, Dvir D, Ben-Dor I, et al. Prevalence and effect of myocardial injury after transcatheter aortic valve replacement. Am J Cardiol. 2013; 111:1337–1343. [PubMed: 23415511]
8. Akkerhuis KM, Alexander JH, Tardiff BE, et al. Minor myocardial damage and prognosis: are spontaneous and percutaneous coronary intervention-related events different? Circulation. 2002; 105:554–556. [PubMed: 11827918]
9. Greenson N, Macoviak J, Krishnaswamy P, et al. Usefulness of cardiac troponin I in patients undergoing open heart surgery. Am Heart J. 2001; 141:447–455. [PubMed: 11231444]
10. Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. J Am Coll Cardiol. 2003; 42:1406–1411. [PubMed: 14563583]
11. Kappetein AP, Head SJ, Généreux 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; 60:1438–1454. [PubMed: 23036636]
12. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol. 2011; 57:253–269. [PubMed: 21216553]

13. Yong ZY, Wiegerinck EMA, Boerlage-van Dijk K, et al. Predictors and prognostic value of myocardial injury during transcatheter aortic valve implantation. Circ Cardiovasc Interv. 2012; 5:415–423. [PubMed: 22668556]
14. Herrmann J. Peri-procedural myocardial injury: 2005 update. Eur Heart J. 2005; 26:2493–2519. [PubMed: 16176941]
15. Thygesen K, Alpert JS, Jaffe AS, et al. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2012; 126:2020–2035.
16. Buellesfeld L, Wenaweser P, Gerckens U, et al. Transcatheter aortic valve implantation: predictors of procedural success–the Siegburg-Bern experience. Eur Heart J. 2010; 31:984–991. [PubMed: 20038513]
17. Grube E, Buellesfeld L, Mueller R, et al. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv. 2008; 1:167–175. [PubMed: 20031675]
18. Svensson LG, Dewey T, Kapadia S, et al. United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. The Ann Thor Surg. 2008; 86:46–55.
19. Freda BJ, Tang WW, Van Lente F, et al. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol. 2002; 40:2065–2071. [PubMed: 12505215]

Clinical Perspective

What is Known?

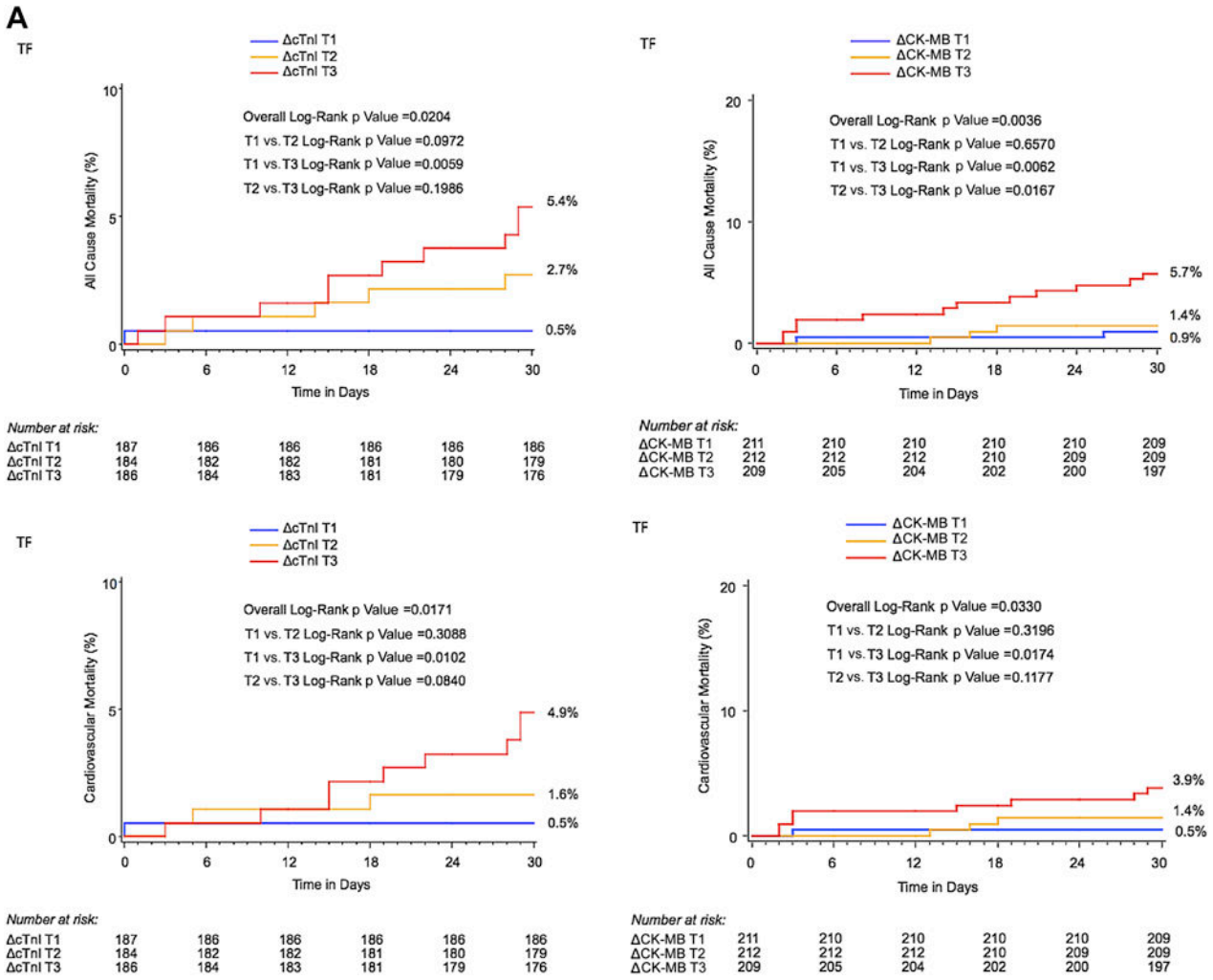
Transcatheter aortic valve replacement has become the standard treatment option for inoperable patients with severe symptomatic aortic stenosis and has been shown to be non-inferior to surgical aortic valve replacement in terms of survival among selected high-risk patients. Recent studies have demonstrated that TAVR is systematically associated with some degree of myocardial injury. The exact clinical significance of cardiac biomarker elevation after TAVR still remains uncertain.

What is New?

Our study, which is the largest published to date on the topic of cardiac biomarker elevation after TAVR, demonstrates that after TF-TAVR a higher elevation of cTnI is associated with higher rates of 30 day all-cause and cardiovascular mortality. A greater rise of CKMB after TF-TAVR is correlated with increased frequencies of 30-day and 1 year all-cause and cardiovascular mortality. The degree of myocardial injury after TA-TAVR had no impact on short and long term survival.

What is Next?

Further studies will be needed not only to substantiate the influence of cardiac biomarker elevation on outcomes after TAVR, especially with newer generation devices, but also to identify precautionary actions that could reduce the amount of myocardial injury after TAVR.



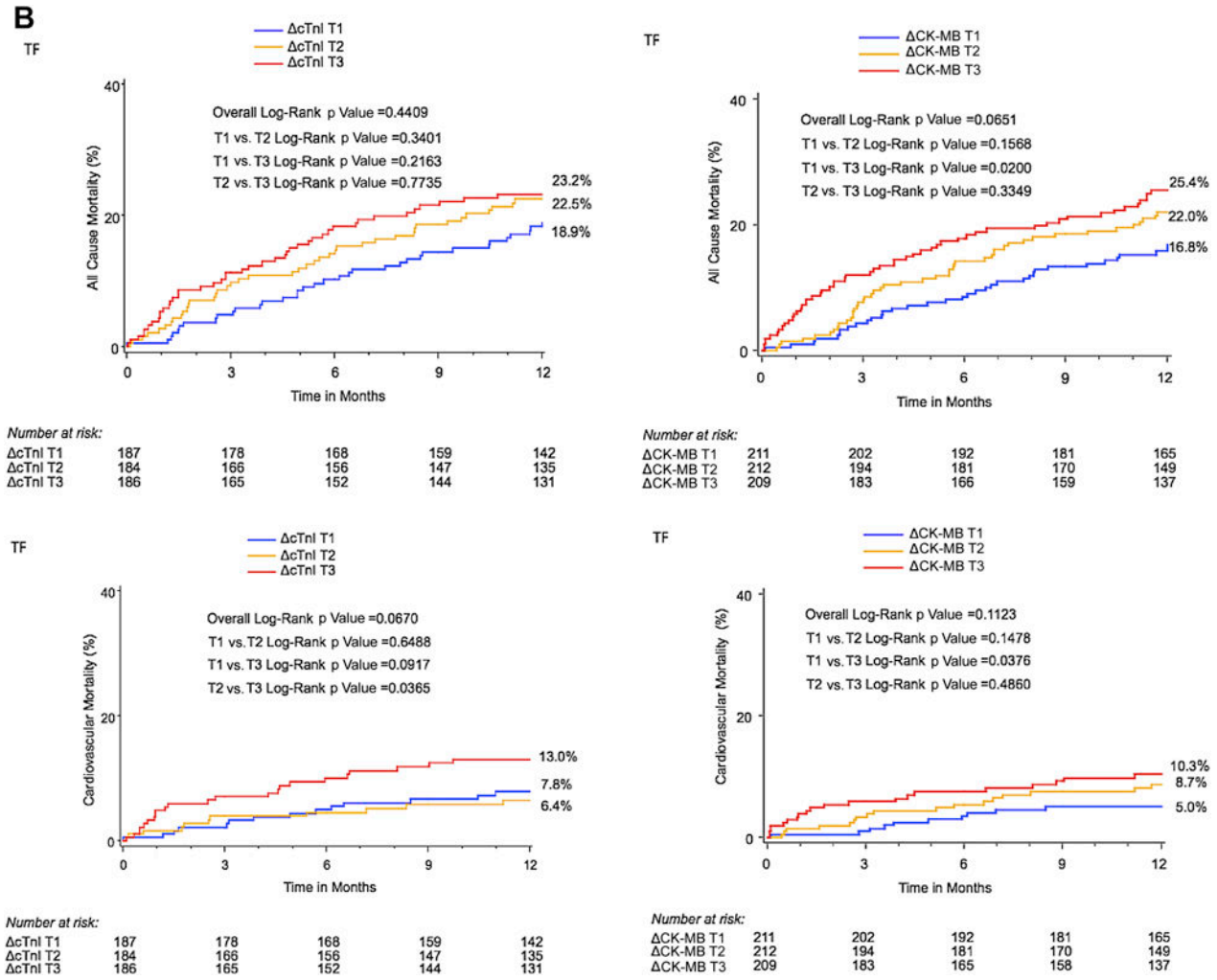
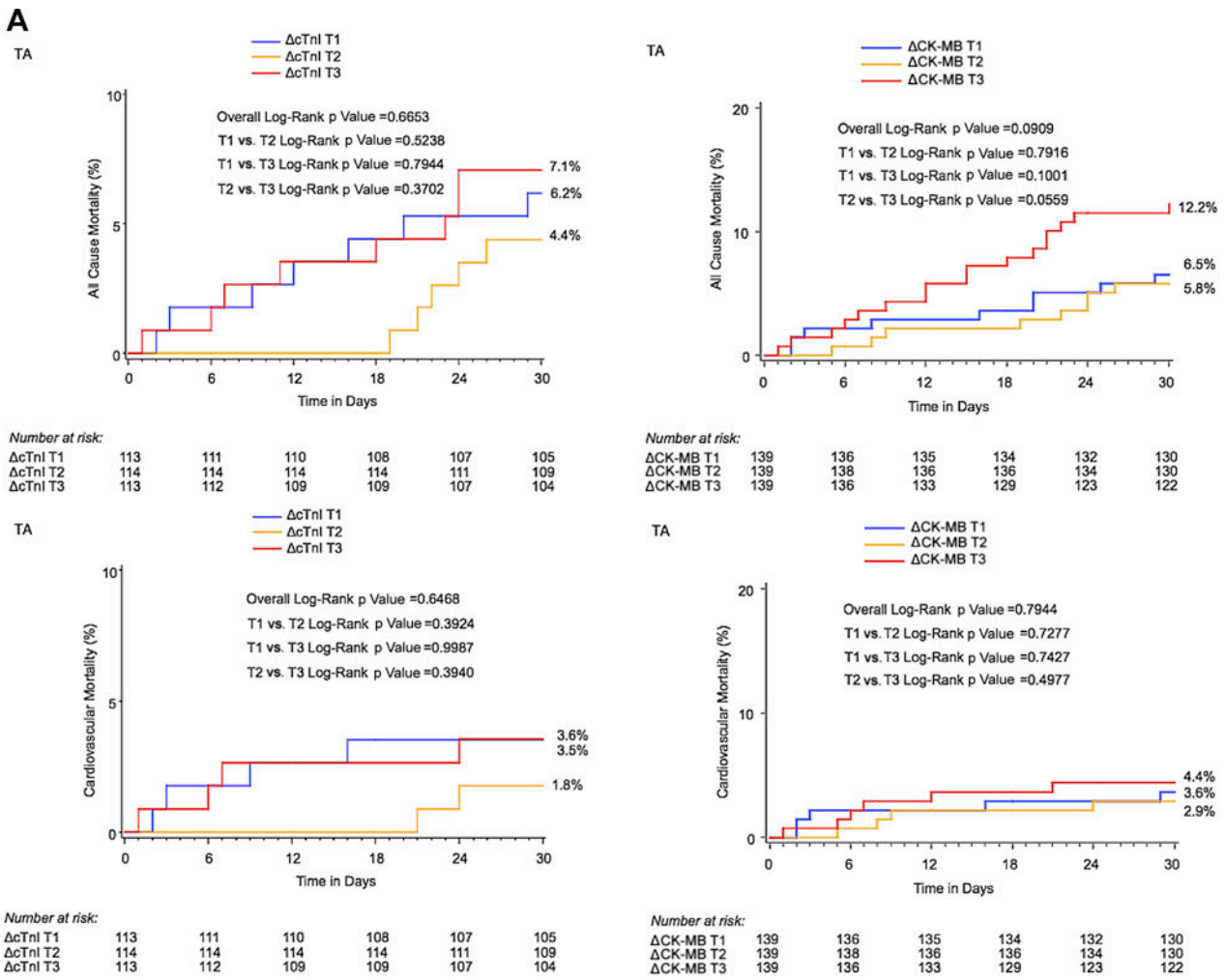


Figure 1. All Cause and Cardiovascular Mortality after TF-TAVR

Thirty day (A) and one year (B) all-cause and cardiovascular mortality rates after TF-TAVR, stratified by cardiac enzyme tertiles



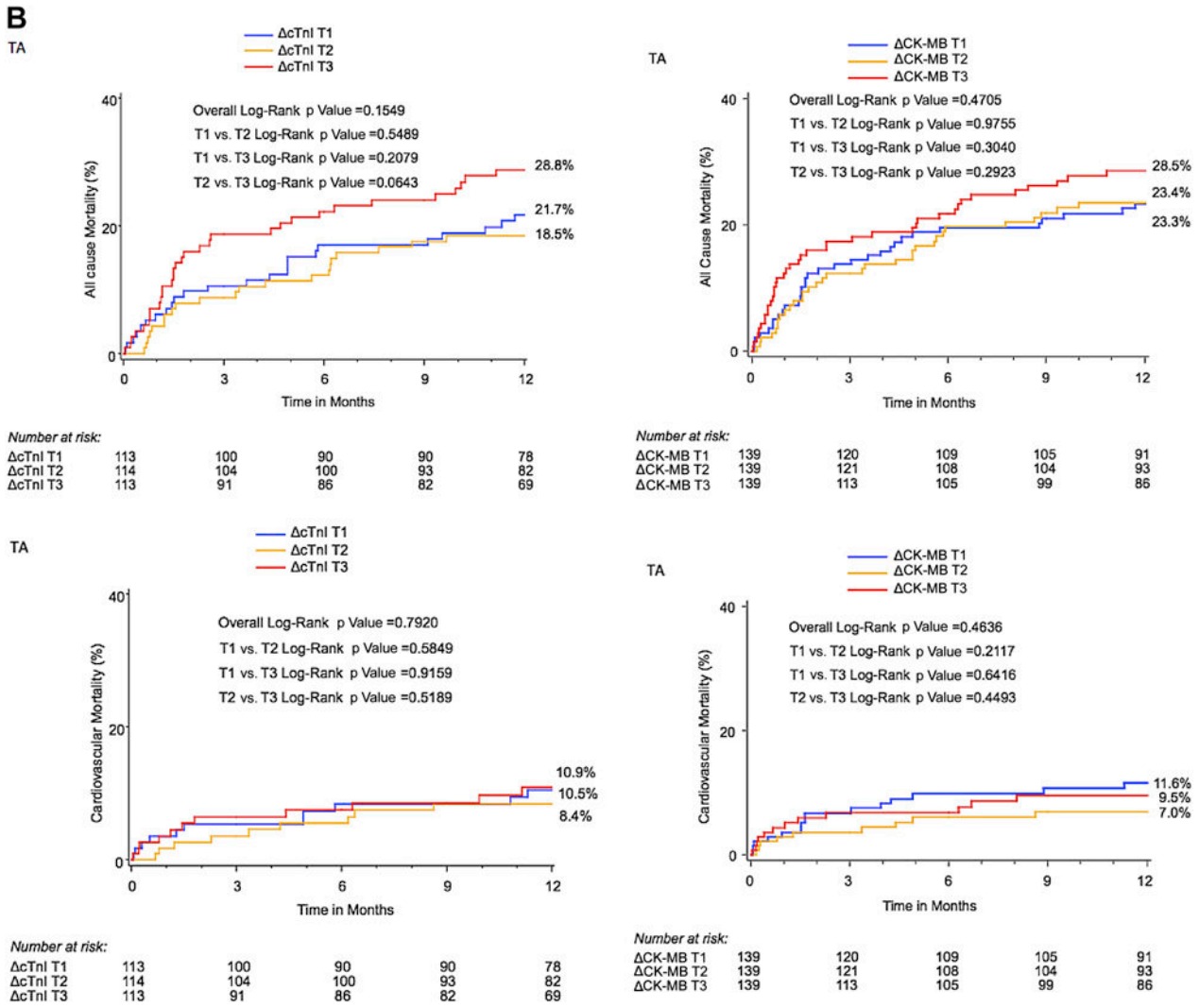


Figure 2. All Cause and Cardiovascular Mortality after TA-TAVR

Thirty day (A) and one year (B) all-cause and cardiovascular mortality rates after TA-TAVR, stratified by cardiac enzyme tertiles.

JACC Cardiovasc Interv. Author manuscript; available in PMC 2016 September 01.

Table 1

Baseline characteristics in the TF group (1A) and the TA group (1B).

A										
	Transfemoral									
	cTnI					CKMB				
Characteristics	**T1**	**T2**	**T3**	**p-value (T1 vs T3)**	**p-value (all groups)**	**T1**	**T2**	**T3**	**p-value (T1 vs T3)**	**p-value (all groups)**
Age (year)	83.0	85.3	85.1	0.006	0.004	83.0	84.4	84.5	0.054	0.10
Male sex (%)	64.2	55.4	49.5	0.004	0.02	63.0	57.1	48.3	0.002	0.009
BMI (Kg/m^2)	28.7	26.8	26.4	0.0005	0.002	27.6	26.7	26.4	0.04	0.10
STS score	10.4	11.5	11.1	0.08	0.02	10.6	11.5	11.2	0.19	0.11
Dyslipidemia (%)	83.9	83.7	85.4	0.68	0.88	82.9	82.1	77.0	0.13	0.25
Hypertension (%)	92.5	92.9	91.9	0.83	0.94	91.5	89.2	89.0	0.39	0.64
History of smoking (%)	43.0	32.6	37.8	0.31	0.12	47.4	39.6	42.1	0.28	0.26
NYHA III-IV (%)	95.2	95.1	94.8	0.64	0.87	93.8	96.2	95.2	0.54	0.52
CAD (%)	79.6	66.3	69.2	0.02	0.01	81.5	73.1	68.9	0.003	0.01
Prior PCI (%)	40.8	28.3	33.5	0.15	0.04	42.9	31.3	29.7	0.005	0.008
Prior CABG (%)	41.9	32.6	32.4	0.06	0.09	46.4	44.3	32.1	0.003	0.005
Diabetes (%)	45.2	36.4	34.1	0.03	0.07	45.0	37.3	36.4	0.07	0.14
PVD (%)	38.8	27.6	35.2	0.47	0.07	24.2	29.5	23.8	0.93	0.22
Cerebrovascular disease (%)	22.0	23.0	18.5	0.39	0.54	26.9	22.5	16.4	0.009	0.03
Renal disease (creat≥2) (%)	17.7	15.3	18.9	0.77	0.65	14.7	14.7	19.6	0.18	0.29
Liver disease (%)	2.7	1.6	1.1	0.26	0.50	2.8	1.9	2.4	0.78	0.81
Chronic atrial fibrillation (%)	25.7	19.8	18.8	0.11	0.22	18.6	21.0	15.4	0.39	0.34
COPD (%)	49.2	46.7	36.0	0.01	0.02	46.9	47.6	44.5	0.62	0.80
Porcelain aorta (%)	3.7	5.4	5.4	0.45	0.69	7.6	5.2	9.1	0.58	0.30

B										
	Transapical									
	cTnI					CKMB				
Characteristics	**T1**	**T2**	**T3**	**p-value (T1 vs T3)**	**p-value (all groups)**	**T1**	**T2**	**T3**	**p-value (T1 vs T3)**	**p-value (all groups)**
Age (year)	83.4	84.9	86.4	0.002	0.008	84.4	84.7	85.3	0.21	0.44
Male sex (%)	67.3	45.6	43.4	0.0003	0.0004	55.8	46.0	36.0	0.0009	0.004
BMI (Kg/m^2)	26.4	26.1	24.8	0.02	0.04	26.3	26.5	24.9	0.04	0.05
STS score	11.2	12.2	11.7	0.18	0.053	12.4	11.5	12.0	0.55	0.28
Dyslipidemia (%)	89.4	88.6	85.8	0.42	0.69	89.9	84.9	82.0	0.06	0.17
Hypertension (%)	97.3	94.7	98.2	0.65	0.30	99.3	98.6	96.4	0.10	0.19
History of Smoking (%)	59.3	47.4	44.2	0.02	0.058	52.2	55.4	50.7	0.21	0.18
NYHA III-IV (%)	94.7	93.9	93.8	0.78	0.95	93.5	98.6	94.2	0.79	0.09
CAD (%)	80.4	84.2	76.1	0.44	0.45	85.4	78.4	74.1	0.02	0.07
Prior PCI (%)	43.4	44.7	50.9	0.26	0.48	45.7	50.4	41.3	0.47	0.32
Prior CABG (%)	58.4	47.4	34.5	0.0003	0.002	63.0	41.7	38.8	0.0001	0.0001
Diabetes (%)	40.7	35.1	33.6	0.27	0.51	40.6	33.1	28.1	0.03	0.09
PVD (%)	55.0	65.8	53.6	0.84	0.13	57.7	62.5	60.9	0.59	0.71
Cerebrovascular disease (%)	22.3	32.5	16.8	0.30	0.02	27.7	26.8	23.0	0.37	0.64
Renal disease (creat≥2) (%)	18.6	22.8	16.8	0.73	0.50	16.7	12.2	19.4	0.55	0.26
Liver disease (%)	0.0	1.8	0.9	0.32	0.37	2.2	3.6	1.4	0.64	0.49
Chronic atrial fibrillation (%)	30.4	26.5	20.4	0.08	0.22	22.6	24.6	16.8	0.22	0.26
COPD (%)	47.8	51.8	34.5	0.04	0.02	42.8	47.5	43.2	0.94	0.68
Porcelain aorta (%)	0	0	2.7	0.08	0.05	0.7	2.9	1.4	0.57	0.37

BMI: Body mass index; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; creat: creatinine; cTnI: cardiac troponin I; NYHA: New-York Heart Association; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; STS: Society of Thoracic Surgeons; T: Tertile.

Table 2

Baseline procedural characteristics for A) transfemoral and B) transapical TAVR cases

A										
	Transfemoral									
	cTnI					CKMB				
	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)
Hemodynamic data										
Mean RA pressure (mmHg)	12.1	10.9	11.0	0.11	0.16	12.5	12.6	11.4	0.16	0.22
Mean PA pressure (mmHg)	28.5	29.5	26.8	0.14	0.07	30.2	29.2	27.6	0.01	0.05
Cardiac index (L/min/m^2)	2.10	2.13	2.15	0.54	0.83	2.09	2.16	2.22	0.24	0.50
Mean AVA (cm^2)	0.68	0.62	0.69	0.98	0.41	0.65	0.60	0.62	0.31	0.056
Mean aortic gradient (mmHg)	37.7	38.4	44.3	0.0003	0.0004	37.2	37.4	41.5	0.009	0.01
Echocardiographic data										
LVEF (%)	50.3	51.9	55.7	<0.0001	0.0002	50.6	52.3	55.3	0.0003	0.001
AVA (cm^2)	0.67	0.68	0.65	0.29	0.33	0.67	0.66	0.65	0.42	0.71
Mean aortic gradient (mmHg)	39.5	43.3	47.7	<0.0001	<0.0001	41.4	42.3	47.3	<0.0001	<0.0001
Procedural data										
Procedural time (min)	113.1	124.5	134.7	0.004	0.01	125.4	125.1	141.7	0.02	0.02
Volume of contrast (ml)	135.5	158.2	145.4	0.58	0.45	157.8	142.7	148.9	0.55	0.58
Prosthesis size										
23 mm (%)	51.6	53.3	61.2	0.07	0.15	47.6	51.7	57.6	0.04	0.12
26 mm (%)	48.4	46.7	38.8	0.07	0.15	52.4	48.3	42.4	0.04	0.12
LM obstruction (%)	0	0	0	N/A	N/A	0	0	0	N/A	N/A
Need for hemodynamic support (CPB or IABP) (%)	2.1	2.2	2.7	0.72	0.92	0.5	1.4	1.9	0.18	0.41
Procedure success (%)	76.5	77.2	71.0	0.23	0.32	82.0	76.9	72.2	0.02	0.06

B										
	Transapical									
	cTnI					CKMB				
	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)
Hemodynamic data										
Mean RA pressure (mmHg)	12.0	11.9	11.5	0.58	0.83	13.0	12.0	12.0	0.26	0.32
Mean PA pressure (mmHg)	29.4	29.2	28.7	0.63	0.88	29.8 6	28.15	29.14	0.71	0.38
Cardiac index (L/min/m^2)	2.30	2.23	2.09	0.10	0.24	2.31	2.10	2.14	0.09	0.09
Mean AVA (cm^2)	0.61	0.59	0.63	0.72	0.62	0.62	0.62	0.59	0.34	0.92
Mean aortic gradient (mmHg)	37.3	40.6	40.8	0.21	0.35	35.39	39.47	39.61	0.07	0.13
Echocardiographic data										
LVEF (%)	51.0	53.0	53.0	0.23	0.37	48.6	53.4	55.5	0.0001	0.0001
AVA (cm^2)	0.67	0.64	0.63	0.08	0.21	0.65	0.65	0.63	0.43	0.73
Mean aortic gradient (mmHg)	42.3	43.6	43.8	0.52	0.80	39.9	42.6	42.4	0.003	0.01
Procedural data										
Procedural time (min)	107.6	116.6	119.6	0.16	0.33	122.7	115.6	119.7	0.68	0.61
Volume of contrast (ml)	108.7	117.0	103.9	0.66	0.47	100.4	120.9	114.0	0.12	0.055
Prosthesis size										
23 mm (%)	34.5	49.6	66.1	<0.0001	<0.0001	48.9	46.7	64.2	0.01	0.007
26 mm (%)	65.5	50.4	33.9	<0.0001	<0.0001	51.1	53.3	35.8	0.01	0.007
LM obstruction (%)	0	0	0	N/A	N/A	0	0	0.72	N/A	N/A
Need for hemodynamic support (CPB or IABP) (%)	15.9	17.5	17.7	0.72	0.93	21.0	11.5	16.5	0.34	0.10
Procedure success (%)	85.0	84.2	75.2	0.07	0.11	77.5	82.7	70.5	0.18	0.052

Table 3

Results

	Transfemoral									
	cTnI					CKMB				
	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)
30-days										
All cause mortality (%)	0.5	2.7	5.4	0.006	0.02	0.9	1.4	5.7	0.006	0.004
Cardiovascular mortality (%)	0.5	1.6	4.9	0.01	0.02	0.5	1.4	3.9	0.02	0.03
Myocardial infarction (%)	0	0.5	0.5	0.32	0.60	0.9	0	0.5	0.57	0.37
Days in hospital post procedure	5.30	5.58	5.95	0.01	0.05	5.45	5.42	5.63	0.42	0.61
Stroke or TIA (%)	3.8	3.3	7.6	0.11	0.10	1.4	4.2	7.7	0.002	0.008
Moderate or severe AR (%)	19.2	15.4	19.4	0.97	0.57	9.2	16.5	14.5	0.11	0.09
Major vascular complications (%)	4.8	8.7	14.0	0.002	0.009	7.1	10.4	14.9	0.01	0.04
Major bleeding (%)	6.4	6.6	13.5	0.02	0.02	5.7	7.1	14.9	0.002	0.002
Need for dialysis (%)	2.2	1.6	3.2	0.50	0.57	0.9	0.9	3.4	0.09	0.09
1-year										
All cause mortality (%)	18.9	22.5	23.2	0.22	0.44	16.8	22.0	25.4	0.02	0.07
Cardiovascular mortality (%)	7.8	6.4	13.0	0.09	0.07	5.0	8.7	10.3	0.04	0.11
Improved >1 NYHA class from baseline	61.1	70.5	67.4	0.28	0.24	65.2	60.6	57.4	0.16	0.37
6 minute walk test (m)	224.5	212.5	216.9	0.64	0.75	236.2	212.0	218.1	0.30	0.33
Change of LVEF from baseline (%)	3.10	2.72	1.78	0.31	0.59	4.41	2.58	2.35	0.15	0.25

	Transapical									
	cTnI					CKMB				
	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)
30-days										
All cause mortality (%)	6.2	4.4	7.1	0.79	0.67	6.5	5.8	12.2	0.10	0.09
Cardiovascular mortality (%)	3.5	1.8	3.6	1.0	0.65	3.7	2.9	4.4	0.75	0.79
Myocardial infarction (%)	0.9	0.9	1.8	0.56	0.77	0.7	0.7	1.5	0.56	0.78
Days in hospital post procedure	6.9	7.4	7.1	0.69	0.48	6.8	7.3	7.7	0.056	0.15

	Transapical									
	cTnI					CKMB				
	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)	T1	T2	T3	p-value (T1 vs T3)	p-value (all groups)
Stroke or TIA (at 30 days) (%)	3.6	1.8	3.6	1.0	0.64	2.2	5.1	6.6	0.07	0.21
Moderate or severe AR at 30 days	11.0	11.0	11.0	1.0	1.0	9.6	8.2	7.1	0.50	0.70
Major vascular complications (%)	0	1.8	5.3	0.01	0.03	0.7	2.9	5.8	0.02	0.05
Major bleeding (%)	5.4	4.4	11.7	0.09	0.07	4.4	7.3	8.8	0.14	0.34
Need for dialysis (%)	2.8	3.5	7.3	0.12	0.21	7.4	1.5	3.0	0.10	0.03
1-year										
All cause mortality (%)	21.7	18.5	28.8	0.21	0.15	23.5	23.4	28.5	0.32	0.48
Cardiovascular mortality (%)	10.5	8.4	10.9	0.92	0.79	11.7	7.0	9.5	0.63	0.45
Improved >1 NYHA class from baseline	71.4	73.0	79.5	0.25	0.49	79.8	69.4	72.7	0.26	0.25
6 minute walk test (m)	245.5	208.6	214.6	0.15	0.15	201.1	195.6	187.7	0.49	0.78
Change of LVEF from baseline (%)	2.28	1.32	−0.37	0.09	0.24	2.27	1.74	−0.03	0.18	0.37

Table 4

Multivariable analysis

	Hazard Ratio	95% CI	P value
30-day all cause mortality			
ΔTnI T3 vs T1	10.21	1.31–79.79	0.03
ΔCKMB T3 vs T1	6.20	1.39–27.71	0.02
30-day cardiovascular mortality			
ΔcTnI T3 vs T1	9.20	1.17–72.61	0.04
ΔCKMB T3 vs T1	8.24	1.03–65.83	0.04
1-year all cause mortality			
ΔCKMB T3 vs T1	1.62	1.06–2.49	0.02
Renal disease (dialysis required)	1.59	1.06–2.39	0.02
1-year cardiovascular mortality			
ΔCKMB T3 vs T1	2.21	1.03–4.72	0.04
LVEF	0.97	0.95–0.99	0.001
Major vascular complication	3.07	1.55–6.08	0.001

Variables included in the multivariable analysis: ΔcTnI; ΔCKMB; Age; STS score; Left ventricular ejection fraction at baseline; Major vascular complication; Renal failure (dialysis required).