JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 15, 2017

ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2017.06.043

EDITORIAL COMMENT

Biomarkers in Transcatheter Aortic Valve Replacement

Prevalent, But Are They Prognostic?*

John K. Forrest, MD, Paul L. Hermany, MD

The elevation of cardiac biomarkers in association with elective transcatheter cardiac procedures has been a topic of significant investigation both in clinical practice and as endpoints in clinical trials. With the development of transcatheter aortic valve replacement (TAVR) and its expanded use in patients undergoing aortic valve replacement, the relationship between periprocedural myocardial injury and TAVR is one in which we continue to gain further insight.

SEE PAGE 1550

In this issue of *JACC: Cardiovascular Interventions*, Stundl et al. (1) present a single-center observational study of 756 consecutive patients undergoing TAVR from 2010 to 2016. The study aimed to better determine whether myocardial injury (by the VARC-2 [Valve Academic Research Consortium-2] definition of biomarker elevation) had clinical significance in routine TAVR. Patients were treated using a variety of TAVR systems, and although a small percentage of cases were performed via the subclavian or direct aortic approach, the vast majority (97%) underwent transfemoral TAVR (TF-TAVR) with conscious sedation. Patients who underwent transapical access were excluded from analysis as were patients who required conversion to open-heart surgery due to procedural complications.

Stundl et al. (1) found that myocardial injury occurred in 51.6% of patients when defined by high-sensitivity troponin I (hsTrop I) elevation and in 7.4% when defined by creatine kinase-myocardial band (CK-MB) elevation. With regard to the primary endpoint, the study found no significant correlation between myocardial injury and all-cause mortality at 1 year. In the patients with elevated hsTrop I, the 1-year mortality was 16.7% (vs. 17.2% in those without), and in patients with elevated CK-MB levels, the 1-year mortality was 16.4% (vs. 17.3% without). Patients with elevated biomarkers were older, more often female, had lower logistic EuroSCOREs, and higher mean transvalvular gradients. Although mortality was not different, the incidence of stroke, major bleeding, and acute kidney injury was higher in patients with elevated cardiac biomarkers.

The authors also examined the relationship between valve type and periprocedural myocardial injury. They found that patients undergoing TAVR with the Lotus system (Boston Scientific, Natick, Massachusetts) had myocardial injury more frequently (81.6%) than patients undergoing TAVR with other systems (Direct Flow 56.4% [Direct Flow Medical, Santa Rosa, California]; CoreValve 51.2% [Medtronic, Minneapolis, Minnesota]; Evolut R 42.7% [Medtronic]; Sapien XT 40.4% [Edwards Lifesciences, Irvine, California]; Sapien 3 36.6% [Edwards Lifesciences]). Additionally, the degree of increase in biomarkers was highest with the Lotus valve. On the basis of their findings, the authors conclude that myocardial injury is not associated with any adverse short- and intermediate-term outcomes after uncomplicated TAVR, but that the frequency and extent of cardiac biomarker elevation correlates with the type of valve prosthesis implanted.

The authors should be commended for adding to the growing literature on cardiac biomarker elevation in the setting of TAVR. By excluding patients undergoing TAVR via the transapical approach and those

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Department of Medicine (Cardiology), New Haven, Connecticut. Dr. Forrest serves as a physician proctor and consultant for Edwards Lifesciences and Medtronic Inc. Dr. Hermany has reported that he has no relationships relevant to the contents of this paper to disclose.

who required conversion to open-heart surgery, they reduced the heterogeneity of the patient population, a frequent confounder in retrospective, observational studies. The results suggest that biomarker elevation alone does not significantly affect mortality in patients undergoing uncomplicated TF-TAVR. It is important to recognize that by including all biomarker elevations, regardless of the presence of ischemic symptoms or signs, the patient population in this study presumably includes a cohort of patients who met VARC-2 criteria for myocardial infarction in addition to the larger cohort who meet criteria only for elevated biomarkers. VARC-2 criteria for myocardial infarction requires both biomarker elevation and new ischemic symptoms or signs (2). Myocardial infarction is a different entity than myocardial injury, and we cannot conclude a lack of association between myocardial infarction during TAVR and adverse outcomes on the basis of this study. A separate analysis of the subgroup of patients within this study that met VARC-2 criteria for myocardial infarction would be of interest.

The lack of prognostic significance related to periprocedural biomarker elevation in this routine TF-TAVR group contrasts with previous publications reporting a significant increase in cardiac and all-cause mortality in patients with elevated biomarker levels following elective percutaneous cardiac procedures. For example, in elective percutaneous coronary intervention (PCI), a direct correlation between the degree of CK-MB elevation in the periprocedural period and the risk of death has been demonstrated with a nearly 8-fold higher mortality rate in this group (3). Even modest cardiac biomarker elevations have corresponded with an increased risk of death in the 3 years following PCI (4). It should be noted, however, that the recent adoption of high-sensitivity troponin assays has complicated the interpretation of isolated elevated cardiac biomarkers. Using such markers, recent studies of patients with normal baseline high-sensitivity troponin T (hsTnT) levels undergoing PCI have shown that up to 80% have elevated circulating levels in the post-procedural period without evidence of increased mortality (5–7).

As with PCI, several previous studies looking at the clinical relevance of elevated cardiac biomarkers in the setting of TAVR have suggested that post-procedural biomarker elevation corresponds with poorer clinical outcomes. In a cohort of 150 patients undergoing TAVR, Barbash et al. (8) found elevated troponin I levels in 90% of patients and elevated CK-MB elevations in 50%. Elevated CK-MB levels were associated with increased 30-day and 1-year mortality; however, the study was confounded by a large number of transapical TAVRs. In a post hoc analysis of the PARTNER (Placement of Aortic Transcatheter Valves) trial, Paradis et al. (9) found that cardiac biomarker elevation in patients undergoing TF-TAVR predicted 30-day all-cause and cardiovascular mortality, and that post-procedural CK-MB elevation predicted 1-year mortality. Another study evaluating only TF-TAVR in 201 patients using early-generation valve systems found that both elevated baseline and post-procedural hsTnT were predictive of 1-year mortality (10).

In comparing the findings of Stundl et al. (1) to the aforementioned studies, it is notable that previous studies were performed before many significant advances in the field of TAVR including next-generation devices, the routine use of conscious sedation, percutaneous access with smaller delivery systems, and the inclusion of patients with lower risk profiles. Taken together, these findings create some uncertainty as to how we should construe such elevations in the context of predicting adverse outcomes and the clinical relevance of asymptomatic cardiac enzyme elevations.

Although Stundl et al. (1) found no correlation between periprocedural myocardial injury and mortality, they do report a correlation between the valve used and biomarker elevation. This is particularly notable with the mechanically expanding Lotus valve. They hypothesize that this finding is due to the transient distension in the left ventricular outflow tract and anchoring of the valve during deployment leading to tissue injury. Certainly, the correlation between increased time of deployment and higher biomarker levels adds credence to this supposition, as does the increased rates of pacemaker implantation for heart block in the Lotus valve subgroup suggesting direct tissue injury during deployment.

Given the retrospective and nonrandomized nature of the study, the results are at best hypothesis generating. One limitation involves the definition of myocardial injury. The frequency of “significant myocardial injury” is clearly dependent on the definition used as well as the type of cardiac biomarker measured. Although 51.6% met the definition of myocardial injury by hsTrop I, only 7.4% met this threshold when CK-MB levels were considered. This disparity reflects the extreme sensitivity of hsTrop I for significant myocardial injury, potentially at the expense of specificity. It remains unclear whether it is worthwhile to explore different thresholds for troponin elevation in attempts to predict which patients are at risk for increased mortality as a result of periprocedural myocardial injury.

Ultimately, given our current understanding of the data, in the absence of symptoms or evidence of

new cardiac dysfunction, it is reasonable to question the utility of the routine measurement of cardiac biomarkers and their clinical relevance immediately following uncomplicated transfemoral TAVR.

ADDRESS FOR CORRESPONDENCE: Dr. John K. Forrest, Department of Medicine (Cardiology), Yale University School of Medicine, New Haven, Connecticut 06510. E-mail: john.k.forrest@yale.edu.

REFERENCES

1. Stundl A, Schulte R, Lucht H, et al. Periprocedural myocardial injury depends on transcatheter heart valve type but does not predict mortality in patients after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2017;10:1550–60.

2. 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. Eur Heart J 2012;33:2403–18.

3. Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. Circulation 2002;106:1205–10.

4. Abdelmeguid AE, Topol EJ, Whitlow PL, Sapp SK, Ellis SG. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. Circulation 1996;94:1528–36.

5. Ndrepepa G, Colleran R, Braun S, et al. High-sensitivity troponin T and mortality after elective percutaneous coronary intervention. J Am Coll Cardiol 2016;68:2259–68.

6. Ndrepepa G, Braun S, Cassese S, et al. Prognostic value of high-sensitivity troponin T after percutaneous coronary intervention in patients with stable coronary artery disease. Rev Esp Cardiol (Engl Ed) 2016;69:746–53.

7. Ricciardi MJ, Davidson CJ, Gubernikoff G, et al. Troponin I elevation and cardiac events after percutaneous coronary intervention. Am Heart J 2003;145:522–8.

8. 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.

9. Paradis JM, 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.

10. Chorianopoulos E, Krumsdorf U, Geis N, et al. Preserved prognostic value of preinterventional troponin T levels despite successful TAVI in patients with severe aortic stenosis. Clin Res Cardiol 2014;103:65–72.

KEY WORDS aortic stenosis, periprocedural myocardial injury, transcatheter aortic valve replacement