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EDITORIAL

High-Sensitivity C-Reactive Protein in Transcatheter Aortic Valve Implantation Prognostic Biomarker and New Potential Therapeutic Avenue

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The introduction of transcatheter aortic valve implantation (TAVI) offered a new therapy to patients with severe aortic stenosis who are not candidates for surgical valve replacement (SAVR)[1,2] or who are at high risk for complications due to surgery.[3] TAVI has proven to be similar to SAVR with respect to disabling stroke or death in patients at intermediate clinical risk.[4] A recent report from the PARTNER 3 trial indicates that, in patients at low surgical risk, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than with SAVR.[5] As TAVI procedure became more routinized and device technology was refined, near-term survival after TAVI improved substantially during the last years. According to a systematic assessment of evidence among 145 studies performed between 2007 and 2016, it appeared that risk-adjusted 30-day and 1-year mortality rates decreased from 10.48% to 2.27% and from 30.24% to 11.35% over time, respectively.[6] In a study analyzing the mortality rate in 6,420 patients undergoing TAVI (UK registry) compared to a matched general population, it was found that relative survival after TAVI was high, corresponding to 95.4%, 90.2%, and 83.8% at 30 days, 1 year, and 3 years, respectively.[7] Increasing age was associated with significantly lower excess hazards after TAVI, with survival rates in patients ages > 85 years approximated those of a matched general population within 3 years. In view of current evolution, it is thus very likely that TAVI will progressively supplant SAVR for AS patients who are eligible for both procedures. Even though a decline of post-TAVI mortality has been acknowledged, the risk remains relatively high for certain yet unidentified patient populations. Data from the international CENTER collaboration study (10,982 patients undergoing transfemoral TAVI) indicate a 30-day risk of stroke of 2.4% after TAVI, which was responsible for a 6-fold increase of 30-day mortality.[8] Independent predictors of stroke were previous cerebrovascular events and renal insufficiency. Strikingly, this study showed that stroke rate did not decline from the early years of TAVI procedures to more recent years. In addition, several studies indicate that the risk of stroke is higher at extended follow-up, with reported rates reaching up to 10.6% at 1-year post-TAVI (reviewed in.[9]) Thus, stroke remains the most devastating complication of TAVI. Since the prognosis of patients who benefit the most from TAVI is likely not only determined by AS severity, but also by multiple comorbidities, and possibly by the extent of extravalvular cardiac damage,[10] biomarkers that would implement clinical scores to identify patients at risk of major cardiovascular events, including stroke, or death could be very useful. Importantly, although valve replacement clearly improves patient outcome,[11,12] baseline comorbidities if left sub-optimally treated or myocardial damage might indeed, in specific cases, be the main cause of poor outcome. Several small size studies indicate that circulating biomarkers of myocardial injury, cardiac mechanical stretch, inflammation or hemostasis may predict TAVI-associated complications and mortality.[13] However, none of these biomarkers have already been implemented in clinical practice, as their role needs to be validated in larger studies. Therefore, the identification of easily accessible pre-procedural circulating biomarkers that would reflect patient risk in a more personalized manner should become a priority.

In this issue, Ungjeong et al.[14] assessed the predictive value of pre-procedural high-sensitivity CRP levels (hsCRP) with respect to 1-year disabling stroke or all-cause mortality in patients who underwent TAVI at the Asian Medical Center (Seoul, Korea) between 2010 and 2017. A total of 243 patients were included. Disabling stroke was defined as a score of at least 2 on the modified Rankin scale at 90 days after the index clinical event. All outcomes were defined according to the Valve Academic Research Consortium-2 criteria.[15] About 26% of the patient population had elevated CRP levels (≥3 mg/L) at baseline. These patients had a higher Society of Thoracic Surgery (STS) score and EuroSCORE, they had more frequent end stage renal disease, and they had lower ejection fraction than those with nonelevated CRP. Strikingly, patients with elevated CRP levels did not have more severe AS. About 16.7% of the patients in the elevated CRP group died or presented disabling stroke compared to 5.5% patients in the nonelevated CRP group. hsCRP ≥3 mg/L was associated with a 3-fold higher risk of composite outcome. Adding the information of CRP elevation to STS score or EuroSCORE significantly improved risk prediction, especially when considering disabling stroke. Neither brain natriuretic peptide nor troponin I levels were significantly associated with TAVI composite outcome, and adding them to CRP in the multivariable model did not improve risk prediction. The authors concluded that pre-procedural hsCRP measurements might be implemented

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in risk prediction scores for TAVI. If validated in larger multicenter studies, measuring pre-procedural hsCRP levels with standardized immunoassays might have important prognostic value to evaluate the risk of disabling stroke, a major complication of TAVI. In agreement with the study by Ungjeong et al., previous work already suggested that inflammation could be important in predicting outcome of TAVI patients. For instance, the study by Kim et al. described a worse 1-year survival for TAVI patients with baseline hsCRP levels >2 mg/L.[16] In this sudy, pre-procedural inflammation, evaluated by levels of growth differentiation 15 (GDF-15), also seemed to be implicated in a lack of post-TAVI ventricular recovery, as assessed by global longitudinal strain (GLS) at 1-year follow-up. Furthermore, GLS at 1 month predicted 1-year mortality. Beside different CRP threshold between the two studies, it could have been informative to know the effect of pre-procedural CRP levels on ventricular function during follow-up of patients from the study of Ungjeong et al. Patients with elevated CRP levels had indeed lower ejection fraction, depicting potential link of hsCRP levels with cardiac damage. This analysis could also have clarified the role of inflammatory processes in potentially adverse post-procedural ventricular remodelling. Notwithstanding, the findings of Ungjeong et al. might pave the way toward new inflammation targeted therapies that could improve risk stratification and long-term survival in TAVI. Indeed, upon acute tissue injury or inflammation, CRP is produced by the liver in response to elevation of pro-inflammatory cytokines such as IL-6, IL-1β, and TGF-β, which therefore represent the main CRP triggers. In acute coronary syndrome (ACS) patients, several studies have been conducted with the aim to determine if targeting these cytokines with available drugs could reduce the inflammatory response at the time of ACS, and subsequent events. The rationale of these studies comes from proven association between hsCRP levels and the occurrence of major cardiovascular events or death in patients who experienced a previous ACS. In a secondary analysis of the Vascular Inflammation Suppression to Treat Acute Coronary Syndromes for 16 Weeks (VISTA-16),[17] the initial and subsequent increases in hsCRP levels during 16 weeks after ACS were associated with a greater risk of the combined major cardiovascular event end point (composite of cardiovascular death, myocardial infarction, nonfatal stroke, or unstable angina with documented ischemia requiring hospitalization), cardiovascular death, and all-cause death despite optimized medical therapies. The randomized double-blind Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial tested the effect of canakinumab, a therapeutic monoclonal antibody targeting the inflammatory cytokine interleukin-1β in patients with previous myocardial infarction and CRP ≥2 mg/L, the primary endpoint efficacy being nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.[18] It was found that patients for whom CRP level decreased from baseline with such treatment had a more favorable prognosis than those with CRP levels that remained elevated. Treatment with Canakinumab led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. Whether these treatments can prevent adverse left ventricular remodeling post-MI is currently unknown.

It should be noted that, in Ungjeong et al.'s study, patients with elevated hsCRP had more severe atherosclerosis or calcification in thoracic aorta. However, this variable did not independently predict composite outcome at 1 year, which is in contrast with post-procedure new-onset atrial fibrillation. This observation might corroborate the data from the CENTER collaboration study showing that patients with stroke had more frequently documented new-onset atrial fibrillation.[7]

Similarly, as in the VISTA-16 study on ACS patients,[17] it would be interesting to determine if, in addition to initial hsCRP level, serial monitoring of hsCRP levels post-TAVI could further help identify patients at greater risk of post-procedural cardiovascular events or death, both on the short and long term. In TAVI patients, it remains to be determined whether hsCRP level represents a surrogate marker of inflammation or whether it should be considered as a direct biological target. In the latter case, interventions targeted to lower pre-procedural CRP levels might then be beneficial to reduce morbidity or mortality rate post-TAVI independently of established background therapies. It also remains to be determined if IL-1β levels or levels of other cytokines that may drive increases in CRP, for example, IL-6, TGF-β, TNF-β, INF-γare elevated in patients with severe aortic stenosis undergoing TAVI and whether these cytokines may predict outcome or may be associated with AS severity or stages of extravalvular cardiac damage.

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The authors declare no competing financial interests.

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. doi:10.1056/NEJMoa1008232.
2. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972–1981. doi:10.1016/j.jacc.2014.02.556.
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. doi:10.1056/NEJMoa1103510.
4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. doi:10.1056/NEJMoa1514616.
5. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019. doi:10.1056/NEJMoa1814052.

6. Mattke S, Schneider S, Orr P, Lakdawalla D, Goldman D. Temporal trends in 30-day and 1-year mortality rates after transcatheter aortic valve replacement: a systematic review and meta-regression analysis. *J Am Coll Cardiol*. 2019;73:A1091. doi:10.1016/j.jacc.2018.12.002.
7. Martin GP, Sperrin M, Hulme W, et al. Relative survival after transcatheter aortic valve implantation: how do patients undergoing transcatheter aortic valve implantation fare relative to the general population? *J Am Heart Assoc*. 2017;6. doi:10.1161/JAHA.117.007229.
8. Vlastra W, Jimenez-Quevedo P, Tchetche D, et al. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke. *Circ Cardiovasc Interv*. 2019;12:e007546. doi:10.1161/CIRCINTERVENTIONS.118.007546.
9. Davlouros PA, Mplani VC, Koniari I, Tsigkas G, Hahalis G. Transcatheter aortic valve replacement and stroke: a comprehensive review. *J Geriatr Cardiol*. 2018;15:95–104. doi:10.11909/j.issn.1671-5411.2018.01.008.
10. Genereux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38:3351–3358. doi:10.1093/eurheartj/ehx381.
11. Baumgartner H, Falk V, Bax JJ, et al. ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. doi:10.1093/eurheartj/ehx391.
12. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2017;135:e1159–e1195. doi:10.1161/CIR.0000000000000503.
13. Oury C, Nchimi A, Lancellotti P, Bergler-Klein J. Can blood biomarkers help predicting outcome in transcatheter aortic valve implantation? *Front Cardiovasc Med*. 2018;5:31. doi:10.3389/fcvm.2018.00031.
14. Ungjeong D, Jun-Min A, Do-Yoon K, et al. Association and prognostic implication of C-reactive protein with risk of 1-year death or disabling stroke after transcatheter aortic valve replacement. association and prognostic implication of C-reactive protein with risk of 1-year death or disabling stroke after transcatheter aortic valve replacement. *Struct Heart*. 2019:this issue.
15. 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 Thorac Cardiovasc Surg*. 2013;145:6–23. doi:10.1016/j.jtcvs.2012.09.002.
16. Kim JB, Kobayashi Y, Moneghetti KJ, et al. GDF-15 (Growth Differentiation Factor 15) is associated with lack of ventricular recovery and mortality after transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2017;10(12). doi:10.1161/CIRCINTERVENTIONS.117.005594.
17. Mani P, Puri R, Schwartz GG, et al. Association of initial and serial c-reactive protein levels with adverse cardiovascular events and death after acute coronary syndrome: a secondary analysis of the VISTA-16 trial. *JAMA Cardiol*. 2019. doi:10.1001/jamacardio.2019.0179.
18. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi:10.1056/NEJMoa1707914.