Mini Review

Interventional Cardiology

Identification of prognostic biomarkers in patients undergoing transfemoral transcatheter aortic valve implantation

Abstract

As surgical risk scores overestimate mortality, risk prediction in patients with severe Aortic Stenosis (AS) undergoing Transcatheter Aortic Valve Implantation (TAVI) remains an unresolved issue. We, therefore, investigated whether the novel biomarkers Mid-Regional pro-Adrenomedullin (MR-proADM) and Growth Differentiation Factor 15 (GDF-15) could add value to risk assessment. Serum levels of 92 patients were collected and stratified by survival. Not only presented patients who died during the follow-up period higher biomarker levels ((MR-proADM (Survivors: 0.922 nmol/l (0.706-1.202) vs. Decedents: 1,347 nmol/l (1,038-1,678), p=0.0003)); (GDF-15 (Survivors: 1675.2 pg/ml (1141.6; 2524.4) vs. Decedents: 2770.0 pg/ml (2401.0-3701.0), p=0.0006))) before TAVI, but by using Kaplan-Meyer analysis in conjunction with Youden index we were able to identify a specific cut-off value determining survival that reached a good level of discrimination ((MR-proADM: AUC=0.73, 95% CI (0.61; 0.85), p=0.002); (GDF-15: AUC=0.73, 95% CI (0.61; 0.85), p=0.002))). The inclusion of the presented biomarkers into binary logistic regression further improved the prognostic value of classical risk predictors (AUC=0.811 (Standard error 0.05; 95% CI (0.693; 0.899)). In addition, serum levels of pro-ADM decreased significantly in surviving patients after TAVI. Therefore, novel biomarkers have the potential to improve risk stratification in patients undergoing TAVI through the provision of individualized and objective information.

Keywords: Biomarkers • Mid-regional pro-adrenomedullin • Growth differentiation • Prognostic value • Survival

Luisa Nowicki, Oliver Dorr*

Department of Cardiology, Justus-Liebig University Giessen, Giessen, Germany

*Author for correspondence:
Oliver Dorr, Department of Cardiology, Justus-Liebig-University Giessen, Giessen, Germany, E-mail: o.doerr@ccb.de

Received date: 01-Dec-2024, Manuscript No. FMIC-24-154672;
Editor assigned: 03-Dec-2024, PreQC No. FMIC-24-154672 (PQ);
Reviewed date: 17-Dec-2024, QC No. FMIC-24-154672;
Revised date: 23-Dec-2024, Manuscript No. FMIC-24-154672 (R);
Published date: 30-Dec-2024, DOI: 10.37532/1755-5310.2024.16(6).936

Introduction

AS is the most common heart valve disease in older patients. Once the diagnostic criteria for severe aortic stenosis are met and the patient experiences common symptoms such as dyspnoea, syncope, or angina pectoris, the relative risk of heart failure and all-cause mortality increases significantly [1]. Since its introduction as an alternative to open surgical valve replacement, guideline recommendations for TAVI have been extended to include intermediate or lower risk patient categories [2-4].

Although TAVI is a less invasive treatment option, it is important to consider the potential complications, including vascular complications, stroke, renal failure, or higher-grade conduction disturbances and ultimately death [5,6]. Despite the rapid evolution of this therapeutic approach, risk stratification is still based on scores that have only been validated in surgical patients. For example, the EuroScore II is used in European and American guidelines for the management of valvular heart disease in the absence of superior alternatives [7-8]. However, surgical risk scores and others,

even those developed specifically for TAVI, have not been able to provide an accurate estimate of mortality [9-11]. Therefore, treatment recommendations for those under 85 years of age remain largely individualised and are based on a subjective judgement.

Given the underlying pathological changes in severe AS, we postulated that the inclusion of disease-specific biomarkers would facilitate an improved, individualised outcome. Therefore, the aim of our review was to investigate the potential benefit of the additional use of novel circulating biomarkers to improve the accuracy of risk stratification [12].

Literature Review

MR-proADM and growth differentiation factor 15 have been studied primarily in the context of heart failure. In cases of volume overload and increased wall stress, adrenomedullin secretion is observed to increase as a compensatory mechanism to prevent tissue congestion [13-15]. Tan et al., showed that MR-proADM, among other biomarkers, had the highest predictive value for all-cause mortality, hospitalisation or symptom progression in patients with moderate to severe AS [16].

GDF-15 is upregulated in response to increased oxidative stress, ischaemia, or mechanical stress [17]. It has been studied in chronic coronary artery syndrome and also in heart failure. To our knowledge, only two other studies have investigated its potential value in patients with AS. Basmadjian et al., demonstrated an association between GDF-15 and ventricular dysfunction and frailty, while a small study by Fabiani et al., showed elevated biomarker levels in association with prognostically unfavourable echocardiographic parameters [18,19]. To date, these pathophysiological pathways have not been investigated in detail in patients with severe AS undergoing TAVI. Therefore, we investigated the potential prognostic role of MR-proADM and GDF-15 in relation to other biomarkers.

Discussion

92 Patients with severe, symptomatic AS (Median aortic valve area: 0.77 cm2 (0.6-0.9)) who were deemed suitable for TAVI by the local heart team were enrolled in this prospective, observational study at the Giessen Heart Centre between July 2017 and September 2019. The median age was 80.7 years (77.2-83.3) and 48 (52.2%) were male. With 55% (46-60) the left ventricular ejection fraction was preserved. As expected, the majority of patients had an elevated cardiovascular risk profile, including a prevalence of diabetes in 28 (30.4%), hypertension in 75 (80.4%), and chronic coronary artery disease in 68 (73.9%). According to the Kidney Disease: Improving Global Outcomes (KDIGO) classification estimated Glomerular Filtration Rate (eGFR) was mildly reduced at 67.5 ml/min/m² (50.4;85.5). 75% (69) of the patients were highly symptomatic with NYHA class III-IV (65.1%), although they were considered to be at intermediate surgical risk (EuroSCORE II: 6.4% (4.4; 10.7)). All patients underwent successful TAVI. According to the Valcular Academic Research Consortium (VARC-2) criteria, acute kidney injury occurred in 16 (17.2%) patients, while vascular or bleeding complications occurred in 10 (10.8%) and 28 (30.4%) patients, respectively. Post-interventional pacemaker implantation was required in 14 cases and only one major stroke was observed. After stratification for survival, only bleeding events were slightly more frequent in deceased patients (Alive: 17/68 (25%) Deceased: 11/24 (45.8%), p=0.006).

A total of 24 patients (26.1%) died during the median follow-up of 620 days. They had significantly higher baseline levels of creatinine (Survivors: 0.95 mg/dL (0.8; 1.2) vs. Decedents: 1.1 mg/dL (0.9; 1.5), p=0.027) and B-type Natriuretic Peptide (BNP) (Survivors: 218.5 pg/mL (127.3;875.8) vs. Descendants: 646 pg/mL (154; 1349)). Patients were stratified by survival during follow-up and baseline biomarker levels were compared between survivors and decedents. Biomarker levels of MR-proADM (Survivors: 0.922 nmol/l (0.706-1.202) vs. Decedents: 1,347 nmol/l (1,038-1,678), p=0.0003) and GDF-15 (Survivors: 1675.2 pg/ml (1141.6-2524.4) vs. Decedents: 2770.0 pg/ml (2401.0-3701.0), p=0.0006) were significantly elevated in decedents compared to survivors. Six months after TAVI, MR-proADM levels (Baseline: 0.922 nmol/l (0.706-1.202) vs. 6m-FU: 0.828 nmol/l (0.642-1.132), p=0.0087) decreased significantly while GDF-15 levels remained relatively unchanged (Baseline: 1675.2 pg/ml (1141.6-2524.4) vs. 6m-FU: 1663.8 pg/ml (1176.5-2538.1), p=0.563).

In a Receiver Operating Characteristics (ROC) analysis, both biomarkers met the required discrimination level (MR-proADM: AUC=0.73, 95% CI (0.61; 0.85), p=0.002; GDF-15: AUC=0.73, 95% CI (0.61; 0.85), p=0.002) (Figure 1). In addition, Kaplan-Meier analysis combined with the Youden J statistic was used to determine the optimal cut-off point for each biomarker to determine survival. In contrast, established risk predictors including eGFR (AUC=0.637), BNP (AUC=0.643), and EuroScore II (AUC=0.523) all showed poor discrimination for predicting death after TAVI.

Binary logistic regression was then performed with BNP, eGFR, EuroSCORE II, GDF-15 and MR-proADM. The combined predictive value of classical risk stratification markers (Panel 1: BNP+eGFR+Euroscore II) and classical risk markers in combination with the new biomarkers investigated here (Panel 2: BNP+eGFR+Euroscore II+GDF-15 +MR-proADM) was calculated (Figure 2). The combination of all three parameters in panel 1 resulted in an increase in discrimination of 0.762 (SE: 0.06, 95% CI (0.638;0.860)) to an acceptable level of correlation. The addition of pro-ADM and GDF-15 further improved the value to an excellent level of 0.811 (SE: 0.05; 95% CI

(0.693;0.899)). However, it should be noted that no statistically significant difference was observed between panels 1 and 2 in a ROC comparison analysis (p=0.417).

Although TAVI is generally a safe treatment option, the participants represented a real-life patient profile in which adverse events and all-cause mortality occurred as expected during the follow-up period. The importance of a differentiated selection of patients is therefore very high. As aortic valve stenosis develops, the heart has to maintain cardiac output while working against a steadily increasing pressure due to the reduced opening area of the valve. It therefore compensates by myocardial hypertrophy. In the later stages, myocardial dilatation and fibrosis are also expected, eventually leading to heart failure. These pathophysiological changes occur due to pressure overload, which is the same mechanism that induces MR-proADM and GDF-15 secretion. It is therefore likely to interpret the serum elevation as a direct consequence of AS and therefore postulate these biomarkers as disease specific.

The present study of 92 patients with severe AS has shown that not only are serum levels of MR-proADM and GDF-15 prior to TAVI elevated but these levels correlate with patient outcomes in terms of all-cause mortality. In light of the findings presented our results are consistent with the existing body of evidence described at the outset.

Therefore, it may be of additional value to consider both biomarkers in conjunction with established risk predictors such as BNP, eGFR and EuroSCORE II to optimize risk prediction in the future. Given the current limitations of risk scores, all patients with aortic stenosis under the age of 85 are the subject of interdisciplinary discussion. While frailty is a key consideration when assessing a patient, it is inherently subjective. Biomarkers on the other hand provide a reliable and objective measure.

Furthermore, the inclusion of pre-interventional laboratory assessment of MR-proADM and GDF-15 as an adjunct to routine parameters such as BNP would be easy to implement with little effort in daily clinical practice. They may also prove useful in predicting the optimal timing for TAVI in patients with severe but asymptomatic aortic stenosis, reflecting the degree of myocardial damage that has already occurred. As both biomarkers are upregulated in response to pressure overload, these findings could be further improved by incorporating advanced cardiac imaging to determine myocardial stress and workload.

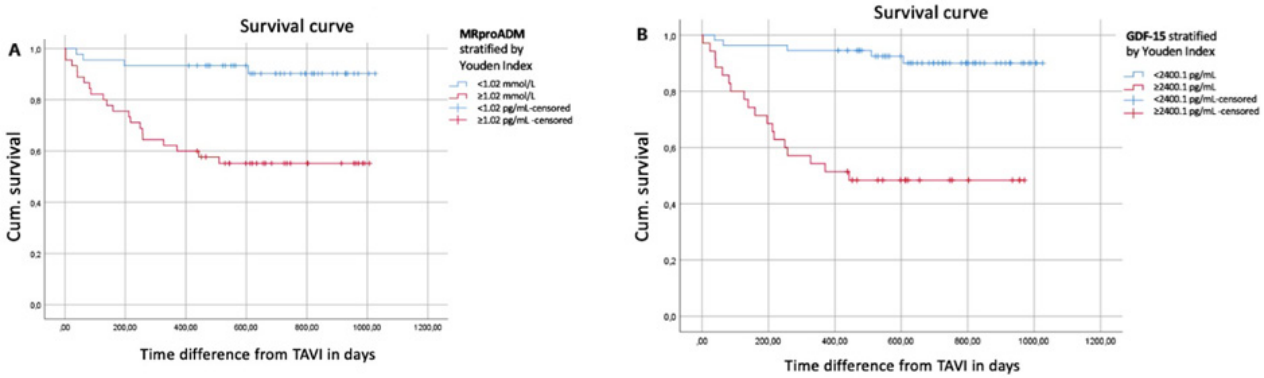

Figure 1: Kaplan-Meyer survival analysis. **Note:** A: Pro-ADM; B: GDF-15 separated according to the Youden index.

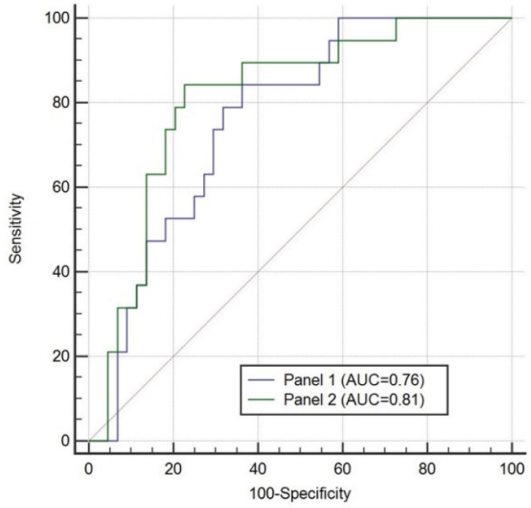

Figure 2: Comparison of the ROC-curves between Panel 1 (eGFR, BNP and EuroScore II) and Panel 2 (eGFR, BNP, EuroScore II, MR-proADM and GDF-15).

It is also worth mentioning that the biomarker levels of MR-proADM decreased six months after successful intervention, suggesting a possible recovery of the myocardium after stress relief by TAVI. However, this statement is speculative and may prove to be a good starting point for further research. In this context, it would also be interesting to determine myocardial fibrosis. As an irreversible change, myocardial fibrosis could explain the steady elevation in GDF-15 levels that persists six months after TAVI.

Conclusion

It is also important to note that the present results are based on a relatively small cohort from a single-centre experience. Therefore, further validation in a larger external cohort with a preferably longer follow-up is needed.

The addition of novel biomarkers such as MR-proADM and GDF-15 may prove useful for risk stratification in patients with severe AS undergoing TAVI and provide a solid foundation on which to further investigate their informative value on myocardial remodelling due to pressure overload.

References

1. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: A population-based study. The lancet. 368(9540):1005-1011 (2006).
2. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 380(18):1706-17015 (2019).
3. Reardon MJ, van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 376(14):1321-1331 (2017).
4. Makkar RR, Thourani VH, Mack MJ, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med. 382(9):799-809 (2020).
5. Winter MP, Bartko P, Hofer F, et al. Evolution of outcome and complications in TAVR: A meta-analysis of observational and randomized studies. Sci Rep. 10(1):15568 (2020).
6. Wolff G, Shamekhi J, Al-Kassou B, et al. Risk modeling in transcatheter aortic valve replacement remains unsolved: An external validation study in 2946 German patients. Clinical Research in Cardiology. 110:368-376 (2021).
7. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 43(7):561-632 (2022).
8. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 77(4):450-500 (2021).
9. Edwards FH, Cohen DJ, O'Brien SM, et al. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. JAMA cardiology. 1(1):46-52 (2016).
10. Debonnaire P, Fusini L, Wolterbeek R, et al. Value of the "TAVI2-SCORe" versus surgical risk scores for prediction of one year mortality in 511 patients who underwent transcatheter aortic valve implantation. Am J Cardiol. 115(2):234-242 (2015).
11. Kötting J, Schiller W, Beckmann A, et al. German aortic valve score: A new scoring system for prediction of mortality related to aortic valve procedures in adults. Eur J Cardiothorac Surg. 43(5):971-977 (2013).
12. Piayda K, Keranov S, Schulz L, et al. Prognostic utility of mid-regional pro-adrenomedullin and growth differentiation factor 15 in patients undergoing transfemoral transcatheter aortic valve implantation. Clin Res Cardiol. 25:1-8 (2024).
13. Myhre PL, Liu Y, Kulac IJ, et al. Changes in mid-regional pro-adrenomedullin during treatment with sacubitril/valsartan. Eur J Heart Fail. 25(8):1396-1405 (2023).
14. Spoto S, Argemi J, Di Costanzo R, et al. Mid-regional pro-adrenomedullin and N-terminal pro-b-type natriuretic peptide measurement: A multimarker approach to diagnosis and prognosis in acute heart failure. J Pers Med. 13(7):1155 (2023).
15. Shuji H, Takuroh I, Takeshi M, et al. Differential responses of circulating and tissue adrenomedullin and gene expression to volume overload. J Card Fail. 6(2):120-129 (2000).
16. Tan ES, Oon YY, Chan SP, et al. Novel predictive role for mid-regional proadrenomedullin in moderate to severe aortic stenosis. Heart. 108(16):1319-1327 (2022).
17. Kempf T, Zarbock A, Widera C, et al. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. Nat Med. 17(5):581-588 (2011).
18. Basmadjian L, Bouabdallaoui N, Simard F, et al. Growth differentiation factor-15 as a predictor of functional capacity, frailty, and ventricular dysfunction in patients with aortic stenosis and preserved left ventricular ejection fraction. Am J Cardiol. 186:11-16 (2023).
19. Fabiani I, Santoni T, Angelillis M, et al. Growth differentiation factor 15 in severe aortic valve stenosis: Relationship with left ventricular remodeling and frailty. J Clin Med. 9(9):2998 (2020).