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Prognostic Utility of Novel Biomarkers of Cardiovascular Stress in Patients with Aortic Stenosis Undergoing Valve Replacement

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Abstract

Objective—In heart failure populations without aortic stenosis (AS), the prognostic utility of multiple biomarkers in addition to clinical factors has been demonstrated. We aimed to determine whether multiple biomarkers of cardiovascular stress are associated with mortality in patients with AS undergoing aortic valve replacement (AVR) independent of clinical factors.

Methods—From a prospective registry of patients with AS, 345 participants who were referred for and treated with AVR (transcatheter [n=183] or surgical [n=162]) were included. Eight biomarkers were measured on blood samples obtained prior to AVR: growth differentiation factor 15 (GDF15), soluble ST2 (sST2), amino-terminal pro-B-type natriuretic peptide (NTproBNP), galectin-3, high sensitivity cardiac troponin T, myeloperoxidase, high sensitivity C-reactive protein, and monocyte chemoattractant protein-1. Biomarkers were evaluated based on median value (high versus low) in a Cox proportional hazards model for all-cause mortality and a parsimonious group of biomarkers selected. Mean follow-up was 1.9±1.2 years; 91 patients died.

Results—Three biomarkers (GDF15, sST2, and NTproBNP) were retained in the model. One-year mortality was 5%, 12%, 18%, and 33% for patients with 0 (n=79), 1 (n=96), 2 (n=87), and 3 (n=83) biomarkers elevated, respectively (p<0.001). After adjustment for the Society of Thoracic Surgeons (STS) risk score, a greater number of elevated biomarkers was associated with increased mortality (referent: 0 elevated): 1 elevated (HR 1.47, 95% CI 0.60–3.63, p=0.40), 2 elevated (HR

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Conflicts of interest: Dr. Lindman is a site co-investigator for the PARTNER Trial, has consulted for Gerson Lehrman Group Research, received assay support from BG-Medicine, and received a research grant and serves on the scientific advisory board for Roche Diagnostics. Dr. Zajarias has consulted for Edwards Lifesciences and is a member of the PARTNER Trial Steering Committee. Dr. Maniar is a site investigator for the PARTNER Trial. Dr. Damiano has consulted for and received grant support from AtriCure, and received grant support and speaking fees from Edwards Lifesciences. Dr. Lasala has consulted for Boston Scientific and Direct Flow Medical, received speaking fees from Boston Scientific and St. Jude, and received stock options from Direct Flow Medical. The other authors report no potential conflicts of interest.

2.89, 95% CI 1.24–6.74, $p=0.014$), and 3 elevated (HR 4.59, 95% CI 1.97–10.71, $p<0.001$). Among patients at intermediate or high surgical risk (STS score ≥ 4), 1- and 2-year mortality rates were 34% and 43% for patients with 3 biomarkers elevated versus 4% and 4% for patients with 0 biomarkers elevated. When added to the STS score, the number of biomarkers elevated provided a category-free net reclassification improvement of 64% at 1 year ($p<0.001$). The association between a greater number of elevated biomarkers and increased mortality after valve replacement was similar in the transcatheter and surgical AVR populations.

Conclusions—These findings demonstrate the potential utility of multiple biomarkers to aid in risk stratification of patients with AS. Further studies are needed to evaluate their utility in clinical decision making in specific AS populations.

Keywords

aortic valve stenosis; biomarkers; transcatheter aortic valve replacement; surgical aortic valve replacement; risk stratification

INTRODUCTION

With the increasing prevalence of calcific aortic stenosis (AS), decreasing operative mortality for aortic valve replacement (AVR), and the transformative innovation of transcatheter AVR (TAVR), risk stratification of patients with AS has become more challenging, complex, and desirable.[1–2] Biomarkers have not figured prominently in the risk stratification of patients with AS; most studies have examined the utility of natriuretic peptides, with some recent studies looking at high sensitivity troponin and other assays.[3–4] Improved risk stratification using biomarkers in patients with AS could aid clinical decisions about when, how, and whether to perform valve replacement. In heart failure populations without AS, the prognostic utility of multiple biomarkers (evaluated in combination) in addition to clinical factors has been demonstrated; whether the same is true for patients with AS is unknown.[5] To address this issue, we examined biomarkers of cardiovascular stress that have been shown to have prognostic utility in heart failure cohorts: growth differentiation factor 15 (GDF15) (fibrosis, inflammation), soluble ST2 (sST2) (myocyte stress), galectin-3 (Gal3) (fibrosis, inflammation), amino-terminal prohormone of B-type natriuretic peptide (NTproBNP) (neurohormonal activation), high sensitivity cardiac troponin T (hs-cTnT) (myocyte injury), myeloperoxidase (MPO) (oxidative stress), high sensitivity C-reactive protein (hsCRP) (inflammation), and monocyte chemoattractant protein-1 (MCP-1) (inflammation).[6–9] We hypothesized that multiple biomarkers reflecting diverse biological pathways would improve risk stratification of patients with AS undergoing surgical AVR or TAVR in comparison to the Society of Thoracic Surgeons (STS) risk score, which is the existing standard.[10]

METHODS

Study population and design

From an ongoing, prospective study of patients with AS in which clinical and echocardiographic data and biospecimens are collected, 349 participants recruited between August 2010 and April 2014 were included who were referred for and treated with AVR

(transcatheter or surgical approach) at Barnes Jewish Hospital in St. Louis, Missouri. Patients seen in the cardiac surgery clinics or multidisciplinary high-risk valve clinic or those identified on the surgery schedule were potentially included. Patients had to be 18 years of age and have severe AS with an aortic valve area $<1.0 \text{ cm}^2$ or aortic valve area index $<0.6 \text{ cm}^2/\text{m}^2$. Patients with prior valve replacement surgery, pulmonary fibrosis, cirrhosis, known active infection or cancer, or end-stage renal disease on dialysis were excluded. Institutional Review Board approval was obtained, and all patients signed a written informed consent.

Clinical variables were obtained through patient interview and chart abstraction. The Society of Thoracic Surgery (STS) risk score was calculated for each patient according to the STS definitions for each of the clinical characteristics using the publicly available website (v2.73). Echocardiographic measurements were made as recommended by the European Society of Echocardiography and described previously and reflect an average of 3 to 5 values.[11 12]

Biomarker and left ventricular tissue analyses

Venous blood was acquired in the clinic or hospital setting an average of 31 (14, first quartile; 57, third quartile) days prior to valve replacement, usually at a time when blood was drawn for clinical purposes. In a subset of patients (16%), blood was collected in the operating room 73 ± 18 minutes after the patient was asleep. Blood samples were processed immediately and stored as aliquots of plasma or serum at -80°C until time of assay. GDF15, sST2, NTproBNP, MPO, Gal3, hs-cTnT, hsCRP, and MCP-1 concentrations were measured from banked samples (1 freeze-thaw cycle). Assay details are provided in the Online Supplement. In a sub-group of patients, left ventricular tissue was obtained from the basal septum of the heart at the time of surgical AVR. Detailed methods for the quantitative measurement of fibrosis and inflammatory cell number in the myocardium are provided in the Online Supplement.

Statistical analysis

Data are presented as frequencies, mean (SD), or median (25th, 75th percentiles). Determination of vital status was assessed by a combination of chart abstraction, in-person or telephone contact, and public record search (up to October 2014). A multivariable Cox proportional hazards model was built including all 8 biomarkers; to make it more clinically meaningful, biomarkers were evaluated based on their median value (high versus low). A step-down variable selection technique was used to identify a parsimonious group of biomarkers; Akaike's information criteria was used to establish a stopping point.[13] Biomarker levels, patient characteristics, medication usage, and echocardiographic measurements were compared between groups determined by the elevated number of the selected biomarkers using analysis of variance and Fisher's exact test for continuous and categorical data, respectively. Non-normal and ordinal data were compared using the Kruskal-Wallis test. Each biomarker was evaluated using the median value as a cut-point for high versus low values and by $\log_2$ transformation standardized to a mean of 0 and standard deviation of 1. The standardized $\log_2$ transformations were utilized to aid in comparison of individual biomarkers. The association between each biomarker and all-cause mortality was

evaluated and described by the hazard ratio using Cox proportional hazards models. The hazard ratio of the standardized log₂ transformation represents the increase/decrease in the likelihood of death for a 1 standard deviation increase in the biomarker. In separate models, adjustment was made for: 1) STS score; and 2) clinical factors, including glomerular filtration rate, sex, diabetes mellitus, obstructive lung disease, NYHA functional class (III/IV vs. I/II), and aortic mean gradient. These 6 clinical factors were obtained from a Cox proportional hazards model for mortality that included 14 variables (age, BMI, coronary disease, atrial arrhythmia, peripheral vascular disease, ejection fraction, mitral regurgitation severity, and TAVR vs. SAVR in addition to the 6 variables already listed) and a backward selection method using $p < 0.20$ set as the selection criteria.

Kaplan-Meier (KM) curves were created for groups of patients based on the number of the selected biomarkers that were elevated and the log-rank test used to evaluate the overall difference between the curves. KM estimates for 1- and 2-year mortality were determined and reported based on the number of biomarkers elevated within different groups defined by the STS risk score (<4 , 4–8, and >8). The probability of death at 1 year was derived from a Cox proportional hazards model having STS score and the number of elevated biomarkers as independent predictors and was used to visually examine the utility of evaluating biomarker elevations in addition to the STS score. Sub-group analyses were performed with separate models evaluating the interactions between the number of biomarkers elevated and several patient characteristics.

The Integrated Discrimination Improvement (IDI) and the category-free Net Reclassification Improvement (NRI) were determined to further describe the added utility of multiple biomarker measurements when added to the STS score.[14 15] The IDI measures the new model's ability to improve integrated (average) sensitivity without sacrificing integrated (average) specificity.[14] The NRI measures the correctness of patient reclassification based on the probability of death at selected time points.[15] All analysis was conducted with SAS v9.4 (SAS Institute Inc., Cary, NC) except for the calculations of the survival-based c-statistic, IDI and NRI, which was conducted with the R software packages SurvC1 by Hajime Uno and Hmisc by Frank Harrell. A more complete list of references is found on the online supplement.

RESULTS

Participants

Among the 348 patients included in the analysis, the average age was 78 years, 44% were female, mean aortic valve area was 0.74 cm² and mean EF 58% (Table 1). Most had heart failure symptoms: NYHA functional class was II in 19%, III in 56%, and IV in 18%. Chest pain consistent with angina was present in 31% and syncope had occurred in 11%. The mean STS score was 7.5 (5.8); 107 (31%) had a lower risk STS score (<4), 112 (32%) had an intermediate risk STS score (4–8), and 126 (37%) had a high-risk STS score (>8). TAVR was performed in 183 patients (53%), including 77, 65, and 41 treated via transfemoral, transapical, and transaortic approaches, respectively. Of the 162 patients treated with conventional surgery, 127 had isolated aortic valve replacement and 35 underwent a concomitant procedure (29 coronary bypass, 4 MAZE, 2 ascending aorta repair). Among

patients treated with transcatheter AVR, 86% (157/183) had coronary disease and 8% underwent a percutaneous coronary intervention between blood collection and the transcatheter AVR procedure. Baseline biomarker levels and clinical, medication, and echocardiographic characteristics are shown for the whole population and according to the number of the selected biomarkers that were elevated (Table 1).

Individual biomarkers and mortality

All patients had each of the 8 biomarkers measured in their banked plasma or serum. The correlations between each of the biomarkers are shown in Online Table 1. During a mean follow-up of 1.9 (1.2) years, 91 (26%) patients died, including 54 patients treated with TAVR and 37 patients treated with SAVR. The associations (unadjusted and adjusted) between each of the biomarkers and mortality are shown based on standardized log-transformed biomarker levels and median values (Online Table 2). GDF15 had the strongest and most consistent relationship with mortality, followed by sST2 and NTproBNP.

Multiple biomarkers in combination

From among the 8 biomarkers evaluated, a parsimonious group of biomarkers was identified that included GDF15, sST2, and NTproBNP (Online Table 3). An elevation in each of these 3 biomarkers was treated equally. One-year mortality was 5%, 12%, 18%, and 33% for patients with 0, 1, 2, and 3 biomarkers elevated, respectively. Increased mortality associated with an increased number of biomarkers elevated was observed in the whole population and the sub-groups treated with TAVR and surgical AVR ($p < 0.001$ for all) (Figure 1a–c).

After adjustment for the STS score or other clinical factors, the increased hazard of death associated with each increased biomarker was 1.7 ($p < 0.001$) (Table 2). After the same adjustment and compared to patients with no biomarkers elevated, those with 2 biomarkers elevated had an almost 3-fold increased hazard of death and those with 3 biomarkers elevated had a greater than 4-fold increased hazard of death ($p < 0.05$ for all) (Table 2). No increased hazard of death was found among patients having only 1 elevated biomarker. Across the spectrum of STS scores from low to high, mortality increased as the number of elevated biomarkers increased (Figure 2). Among those at intermediate or high surgical risk with an STS score ≥ 4 , those with 3 biomarkers elevated had 1- and 2-year mortality rates of 34% and 43%, whereas those with no biomarkers elevated had 1- and 2-year mortality rates of 4% and 4%. The relationship between an increased number of elevated biomarkers and increased mortality was consistent across sub-groups, including the transcatheter and surgical AVR populations, albeit with an even stronger relationship among patients without coronary disease (Figure 3).

Added prognostic utility of multiple biomarkers

The 1-year survival c-statistic for the STS score plus number of elevated biomarkers was 0.702 (95% CI 0.632–0.771) compared to the STS score alone (0.667, 95% CI 0.595–0.738) ($p = 0.16$ for difference). Compared to the STS score alone, addition of the number of elevated biomarkers provided a 1-year category-free NRI of 64% (95% CI 41–87%, $p < 0.001$), including improved reclassification of events (34%) and non-events (30%) (Table 3). The IDI was also significant at 1 year (0.037, $p < 0.001$). A similar improvement in net

reclassification was observed for 2-year mortality (Table 3). Similar results were obtained when evaluating reclassification from adding the number of elevated biomarkers to a clinical model (Table 3).

Biomarkers and tissue fibrosis and inflammation

The associations between each of the biomarkers and myocardial tissue fibrosis and inflammation are shown in Online Tables 4 and 5. Representative images are shown in Online Figure 1. Only hs-cTnT and the number of elevated biomarkers showed an association with percent collagen area ($p<0.05$), whereas GDF15, sST2, hs-cTnT, NTproBNP, and MCP-1 all showed an association with the number of macrophages in the myocardium ($p<0.05$).

DISCUSSION

In this prospective cohort of 345 patients with severe AS treated with surgical AVR or TAVR, we showed that multiple biomarkers of cardiovascular stress in combination provide an improved estimate of mortality compared to the STS score alone, which is the most commonly used risk score for patients with AS. After adjustment, an increased number of elevated biomarkers (GDF15, sST2, and NTproBNP) was associated with a higher hazard of mortality after valve replacement. Among patients at intermediate or high surgical risk with an STS score ≥ 4 , those with elevations in all 3 biomarkers had a 10-fold higher 1- and 2-year mortality than those with no elevated biomarkers. Importantly, the number of biomarkers elevated improved risk reclassification both by increasing the estimated mortality in those who died and decreasing the estimated mortality in those who survived and its prognostic utility was consistent across sub-groups. Despite the differences in the transcatheter and surgical AVR populations, the association between an increased number of elevated biomarkers and increased mortality after valve replacement was consistently observed in both treatment populations. Collectively, these findings provide a proof-of-principle demonstration of the potential utility of multiple biomarkers to aid in risk stratification of patients with AS. Further studies are needed to evaluate their utility in clinical decision making in specific AS populations.

As in other valvular heart diseases, biomarkers have not played a significant role in the evaluation and management of patients with AS.[10] Natriuretic peptides are the only biomarkers that have been widely utilized in patients with AS, although their role in clinical management decisions is not clearly defined. The U.S. guidelines on valve disease do not incorporate natriuretic peptide levels into clinical decision making, whereas the European guidelines indicate that valve replacement may be considered (class IIB recommendation) in patients with asymptomatic severe AS with a “markedly elevated natriuretic peptide level.” [10 16] There are emerging, but limited, data on the potential prognostic utility of other biomarkers, such as high sensitivity troponin in patients with AS.[4] Given the adverse prognosis associated with myocardial fibrosis in patients with AS, there has been interest in whether biomarkers that reflect myocardial fibrosis might aid in risk stratification.[17] In this regard, the lack of a significant association between any of the circulating biomarkers and tissue fibrosis (except for hs-cTnT) suggests the association between “biomarkers of

fibrosis” and the presence of myocardial fibrosis may be weaker than anticipated. Perhaps some of these biomarkers of cardiovascular stress better reflect the degree of myocardial inflammation.

Given the complex cardiovascular and systemic pathophysiology that underlies AS and influences survival in patients with the disease, it is likely that multiple biomarkers reflecting diverse biological pathways (cardiac and systemic) will be more useful in the prediction of clinical outcomes than any one biomarker alone. Indeed, the prognostic utility of combining multiple biomarkers to predict incident heart failure and mortality in the general population and mortality in patients with non-valvular heart failure has been amply demonstrated.[5 18]

Our results demonstrate the potential utility of multiple biomarkers to improve risk stratification of patients with AS. Further studies are needed to evaluate how such biomarker panels might influence patient management and treatment decisions. In lower risk, perhaps asymptomatic, patients with severe AS, discerning the optimal timing of valve replacement surgery and identifying who might benefit from earlier surgical intervention as opposed to careful observation has been a management question that has generated considerable debate. [2 10 16] Multiple biomarkers of cardiovascular stress may identify a group of patients who would benefit from earlier surgery despite the absence of symptoms to maintain long-term cardiac performance, optimal quality of life, and freedom from heart failure.

At the other clinical extreme are patients, now often considered for TAVR, with advanced symptoms and numerous comorbidities. Even with TAVR, many of these patients either die soon after the procedure or do not experience an improvement in quality of life, raising questions about the potential benefit versus futility of treatment with TAVR.[19] In these patients, using multiple biomarkers in combination with other clinical factors or risk scores may identify those unlikely to benefit from TAVR. Our observation of the effective stratification of mortality risk beyond the STS score suggests the potential utility of a multimarker approach (perhaps with more biomarkers that reflect disease in other organs) in combination with more accurate clinical risk scores to identify a sub-group of patients who have a dismal prognosis even with TAVR.

An additional group of patients with AS in whom a more refined risk stratification is needed are those at intermediate to high risk in whom treatment with TAVR or surgical AVR is feasible. With clinical trials showing similar outcomes after treatment with TAVR or surgical AVR, there will likely be an increasing tendency to treat these patients with the less invasive approach.[20 21] However, a sub-group of these patients—perhaps with coexistent significant non-aortic valve disease such as mitral or tricuspid regurgitation or multivessel coronary disease—may benefit from surgical AVR that allows for concomitant mitral or tricuspid valve repair or coronary bypass. A panel of multiple biomarkers that provides insight into anticipated survival may help guide the decision between a more complete surgical procedure (including correction of other valve abnormalities) versus a less invasive approach with more selective treatment of AS via TAVR.

Limitations

Several limitations should be considered when interpreting these findings. While this cohort of patients was not exclusively comprised of those at higher surgical risk referred for consideration of TAVR, such patients were a large component of our study population as reflected in the older age, relatively high mean STS score, and high prevalence of significant comorbidities. However, one-third of our cohort had an STS score <4 and we found no significant interactions for the relationship between the number of elevated biomarkers and mortality based on age or STS score. Additionally, we used the STS score for our analyses on the utility of the biomarkers in reclassifying risk. The STS score was designed to predict operative mortality and peri-operative morbidity, not long-term mortality.[22] However, the STS score performs reasonably well in predicting longer term mortality and is the most commonly utilized risk score to assess risk in patients with AS; a better alternative risk score does not currently exist.[20 21 23] Moreover, the prognostic utility of the number of biomarker elevations was similar when adjusting for important clinical factors instead of the STS score. We lacked data on frailty, however, which could be prognostically useful in this patient population. Finally, the evaluation of the association between the biomarkers and ventricular fibrosis may have been influenced by sampling bias and our findings should be confirmed with cardiac magnetic resonance imaging studies that measure diffuse fibrosis of the entire ventricle.

Conclusion

A multimarker approach including biomarkers from diverse biological pathways provided a net improvement in risk stratification for mortality in patients with severe AS undergoing valve replacement. Further studies are needed to evaluate the utility of this approach to influence clinical management decisions in distinct populations of patients with AS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. *N Engl J Med.* 2014; 371:744–56. [PubMed: 25140960]
2. Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. *Circ Res.* 2013; 113:223–37. [PubMed: 23833296]

3. Bergler-Klein J, Klačar U, Heger M, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation*. 2004; 109:2302–8. [PubMed: 15117847]
4. Chin CW, Shah AS, McAllister DA, et al. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J*. 2014; 35:2312–21. [PubMed: 24829362]
5. Ky B, French B, Levy WC, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circ Heart Fail*. 2012; 5:183–90. [PubMed: 22361079]
6. Kempf T, von Haehling S, Peter T, et al. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol*. 2007; 50:1054–60. [PubMed: 17825714]
7. Ky B, French B, McCloskey K, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circ Heart Fail*. 2011; 4:180–7. [PubMed: 21178018]
8. Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004; 110:2168–74. [PubMed: 15451800]
9. Braunwald E. Biomarkers in heart failure. *N Engl J Med*. 2008; 358:2148–59. [PubMed: 18480207]
10. Nishimura RA, Otto CM, Bonow RO, et al. 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 Practice Guidelines. *Circulation*. 2014; 129:e521–643. [PubMed: 24589853]
11. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009; 10:1–25. [PubMed: 19065003]
12. Lindman BR, Arnold SV, Madrazo JA, et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in patients with severe aortic stenosis. *Circ Heart Fail*. 2011; 4(3):286–92. [PubMed: 21357546]
13. Harrell, FE, Jr. Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis. New York, NY: Springer-Verlag; 2010.
14. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Statistics in medicine*. 2008; 27:157–72. [PubMed: 17569110]
15. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Statistics in medicine*. 2011; 30(1):11–21. [PubMed: 21204120]
16. Vahanian A, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012; 33:2451–96. [PubMed: 22922415]
17. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol*. 2011; 58(12):1271–9. [PubMed: 21903062]
18. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. *Circulation*. 2012; 126:1596–604. [PubMed: 22907935]
19. Lindman BR, Alexander KP, O'Gara PT, et al. Futility, Benefit, and Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2014; 7:707–16. [PubMed: 24954571]
20. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011; 364:2187–98. [PubMed: 21639811]
21. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014; 370:1790–8. [PubMed: 24678937]
22. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. *Ann Thorac Surg*. 2009; 88:S23–42. [PubMed: 19559823]
23. Dewey TM, Brown D, Ryan WH, et al. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. *J Thorac Cardiovasc Surg*. 2008; 135:180–7. [PubMed: 18179938]

STUDY SUMMARY AND SIGNIFICANCE

What is already known about this subject?

While some studies have demonstrated the prognostic utility of natriuretic peptides, biomarkers have not figured prominently in the risk stratification of patients with AS. In heart failure populations without AS, the prognostic utility of multiple biomarkers (evaluated in combination) in addition to clinical factors has been demonstrated.

What does this study add?

We showed that multiple biomarkers of cardiovascular stress in combination provide an improved estimate of mortality in patients undergoing AVR compared to the clinical factors or the STS score, which is the most commonly used risk score for patients with AS. These findings provide a proof-of-principle demonstration of the potential utility of multiple biomarkers to aid in risk stratification of patients with AS.

How might this impact on clinical practice?

A multimarker approach including biomarkers from diverse biological pathways provided a net improvement in risk stratification for mortality in patients with severe AS undergoing valve replacement. Further studies are needed to evaluate the utility of this approach to influence clinical management decisions in distinct populations of patients with AS.

Figure 1. Multiple biomarkers and mortality after transcatheter or surgical aortic valve replacement

Kaplan-Meier curves are shown for number of biomarkers elevated (0, 1, 2, or 3) for patients treated with surgical (SAVR) or transcatheter aortic valve replacement (TAVR) (a), TAVR only (b), or SAVR only (c).

Figure 2. STS score, biomarker elevations, and mortality

Kaplan-Meier estimates for 1 year mortality are shown according to Society of Thoracic Surgeons (STS) score and number of biomarkers elevated (0, 1, 2, or 3) for patients treated with surgical (SAVR) or transcatheter aortic valve replacement (TAVR) separated by STS groups (<4, 4–8, and >8) (a) and combined into intermediate and high risk patients with STS 4 (b). Based on a Cox proportional hazards model developed with STS score and the biomarkers, predicted 1 year estimates of mortality are shown for the spectrum of STS scores representing patients in our study according to the number of biomarkers elevated (c).

Figure 3. Sub-group analyses for the biomarker elevations and mortality

The hazard ratio for mortality is shown for each additional biomarker elevated in various sub-groups as well as the interaction p-value. Abbreviations: EF, ejection fraction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; CAD, coronary artery disease; GFR, glomerular filtration rate; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

Table 1

Relationship Between Baseline Characteristics and the Number of Biomarkers Elevated

	All (n=345)	No Biomarkers Elevated (n=79)	1 Biomarker Elevated (n=96)	2 Biomarkers Elevated (n=87)	3 Biomarkers Elevated (n=83)	p-value
Biomarker levels						
GDF15 (pg/mL)	2023 (1427, 2885)	1252 (851, 1514)	1684 (1352, 2059)	2469 (2016, 3294)	3276 (2607, 4323)	<0.001
sST2 (ng/mL)	33 (24, 46)	20 (15, 27)	30 (22, 40)	36 (27, 49)	48 (40, 63)	<0.001
MPO (ng/mL)	75 (53, 128)	76 (53, 154)	68 (51, 112)	75 (53, 140)	76 (55, 116)	0.68
NTproBNP (pg/mL)	1402 (580, 3583)	465 (189, 816)	1018 (495, 1668)	1956 (1095, 4142)	5166 (2610, 8966)	<0.001
Galectin-3 (ng/mL)	19 (14, 25)	15 (12, 19)	18 (14, 22)	20 (14, 26)	24 (19, 30)	<0.001
hs-cTnT (pg/mL)	25 (16, 42)	14 (12, 19)	22 (16, 32)	31 (20, 44)	43 (27, 66)	<0.001
hsCRP (mg/L)	3.7 (1.7, 7.8)	2.9 (1.5, 5.4)	2.7 (1.6, 7.5)	3.8 (2.1, 7.7)	5.9 (3.0, 15.2)	<0.001
MCP-1 (pg/mL)	204 (169, 245)	183 (152, 221)	197 (164, 224)	222 (173, 255)	215 (181, 276)	<0.001
Clinical characteristics						
Age (years)	78 (11)	71 (11)	78 (10)	82 (9)	82 (9)	<0.001
Female	151 (44%)	36 (46%)	45 (47%)	33 (38%)	37 (45%)	0.63
Body mass index (kg/m ²)	28.8 (6.5)	30.1 (6.2)	29.8 (6.7)	28.0 (6.4)	27.1 (6.0)	0.005
SBP (mmHg)	133 (23)	137 (16)	132 (22)	135 (25)	128 (25)	0.031
STS score	7.5 (5.8)	3.6 (3.3)	6.4 (5.1)	9.0 (6.1)	10.7 (5.5)	<0.001
Atrial arrhythmia	110 (32%)	4 (5%)	28 (29%)	35 (40%)	43 (52%)	<0.001
Coronary disease	248 (72%)	48 (62%)	66 (69%)	62 (71%)	72 (87%)	0.002
Previous CABG	116 (34%)	19 (24%)	26 (27%)	34 (39%)	37 (45%)	0.014
Prior myocardial infarction	86 (25%)	15 (19%)	15 (16%)	24 (28%)	32 (39%)	0.003
Obstructive lung disease	155 (45%)	28 (35%)	40 (42%)	43 (49%)	44 (53%)	0.10
Peripheral vascular disease	191 (55%)	27 (34%)	52 (54%)	53 (61%)	59 (71%)	<0.001
Diabetes	123 (36%)	21 (27%)	31 (32%)	32 (37%)	39 (47%)	0.048
Syncope	38 (11%)	11 (14%)	7 (7%)	11 (13%)	9 (11%)	0.50
Angina	107 (31%)	30 (38%)	29 (30%)	24 (28%)	24 (29%)	0.49
NYHA class III/IV	253 (73%)	40 (51%)	70 (73%)	67 (77%)	76 (92%)	<0.001
GFR (mL/min/1.73m ²)	70 (27)	85 (21)	74 (21)	66 (32)	58 (24)	<0.001

	All (n=345)	No Biomarkers Elevated (n=79)	1 Biomarker Elevated (n=96)	2 Biomarkers Elevated (n=87)	3 Biomarkers Elevated (n=83)	p-value
Medications (%)						
ASA or antiplatelet	242 (70%)	58 (73%)	66 (69%)	59 (68%)	59 (71%)	0.86
β blockers	204 (59%)	44 (56%)	53 (55%)	50 (57%)	57 (69%)	0.23
ACE-I or ARB	156 (45%)	35 (44%)	50 (52%)	38 (44%)	33 (40%)	0.41
Calcium channel blocker	96 (28%)	25 (32%)	33 (34%)	13 (15%)	25 (30%)	0.013
Statins	227 (66%)	59 (75%)	63 (66%)	53 (61%)	52 (63%)	0.25
Loop diuretic	172 (50%)	15 (19%)	46 (48%)	47 (54%)	65 (77%)	<0.001
Aldosterone antagonist	29 (8%)	2 (3%)	7 (7%)	9 (10%)	11 (13%)	0.07
Echocardiography						
AVA index (cm ² /m ²)	0.38 (0.10)	0.41 (0.10)	0.39 (0.09)	0.36 (0.10)	0.37 (0.10)	0.004
Mean gradient (mmHg)	42 (13)	41 (11)	42 (13)	43 (14)	41 (14)	0.52
Peak gradient (mmHg)	68 (20)	67 (18)	69 (20)	70 (20)	67 (23)	0.49
Ejection fraction (%)	58 (15)	64 (13)	60 (14)	57 (15)	49 (15)	<0.001
LVED dimension (cm)	4.6 (0.7)	4.4 (0.8)	4.5 (0.7)	4.6 (0.7)	4.7 (0.7)	0.035
LVES dimension (cm)	3.1 (0.9)	2.8 (1.0)	2.9 (0.8)	3.2 (0.9)	3.5 (1.0)	<0.001
LV mass index (g/m ²)	119 (38)	119 (39)	110 (32)	125 (40)	124 (41)	0.07
e' (cm/s)	5.4 (1.7)	5.7 (1.9)	5.4 (1.6)	5.1 (1.4)	5.4 (1.9)	0.27
E/e'	20 (11)	17 (9)	20 (9)	21 (12)	22 (11)	0.008
Moderate/severe MR	37 (11%)	2 (3%)	5 (5%)	14 (16%)	16 (19%)	<0.001
PASP (mmHg)	41 (13)	35 (10)	37 (12)	44 (13)	48 (13)	<0.001
Treatment and outcome						
TAVR (%)	183 (53%)	26 (33%)	42 (44%)	57 (66%)	58 (70%)	<0.001
Died (%)	91 (26%)	7 (9%)	15 (16%)	31 (36%)	38 (46%)	<0.001

Data shown as n (%), mean (SD), or median (25th, 75th percentiles).

The 3 biomarkers considered for elevation included GDF15, sST2, and NTproBNP (based on their median values).

Continuous variables were evaluated for differences using an overall F-test from an analysis of variance; Fisher's exact test was used to identify differences in distributions among levels of categorical data; non-normal and ordinal data were compared using the Kruskal-Wallis test.

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Abbreviations: SBP, systolic blood pressure; STS, Society of Thoracic Surgeons; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; GFR, glomerular filtration rate; ASA, aspirin; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; LVED, left ventricular end-diastolic dimension; LVES, left ventricular end-systolic dimension; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; TAVR, transcatheter aortic valve replacement.

Table 2

Multivariable Models for Mortality

	Unadjusted		Model 1 *		Model 2 **	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Biomarkers elevated (referent is 0 elevated)						
1 biomarker elevated	1.70 (0.69,4.17)	0.25	1.47 (0.60,3.63)	0.40	1.44 (0.58,3.55)	0.43
2 biomarkers elevated	3.78 (1.67,8.60)	0.002	2.89 (1.24,6.74)	0.014	2.95 (1.27,6.86)	0.012
3 biomarkers elevated	6.49 (2.90,14.54)	<0.001	4.59 (1.97, 10.71)	<0.001	4.30 (1.85,9.98)	<0.001
Biomarkers elevated (per additional biomarker elevated)	1.90 (1.53,2.36)	<0.001	1.70 (1.35,2.15)	<0.001	1.66 (1.32,2.09)	<0.001

The 3 biomarkers considered for elevation included GDF15, sST2, and NTproBNP (based on their median values).

* Model 1 adjusts for the Society of Thoracic Surgeons (STS) Score.

** Model 2 adjusts for glomerular filtration rate, sex, diabetes mellitus, obstructive lung disease, New York Heart Association functional class (III/IV vs. I/II), and aortic mean gradient.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 3

Reclassification of Mortality Risk with Multiple Biomarkers

	STS score + Multiple Biomarkers	Clinical factors* + Multiple Biomarkers
1 Year		
IDI	0.037 (0.018,0.058) p<0.001	0.041 (0.020,0.061) p<0.001
Category-free NRI	64.0% (41.4,86.6) p<0.001	59.4% (36.4,82.4) p<0.001
Among events	34.1% (14.7,53.4)	25.3% (5.4,45.2)
Among non-events	29.9% (18.2,41.7)	34.1% (22.5,45.7)
2 Years		
IDI	0.047 (0.023,0.071) p<0.001	0.049 (0.024,0.073) p<0.001
Category-free NRI	64.6% (42.1,87.1) p<0.001	57.0% (34.0,80.1) p<0.001
Among events	36.3% (17.1,55.4)	25.3% (5.4,45.2)
Among non-events	28.3% (16.6,40.1)	31.7% (20.0,43.5)

Multiple biomarkers were evaluated as per 1 elevation in the biomarkers.

* Clinical factors include: glomerular filtration rate, sex, diabetes mellitus, obstructive lung disease, New York Heart Association functional class (III/IV vs. I/II), and aortic mean gradient.

Abbreviations: STS, Society of Thoracic Surgeons; IDI, integrated discrimination index; NRI, net reclassification improvement.