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Prime time for machine learning to predict clinical outcomes in valvular heart disease?

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This article refers to ‘Plasma biomarkers associated with adverse outcomes in patients with calcific aortic stenosis’ by M.K. Vidula *et al.*, published in this issue on pages xxx.

Optimal treatment of asymptomatic patients with severe aortic stenosis (AS) remains unclear.¹ Risk stratification for disease progression and adverse outcomes, such as death or readmission for heart failure, is therefore of great importance. This could ultimately lead to better and timely selection of patients for either surgical or transcatheter aortic valve replacement (AVR) in combination with optimal medical therapy.

Recently, several studies showed that plasma biomarkers can be used as a promising tool in the prognosis and risk stratification in AS patients. For example, a systematic review and meta-analysis by White *et al.*² reported that high levels of B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin and galactin-3 were associated with an increased risk of all-cause mortality in AS patients. Allen *et al.*³ confirmed the ability of NT-proBNP as a prognostic tool, where both low and very high levels are associated with worse outcome after transcatheter AVR. However, sample size and/or number of biomarkers in these studies were relatively small.⁴ In addition, these studies used traditional regression analysis to establish their risk prediction models. Machine learning is a promising tool to improve risk stratification. It can process large amounts of data and can perform tasks, which humans are not capable of. Machine learning is increasingly used in several areas of research, including in patients with cardiovascular disease, such as heart failure.⁵ Recently, this Journal published a paper showing that a machine learning approach was superior to regression analysis in identifying patients with heart failure at risk for death and heart failure hospitalization.⁶ The number of studies using machine learning for risk stratification is rapidly growing, resulting in novel applications in clinical decision-making.⁷ Since a major strength of machine learning is handling large amounts of data, it is particularly useful to apply to data with multiple biomarkers. This makes it not only useful for risk stratification, but also to identify clusters of patients with similar pathophysiology, based on their biomarker profiles. This can potentially lead to individualized treatments based on the pathophysiological profiles. Whilst

patients with valvular heart disease often display symptoms of heart failure, these applications of multimarker analysis and machine learning in valvular heart disease have been largely lacking.

In this issue of the Journal, the study by Vidula *et al.*⁸ is the first to use a machine learning approach with multiple biomarkers to assess pathophysiology and prognosis in patients with AS. The study size was larger than previous studies on biomarkers in AS, with 708 patients included. In order to accomplish this, the authors measured 49 key circulating plasma biomarkers. To assess the relationship between different proteins, network analyses were performed. By creating a network connectivity backbone, the authors found one densely connected biomarker cluster, with biomarkers of angiogenesis, atherothrombosis, extracellular matrix turnover, inflammation, tissue remodelling/inflammation/fibrosis and renal dysfunction. This is in line with previous studies, implicating that the pathophysiology of AS consists of multiple connecting pathways.⁹ This may result in the possibility of several targets for treatment. In both unadjusted and adjusted analysis, NT-proBNP was the most strongly associated biomarker with risk of death, and also with risk of the combined endpoint of death and hospitalization for heart failure. This was suggested before, but has not been seen in such a larger cohort.³ The authors generated a classification predictive model by using model selection by a tree-based pipeline optimizer platform (TPOT). This model includes the most important biomarkers for risk of death or hospitalization for heart failure. It showed that interleukin-6 (inflammation) and fibroblast growth factor-23 (calcification) had the highest importance, which in other terms means that these are the variables with relatively the highest influence in the model. Also, the model could differentiate and classify patients in tertiles of risk (low, medium and high). Thereby, this model was able to define a risk score in subgroups of mild, moderate and severe AS.

Some limitations of this study should be acknowledged, as they may limit broader applicability of the model. Firstly, patients with low-flow low-gradient AS were excluded, while they might be particularly relevant for the readers of a heart failure specialty journal. Secondly, while almost half of the patients had severe AS, it is unclear what proportion of these patients were symptomatic and received AVR. It is also unclear what the reason was that patients

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with mild to moderate AS received treatment, such as AVR (12%). Thirdly, echocardiographic criteria to assess the severity of AS, other than aortic valve area, are missing in this study. The new European Society of Cardiology guidelines for the management of valvular heart disease state that this approach has multiple technical limitations and additional parameters should be measured to accomplish adequate clinical decision-making.¹ In addition, including echocardiographic criteria might further improve the accuracy of the risk prediction models. Adding multiple imaging data might be particularly suitable for a machine learning approach that preferably uses large amount of data from different domains. Fourthly, the timing of biomarker measurement in relationship with the time to interventions is also unclear. Lastly, this study lacks an external validation cohort. Since the risk prediction model was built on the initial cohort, it might overestimate its accuracy and applicability to another patient cohort.

Despite these limitations, this paper is important, interesting and novel in that it applies the machine learning and biomarker approach to valvular heart disease. With this study, the authors showed once again that the usage of biomarkers in prediction of disease progression and clinical decision-making is promising. As such it paves the way for future research.

What are the future perspectives?

- (1) Improving risk prediction in patients with AS remains important to improve clinical decision-making. This is particularly relevant for asymptomatic patients with severe AS and patients with low-flow low-gradient AS, where prognosis of these patients is worse and management and diagnosis are challenging.^{10,11}
- (2) Data on biomarkers might also provide us better tools to establish which patients might be particularly suitable for surgical or transcatheter AVR.
- (3) Readmission rates for heart failure after AVR remain high, in both the surgical and transcatheter intervention group.¹² This may be because adverse remodelling has already taken place, when symptoms are present. Currently, there are studies like the PROGRESS trial, in which clinical outcome after transcatheter AVR is compared to clinical surveillance in patients with moderate AS.¹³ It is crucial to identify pathophysiological pathways that are related to progression of AS. This might lead to therapies that prevent progression and delay the development of symptoms. It may also help in determining an appropriate timing of AVR. Identification of these pathways can also help in identifying patients who need concomitant optimal medical therapy.
- (4) Supervised machine learning techniques might also be used to identify novel biomarkers or imaging characteristics that might further improve our understanding of the pathophysiology and risk predictors of poor outcomes in patients with AS. For instance, artificial intelligence application to echocardiographic images automatically detects signs which

can predict worse outcome. This technique is under construction in different studies, and shows some promising results.^{14,15} It is getting closer to be implemented in real clinical decision-making.

A combination of biomarker assessments, new echocardiographic parameters and baseline clinical characteristics may ultimately lead to an accurate risk prediction model for worse outcome in AS patients. This model should be created and validated in different cohorts, to optimize its accuracy. Vidula *et al.*⁸ made the first big step in this process and we look forward to more coming studies on this topic and their clinical application. Get ready! Its prime time for machine learning approaches in predicting outcomes in valvular heart disease.

Conflict of interest: none declared.

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