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EDITORIAL COMMENT

Predicting Futility in Transcatheter Aortic Valve Replacement

Good Getting Better?*

Olina Dagher, MD,[a,b] Walid Ben Ali, MD, PhD,[a] Thomas Modine, MD, PhD, MBA[c]

As the indications for transcatheter aortic valve replacement (TAVR) are expanding to lower-risk patients, there is an increasing recognition that a sizable portion of TAVR recipients fail to derive a benefit from the procedure. Termed "cohort C" patients, these individuals often have a burden of comorbidity that is too severe to allow for physiologic or functional improvement postintervention. Among the pivotal high-risk trials, up to 50% of patients experienced poor outcomes after TAVR at 1 year.[1,2] An expert consensus document of the American College of Cardiology defined 2 instances in which TAVR is deemed futile: patients with a life expectancy of <1 year and patients who have a chance of "survival with benefit" of <25% at 2 years.[3] "Survival with benefit" implies survival with a meaningful outcome, such as an improvement in life expectancy or quality of life. In light of the growing elderly population and high therapeutic costs, a considerable interest now lies in better identifying patients in whom TAVR is likely to be futile.

With this in mind, in this issue of *JACC: Asia*, Maeda et al[4] used predictive modeling to estimate 1-year mortality after TAVR from a nationwide registry in Japan, the J-TVT (Japan-Transcatheter Valve Therapies) registry. Patients of intermediate to high operative risk (mean Society of Thoracic Surgeons Predicted Risk of Mortality score of 7.3% ± 4.8 %) who underwent TAVR between 2013 and 2018 were randomly assigned to a derivation cohort (n = 12,316) and a validation cohort (n = 5,339) in a 7:3 ratio. Overall, the mean age was 84.4 ± 5.2 years, mean body mass index was 22.3 ± 5.5 kg/m^2, and 68.8% were female. Patients on long-term dialysis were excluded. The statistical prediction was constructed using multivariable Cox proportional hazards regression analysis and incorporated 27 variables, including baseline demographics, preprocedural New York Heart Association functional class, cardiovascular history, echocardiographic findings, and biochemistry. At 1 year, all-cause mortality was 8.2%. The model performance was assessed using 2 properties: 1) discrimination, that is, the model's ability to distinguish between patients with different outcomes; and 2) calibration, that is, the agreement between predicted and observed risks in groups of individuals with similar risk predictions. Regarding discriminatory accuracy, the Harrel's C-index was 0.732, and the area under the receiver-operating characteristic curve was 0.733 (95% CI: 0.709-0.757). A total of 349 patients (2.8%) had at least 1 missing value. To account for the missing data, the authors conducted an additional analysis with multiple imputation using Cox proportional hazards in 50 generated data sets. The pooled C-index from the 50 imputed validation cohorts was 0.730. Regarding calibration, 10 equally sized groups were formed in the validation cohort based on the predicted 1-year mortality. The predicted survival probabilities were then compared with the observed survival from the Kaplan-Meier curve. This revealed good calibration. The factors most strongly associated with 1-year mortality included age of ≥85 years, male sex, low body mass index, New York Heart Association

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From the [a]Department of Surgery, Montreal Heart Institute, Montreal, Quebec, Canada; [b]Department of Cardiac Sciences, Libin Cardiovascular Institute, Calgary, Alberta, Canada; and the [c]Service Médico-Chirurgical: Valvulopathies-Chirurgie Cardiaque-Cardiologie Interventionelle Structurelle, Hôpital Cardiologique de Haut Lévèque, Centre Hospitalier Universitaire Bordeaux, Pessac, France.

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functional class III or IV, chronic obstructive pulmonary disease, peripheral vessel disease, malignancy, immunodeficiency, porcelain aorta, lower hemoglobin, elevated creatinine, lower serum albumin, and emergency procedures.

Most previously published prognostic models predicted in-hospital or 30-day mortality following TAVR. The authors should therefore be congratulated for generating a risk model on longer-term mortality. Another strength of this model is that data were gathered from a large, multicenter cohort of an underrepresented population and with little missingness. This study shows the importance and benefits of collaborative research and data registries: good quality results depend on good quality data. In addition, the number of events per variable ratio in the derivation cohort was 34, reducing the risk of overfitting.

Many steps and challenges remain before any prediction model can positively affect clinical decision making. In fact, most published prediction models will never be implemented in practice. First, the development of a prediction model cannot be considered complete without external validation. External validation on a large, completely independent data set is important to confirm generalizability. Finding these external series can be stringent, and running external validation can reveal deceiving score performances. Second, survival without an improved quality of life is considered an undesirable outcome by many patients. Because postoperative quality of life assessment was not included in the J-TVT registry, the authors could not study this outcome in their model.[3] Third, the model developed by Maeda et al[4] did not include physical or cognitive components of frailty. These markers were shown to be strong predictors of mortality following TAVR.[5] To be fair, frailty assessment measures have not been routinely used in practice. Reasons include a lack of a consensus on which tools to use and the added time and labor required to perform the tests. This leads to incompleteness of collection. Nonetheless, systemic frailty assessments should be important components of each patient-centered decision-making discussion, as recommended by the American Heart Association/American College of Cardiology guideline for the management of patients with valvular heart disease.[6] Finally, the simpler the model, the higher its chances of being widely accepted in practice. The 27 variables studied by Maeda et al[4], despite being readily available, might represent a barrier to a wider use of their model.

The interpretation of the predictive accuracy of a model goes beyond statistical performance. To have clinical significance, a risk model should augment what is already being done. A model with 70% accuracy might not be useful if clinical judgment is right 90% of the time. After 2 decades of experience in TAVR, the patient pathway has evolved because of advances in cardiac imaging, technologies, and expertise. There has been increased subspecialization in both cardiology and cardiac surgery, as well as the implementation of multidisciplinary heart teams. Comprehensive geriatric assessments have been added to an increasing number of TAVR programs and have proven to be invaluable.[7] One can therefore wonder how good heart teams have become in predicting futility after TAVR. Conducting a study to evaluate heart teams' subjective estimates of postoperative prognosis in very-high-risk patients undergoing TAVR would be interesting. This estimate could be used as a comparator for statistical predictive risk models specifically designed for this population. Discrimination accuracy of clinical judgment might be a more suitable comparator than the Society of Thoracic Surgeons score or the EuroSCORE (European System for Cardiac Operative Risk Evaluation), which were not clearly validated in all TAVR populations.

The prediction model presented by Maeda et al[4] confronts an unmet need: reliably predicting futility in TAVR recipients. One of the most difficult tasks in medicine is knowing when not to offer a treatment that won't help, to honor the principle of first "doing no harm." Effectively communicating this thought to patients and their families might be even more challenging. Therefore, no matter how good a heart team's assessment is, we need an objective tool that has a predictive accuracy at least similar to that of clinical judgment to support the decision of not offering TAVR. With collaborative research, international initiatives, and advancements in machine learning in this era of big data, the medical community is getting better at predicting outcomes. More importantly, we are getting better at adopting a holistic approach to patient assessment. When evaluating potential TAVR-related futility, careful attention should be given to a wide variety of factors, including comorbidities, laboratory data, baseline frailty, mobility, and cognition. Ultimately, the goal is to inform an honest dialog about treatment goals that are both achievable by the primary health care team and desirable to the patient.

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ADDRESS FOR CORRESPONDENCE: Dr Thomas Modine, UMCV, hopital cardiologique, Haut Lévèque CHU de Bordeaux, Avenue du Haut Lévêque, 33600 Pessac, France. E-mail: t1modine@yahoo.fr.

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