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EDITORIAL COMMENT

Transcatheter Aortic Valve Replacement in Patients With Chronic Lung Disease

Utile or Futile?*

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Transcatheter aortic valve replacement (TAVR) has become an established and valuable treatment option for patients with severe symptomatic aortic stenosis, who are deemed inoperable or estimated at increased surgical risk (1-3). Randomized trials currently assess TAVR in younger, lower-risk, and asymptomatic patients with severe aortic stenosis (NCT02825134, NCT02675114, NCT02701283, and NCT03042104). On the other end of the spectrum, TAVR has been shown to be futile in a considerable proportion of high and extreme surgical risk patients because of comorbid conditions, which may limit life expectancy or recovery of quality of life irrespective of treatment of aortic stenosis (4).

Chronic lung disease (CLD) constitutes a frequent comorbidity in patients with severe aortic stenosis, has been associated with increased mortality rates after TAVR (5-7), and suggested to go along with a higher proportion of patients where TAVR is considered futile compared with non-CLD patients (7). In this context it is important to ascertain the use of TAVR in CLD patients with regard to clinical endpoints and quality-of-life measures.

In this issue of *JACC: Cardiovascular Interventions*, Crestanello et al. (8) present a post hoc analysis of the effect of chronic lung disease at baseline on long-term outcomes in 1,030 extreme or high surgical risk patients undergoing TAVR. The cohort was derived from the CoreValve U.S. Pivotal trials—a series of well-conducted studies with standardized assessment of baseline characteristics and high validity in outcome ascertainment. The prevalence of CLD at baseline was 55% and objective pulmonary function test measures were available for more than 75% of the study patients to support CLD categorization rendering the CLD cohort one of the most comprehensive reported to date. On the one hand a higher mortality rate after TAVR was observed in patients with moderate or severe CLD (3-year mortality ~52-53% vs. 37.7% in non-CLD patients), and on the other hand symptomatic improvement was reported in the majority of surviving patients with more than 80% remaining in New York Heart Association functional class ≤II and an average rise in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score of more than 20 points sustained at 3-year follow-up. However, when integrating survival and health-related quality of life (KCCQ score) into a single summary measure, the proportion of patients experiencing a favorable health benefit amounted to just over 40% at 1 year and 20% at 3 years, both roughly 10% lower than in non-CLD patients.

These results confirm previous findings of trials and registries, that used the same Society of Thoracic Surgeons score based definition for CLD in cohorts derived from similar populations reporting functional improvement in most CLD patients after TAVR, but to a lower extent and associated with higher mortality rates than in non-CLD patients (6,7). The findings support the notion that CLD frequently goes along with other comorbidities and that CLD subgroups often comprise patients, who probably belong to the sicker and frailer among subjects already considered at high or extreme surgical risk. As a result, the lack of a consistent signal for CLD as an independent

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predictor of survival after TAVR in the published data is unsurprising (7,9).

The low rates of patients with a favorable health benefit at 1 and 3 years of follow-up in the moderate-severe CLD subgroup need to be interpreted in the context of the generally low rates observed (non-CLD patients: 54.2% at 1 year, 31.6% at 3 years). Moreover, there was no group receiving medical therapy alone available that could have served as a comparison, as at the time of the CoreValve Extreme Risk U.S. Pivotal trial the efficacy of TAVR was already proven and no such group was included due to ethical reasons (1). However, data from the PARTNER I (Placement of AoRtic TraNscathetER Valves I) trial cohort B showed that the survival benefit of TAVR compared with standard therapy was preserved in the subcohort of CLD patients with a number needed to treat amounting to <6 to save 1 patient's life after 2 years, notably in subjects deemed inoperable (6).

As in the majority of studies evaluating the role of CLD in TAVR patients, Crestanello et al. (8) applied the Society of Thoracic Surgeons score-based definition to ascertain CLD status, a single categorical variable used for stratification of cardiac surgical risk, but unlikely to adequately reflect the heterogeneous entities of pulmonary disease. It contains neither information regarding the predominance of an obstructive or restrictive functional component nor the type of lung disease. There is potential for misclassification of disease and CLD category, as measures of pulmonary function were not available for the entire cohort. Furthermore, congestive heart failure and pulmonary congestion likely affect pulmonary function tests (10), which is supported by the fact that pulmonary function measures have been shown to improve after aortic valve replacement (11).

The majority of the variables reported by Crestanello et al. (8) to be predictive of mortality within the subcohort of patients with moderate-severe CLD have been previously described as predictors in TAVR patients irrespective of CLD status. They comprise measures of frailty (assisted living, unintentional weight loss) (12), procedural outcome (greater than or equal to moderate aortic regurgitation) (13), and baseline flow state (left ventricular stroke volume index ≤35 ml/m^2) (14). Baseline diffusing capacity of lung carbon monoxide as a measure of pulmonary function predicted mortality as well as health benefit with a limited but statistically significant effect size. Strong and consistent predictors of mortality and poor outcomes reported in previous studies are home oxygen dependency (6,12), pulmonary hypertension (6,15), and a low baseline 6-min walk test distance (6,7).

Health benefit, the endpoint used by Crestanello et al. (8), integrates survival and the favorable development of the KCCQ score after TAVR into a single measure. It thereby adequately reflects the mid- to long-term outcome relevant for patients, and provides a measure that can be valuable in the decision making process of the heart team and in the communication with the patient. However, in these high- and extreme-risk populations the clinically most relevant challenge remains the identification of patients where TAVR is futile. In this regard, risk estimation derived from large cohorts with a limited level of granularity is unlikely to provide sufficient discrimination to reliably identify such patients (12). In other words, risk estimates or the presence of a predictor do not allow for the conclusion that a patient would not benefit from TAVR, but merely that he or she is at higher risk of experiencing an adverse outcome. Hence, in the majority of cases, where the question of futility arises, the heart team needs to assess and integrate the complex combination of comorbid conditions, psychosocial circumstances, factors of frailty, and the patient's wishes to finally reach a therapeutic consensus on an individual case-by-case basis. In view of the reproducible outcomes particularly among patients undergoing TAVR by the transfemoral access route, the option to forgo orotracheal intubation by performing the intervention under conscious sedation, the favorable current procedural event rates, and the low number needed to treat to prevent mortality, the decision to undergo TAVR is similar among patients with and without CLD.

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