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Editorial

What Do Patients Expect from a Transcatheter Aortic Valve Replacement? The Importance of Considering Meaningful Nonmortality Outcomes

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Thanks to bioengineering developments and carefully designed randomized trials, health care providers can present transcatheter aortic valve replacement (TAVR) as a safe and effective alternative to surgery for patients with severe symptomatic aortic stenosis (AS) in the low to high surgical risk range, with realistic expectations to improve the quantity and quality of life (QOL) compared with baseline. TAVR is one of the most disruptive breakthroughs in cardiovascular medicine from the past decade, as exemplified by the exponential growth of procedural volumes, and practice-changing high-grade guidelines recommendations.[1-3] There however remains a nontrivial subset of individuals who, despite procedural success, are not considered disability-free 1 year after TAVR, and by extension do not experience what has been coined a "meaningful" survival.[4] In a carefully conducted multicentre prospective cohort study, Afilalo et al. showed that a subset of 20% of TAVR patients bore more deficits at 1 year compared with their pre-TAVR status, and that 35% were either dead or had worsening disabilities.[5] In the **T**ranscatheter **V**alve **T**herapy (TVT) Registry cohort, 37.7% of 7014 all-comer patients who underwent TAVR between 2011 and 2016 either have died, experienced a significant decline in health status, or improved their status but their status remained below an unacceptable threshold a year after the procedure.[6] Trial endpoints traditionally included composites of cardiovascular events considered important enough to alter significantly the life course of patients, but which do not take into consideration all the subtleties involved in patients' decision-making processes. For understandable reasons related to regulatory evidentiary standards requirements, objective intermediate outcomes intimately related to QOL, such as days alive and out of hospital, were either at best reported as prespecified secondary endpoints, and at worst not reported in major TAVR trials.

Although achieving device success is less of a challenge in the contemporary era characterized by careful patient selection and state of the art techniques, patients deserve to be presented with realistic expectations regarding the potential benefits of TAVR, beyond the likelihood of technical success and of life prolongation. Where do we draw the line between a truly successful procedure and futility in the long run? Personal definitions of effectiveness and futility fluctuate on the basis of patients' individual life goals, and the weights to be given to different outcomes vary between providers and patients.[4,7] The shared decision to undergo or to forego TAVR needs to reflect an accurate balance of patients' inclinations between improved well-being and prolonged survival, as previously advocated.[8,9] A large proportion of $\geq$ 60 year old heart failure (HF) patients would not trade years of life for a better QOL, but this preference reverses as patients grow older and less functional.[10] So how should an optimal patient-centred outcome for TAVR be characterized? Many operational definitions have been proposed, but the best answer arguably is not a one-size-fits-all universal solution.

As the TAVR procedural volume grows across Canada, a contemporary full-scale appraisal of midterm patient-centred outcomes remains to be conducted.[11] In that regard, Nazzari et al. provide valuable insights on important intermediary endpoints fairly related to QOL in the April issue of the *Canadian Journal of Cardiology*.[12] In brief, the authors report the incidence of all-cause and HF-related hospitalizations, as well as their prognostic effect, in 720 consecutive patients with severe symptomatic AS who were discharged alive after successful TAVR at St Paul's Hospital or Vancouver General Hospital between 2010 and 2015 (mean Society of Thoracic Surgeons [STS] score: 6.9%). Their first striking finding is that nearly 60% of patients were rehospitalized within 1 year (21.4% for HF), a figure mirroring the national level.[11] Second, although HF hospitalizations within a year of TAVR unsurprisingly were associated with higher rates of subsequent rehospitalizations, their average number was staggering: 2.36 events per patient-year, most of them not attributed to HF. The median number of days alive and out of hospital was 301.7 in these patients during the first year after TAVR,

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meaning that they spent on average 17% of their time in a hospital during that period. The third noticeable finding is that the 1-year mortality rate was 25.0% after an HF hospitalization occurring within 1 year after TAVR, much higher than for other patients. This latter finding does not imply a causal relationship between HF rehospitalizations and subsequent mortality, but rather exemplifies the fact that patients who are the most susceptible to be rehospitalized are also the most likely to die earlier in the long run.

Simply put, the study by Nazzari et al.[12] reiterates that rehospitalization rates are high among patients discharged alive after successful TAVR, and that rehospitalizations presage rehospitalizations and subsequent mortality. Most of the hospitalizations are related to a non-HF primary diagnosis, reflecting the multimorbidity burden and impaired physiologic resilience of patients who undergo TAVR. Although these Canadian figures might appear upsetting, they closely mirror the clinical practice in the United States. In an unselected cohort of 12,182 patients aged $\geq$ 65 years who underwent TAVR between 2011-2013 and were included in the TVT Registry (mean STS score, 7.1%), the all-cause readmission rate was 53.2% at 1 year.[13]

The study by Nazzari et al.[12] has some limitations worth mentioning. First, the endpoint ascertainment method for HF rehospitalizations through administrative health databases lacks granularity. Consequently, whether the mechanisms underlying the etiology for HF decompensations are attributable to valve-specific issues, poor adherence to medical therapy, or concomitant but unrelated cardiovascular diseases, is unknown. Second, the accrual period for the mortality endpoint did not begin at the same time for patients with and without a first hospitalization. For those who were hospitalized after their TAVR, the beginning of the follow-up (time 0) started at discharge of the first rehospitalization. For the group of patients who were not rehospitalized, time 0 started at the landmark of 30 days or 1 year. Patients who died without being hospitalized before this landmark were excluded in this group, leading to the constitution of a survivor cohort, potentially introducing a bias in favour of this group. However, the magnitude of this potential bias is unknown because the number of patients who died without being hospitalized during the first year is not provided. Finally, a common pitfall of all outcomes studies where technology, operator experience, and procedural planning progress faster than outcomes accrue is that the data might partly be obsolete at the time of analysis.

Despite these limitations, the study by Nazzari et al.[12] reiterates the fact that regardless of the high device success rate achieved in contemporary practice, procedural success does not equate to meaningful survival.[4] More research is required to establish the true figures of "disability-free" survival after TAVR, and to understand how to identify and follow-up patients the most at risk of repeat hospitalizations, disability, and poor QOL. Simple scales such as the Essential Frailty Toolset can predict mortality and worsening disability 1 year after TAVR.[5] It is unclear whether the observed high readmission rates simply reflect an inevitable clinical course of a frail, multimorbid, and functionally declining population. What is clear, as has already been advocated by scientific societies, is that realistic expectations not only with regard to quantity, but also of QOL should be provided to patients contemplating a TAVR. In the 2016 Canadian Cardiovascular Society transcatheter aortic valve implantation quality report, Asgar et al. revealed that pre- and post-TAVR QOL are reported in only 31.9% and 12.4% of patients, respectively.[9,11] Stronger reporting is of utmost importance to draw a realistic portrait of patient-centred outcomes in Canada.

The **Asp**irin in **R**educing **E**vents in the **E**lderly (ASPREE) trial, which used disability-free survival as a primary endpoint (composite of death, dementia, or persistent physical disability) for the comparison of aspirin vs placebo in primary prevention among community-dwelling elderly individuals,[14] should be emulated in the transition toward selection of patient-centred endpoints tailored to reflect a healthy lifespan. Early patient engagement in the design phase of trials has been used successfully in the past,[15] and could be leveraged not only to revamp the choice of endpoints in future TAVR trials, assuming regulators are aligned with this framework, but also to optimize recruitment and retention. As such, opportunities for research funding are available through the Canadian's Strategy for Patient-Oriented Research, a result of partnerships between the Canadian Institutes of Health Research and multiple stakeholders, aiming "to establish an integrated, leading-edge, pan-Canadian clinical research infrastructure along the full continuum of patient-oriented research."[16]

Patients suffering from severe symptomatic AS bear a dismal vital prognosis, and frequently need to cope with a miserable QOL: TAVR is often a last-resort solution to allow them to resume their activities of daily life. The findings of Nazzari et al.,[12] however, reiterate that TAVR is not a panacea, and that unfortunately a subset of patients who experience multiple rehospitalizations remains. As geriatric cardiology emerges as a discipline,[17] and as patient-engagement in trials gains further momentum, we need to capitalize on these opportunities to expand the integration of truly patient-oriented metrics for the identification of "meaningful" procedural success.

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