Editorial

Precision Medicine in TAVR: How to Select the Right Device for the Right Patient

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See article by Ueyama et al., pages 27–36 of this issue.

Transcatheter aortic valve replacement (TAVR) represents a first-line option for the treatment of patients with severe symptomatic aortic stenosis across the entire spectrum of surgical risks. Given the expected growth of TAVR procedures in low-risk patients, many factors other than the primary endpoints of pivotal TAVR trials (either death, or the composite of death or stroke) need to be considered during the selection of a treatment strategy. Such factors include the risk of procedural complications (permanent pacemaker implantation, stroke, new-onset atrial fibrillation, vascular complications, etc), device hemodynamic performance and durability (paravalvular leak [PVL], reinterventions), indication for antithrombotic therapy, and patient quality of life. The pivotal TAVR trials have indicated that some complications with TAVR vs surgical aortic valve replacement (SAVR) vary according to the device under study. For example, rates of permanent pacemaker implantation were higher with TAVR vs SAVR in trials evaluating self-expanding valves, but not in the those evaluating balloon-expandable valves.1,2 TAVR represents a suitable option for all risk groups, but how do we personalise care and select the most appropriate device for our patients?

In this issue of the Journal, Ueyama et al. attempt to answer this question by presenting a network meta-analysis to compare and contrast the safety and efficacy of different TAVR devices.18 Their network meta-analysis included 10,300 participants from 11 randomized trials. Among these trials, 7 compared SAVR with TAVR, and 4 compared 2 different TAVR devices. In brief, their study suggests that (Table 1): 1. All TAVR valve systems are associated with similar long-term survival compared with SAVR, mirroring the findings of most trials when taken individually. Also, no TAVR device is clearly superior to the other devices. 2. Only mechanically expandable valves and self-expanding valves are associated with lower risk of long-term disabling stroke compared with SAVR. Balloon-expandable valves are associated with a similar risk of stroke compared with SAVR, but also with a 3-fold increased risk compared with mechanically expandable valves. 3. Conversely, both mechanically expandable valves and self-expanding valves are associated with higher risks of long-term permanent pacemaker implantation compared with both SAVR and balloon-expandable valves. Mechanically expandable valves are also associated with more pacemaker implantations than self-expanding valves. 4. Both balloon-expandable valves and self-expanding valves are associated with higher risks of long-term, moderate-to-severe PVL compared with SAVR. Balloon-expandable valves are, however, associated with lower risk of PVL compared with self-expanding valves.

The network meta-analysis by Ueyama et al. was conducted rigorously and includes the most updated evidence from high-quality randomized trials.18 It certainly is not the first TAVR meta-analysis to be published,3-4 but it is the first one, to our knowledge, to have assessed the comparative effectiveness of different TAVR systems using a network approach, permitting the ranking of multiple treatment strategies based on both direct and indirect comparisons. However, their conclusions should not be considered as definitive.
due to intrinsic limitations of network meta-analyses. Indeed, if treatment A is safer than treatment B, and that treatment B is safer than treatment C, does that necessarily mean that treatment A is safer than treatment C? The true answer is that it depends on the conditions in which the measures were taken in each of the trials included in the direct and indirect comparisons. To accept the conclusions drawn from indirect evidence as the truth, we must first verify that: (1) summary effect estimates of direct comparisons are valid and not contaminated by heterogeneity across trials (often summarised by the $I^2$ test in traditional meta-analyses); and that (2) transitivity of indirect comparisons is not violated, that is, the assumption that all studies included in the network meta-analysis were conducted under similar conditions regarding the presence of effect modifiers.

The assumption that patient populations, reliability of data sources, and endpoint definitions are similar across the trials included in a network meta-analysis is crucial if one is claiming that the findings obtained from indirect comparisons reflect the truth. This assumption is virtually impossible to verify, but it is, in any case, never totally accurate. Evolving device designs, access route patterns, sheath sizes, and institutional volume-outcome relationship may also all magnify heterogeneity across studies and blur interpretation of the analysis of the pooled data. A noteworthy illustration of violation of transitivity in the Ueyama et al. meta-analysis is that mechanically expandable valves were only evaluated in a group including patients considered to be at high-to-extreme surgical risk. With the information available, it cannot be verified whether the conclusion drawn from the study can be used in an indirect comparison with other types of devices studied in trials enrolling different categories of patients. A myriad of other unknown (observed and unobserved) effect modifiers may also exist, further complicating interpretation of the indirect comparisons presented in the study.

As the prevalence of aortic stenosis and the use of TAVR continue to grow, and as position statements are published to promote best practices, understanding how different devices yield different complication rates will be instrumental from both the patient and the public health perspectives. To contrast the long-term safety and comparative effectiveness of the different TAVR device systems available, the most rigorous option would be to conduct direct head-to-head comparisons in large-scale, properly powered, randomized trials. The likelihood that such a trial will be conducted in the near future is low due to high expected costs, lack of interest from industry sponsors, and of the need for large sample sizes. Ubiquitous availability of electronic health records and other technologies should be leveraged to facilitate the conduct of large, pragmatic, technology-enabled, comparative-effectiveness, randomized trials incorporating streamlined operational processes. For example, the National Patient-Centered Clinical Research Network (PCORnet), an electronic health record data infrastructure standardized into interoperable common data models, has been used to conduct a randomized controlled trial of 15,000 participants in the United States at a fraction of the usual cost. The investigators of the Aspirin Dosing—A Patient-centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) trial capitalized on the availability of electronic health records, online study platforms, and health plan claims to evaluate the comparative effectiveness of 2 doses of aspirin in the secondary prevention of atherosclerotic cardiovascular disease. Isolated European national registries may also be suited to address these questions in future registry-based randomized trials, including the Swedish Web-system for Enhancement and Development of Evidenced-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEPED-HEART) registry and the Western Denmark Heart Registry (WDHR). Leveraging national registries to conduct observational studies assessing the real-life safety and comparative effectiveness of different TAVR devices should also be considered, using rigorous, prespecified statistical analysis plans incorporating strategies accounting for practice variations across hospitals and heterogeneity in case-mix. To our knowledge, however, no such registry is fit for this purpose in North America in the structural arena. In Canada, the first Canadian National TAVI Quality Report was published in 2016 and demonstrated the feasibility of collecting data on TAVR quality indicators, including selected outcomes (mortality, stroke, readmissions). However, the absence of a dedicated registry mandating systematic data collection of standardized definitions and of interoperable electronic health record systems in the country all contribute to limit the hope of answering these questions in the Canadian context within a short-term horizon. In the United States, the Transcatheter Valve Therapy (TVT) registry of the Society of Thoracic Surgeons/American College of Cardiology includes virtually all commercial TAVR procedures performed throughout the country and incorporates multiple measures to preserve data quality, including central adjudication of important outcomes and auditing for data completeness and accuracy. It has been used extensively to evaluate TAVR outcomes in the United States, but its governance principles to this point have not permitted evaluation of the comparative effectiveness of different devices. In Europe, the valvular disease program of the European Unified Registries on Heart Care Evaluation And Randomized Trials (EuroHeart), a harmonized, multinational data infrastructure designed to facilitate the conduct of observational studies and randomized registry trials, is expected to be launched in the first quarter of 2021.

Ueyama et al.’s meta-analysis raises an important question that has yet to be addressed. Their initiative paves the way to future studies evaluating the comparative effectiveness of different TAVR systems, but by itself it does not help clinicians select the most appropriate device for our patients due to limitations related to heterogeneity across studies in terms of

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Table 1. Ranking of SAVR and TAVR devices for risk of developing long-term outcomes

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<tr>
<th>Outcomes</th>
<th>Ranking (from higher to lower risk)</th>
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<tr>
<td>All-cause death</td>
<td>SAVR &gt; BEV = SEV = MEV</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>BEV = SAVR &gt; SEV = MEV</td>
</tr>
<tr>
<td>New permanent pacemaker</td>
<td>MEV &gt; SEV &gt; BEV = SAVR</td>
</tr>
<tr>
<td>Moderate-to-severe paravalvular leak</td>
<td>SEV &gt; BEV &gt; SAVR</td>
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BEV, balloon-expandable valve; MEV, mechanically expandable valve; SAVR, surgical aortic valve replacement; SEV, self-expanding valve; TAVR, transcatheter aortic valve replacement.

* No significant difference was observed between MEV and any other device.
patient populations, methods, study periods, and endpoint definitions. Conducting carefully designed randomized controlled trials and comparative-effectiveness observational studies leveraging pre-existing national registries or electronic health records, developing new data infrastructures to allow cost-effective device surveillance, and leveraging mobile technologies to facilitate the conduct of patient-oriented studies will require concerted, collaborative efforts from cross-sector stakeholders in Canada and globally. Standardisation of endpoints for future studies will also be crucial from a regulatory perspective.17 Orchestrating partnerships between researchers, patients, clinicians, regulators, health technology, and the device industry will be instrumental to facilitate the conduct of high-quality comparative-effectiveness research to refine and personalise the selection of optimal TAVR devices according to patients’ characteristics.

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References