Transcatheter Aortic Valve Implantation in the Era After Commercialization
Quo Vadis in the Real World?

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Transcatheter, transarterial aortic valve implantation (TAVI) is a revolutionary approach for the treatment of aortic valve stenosis, a lingering but malignant disease characterized by a long, symptom-free latency period but a high rate of death after the onset of symptoms.1,2 Introduced only recently in 2002,3 TAVI has entered the clinical arena in an unprecedented fashion. Offering for the first time a definite, catheter-based treatment option for nonsurgical and high-risk patients with symptomatic severe aortic stenosis, TAVI has been adopted rapidly in Europe despite the absence of data in larger patient populations and the lack of randomized studies. Initial first-in-humans feasibility and safety studies had been conducted by expert operators in highly specialized centers and selected patient groups in Europe and Canada that demonstrated a remarkable clinical success, but also unanticipated problems.4–7 However, the significant clinical benefit in the high-risk elderly patient population, for whom few options were available previously, led to a unique dissemination of TAVI, especially after Conformité Européenne (CE) approval of the balloon-expandable Edwards SAPIEN (Edwards Lifesciences Inc, Irvine, CA) and the self-expandable Medtronic CoreValve (Medtronic, Inc, Minneapolis, MN) prosthesis in 2007. To date, more than 10,000 TAVI procedures have been performed worldwide with these devices, and the number of procedures is increasing continuously.

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With this transfer into the real world, the value of TAVI in daily clinical practice now must be demonstrated. Randomized controlled clinical trials are the “gold standard” for evaluation of treatment effectiveness, providing the highest-quality data and evidence. The Placement of Aortic Transcatheter Valves (PARTNER) trial,8 conducted mainly at US centers, is the first prospective, multicenter, randomized controlled clinical trial in the setting of TAVI to evaluate the safety and effectiveness of transfemoral and transapical TAVI with the SAPIEN valve in a stratified population of high-risk (cohort A) and nonoperable (cohort B) patients with symptomatic severe aortic stenosis. The superiority of transfemoral TAVI over optimal medical therapy including balloon aortic valvuloplasty has already been proven for the nonsurgical candidates, showing a compelling number of only 5 patients needed to be treated to prevent 1 death within the first year, and the results for patients at high surgical risk who are nevertheless considered candidates for surgery are eagerly awaited. However, owing to the protocol-mandated inclusion and exclusion criteria, the study population remains highly selected and does not reflect the current real-world scenario.

Registry data provide an important link between randomized controlled clinical trials and the real world, also assessing the huge number of patients who are not eligible in randomized clinical trials because of the strict selection criteria.9 Nonrandomized prospective registries, therefore, provide valuable additional information during postmarketing surveillance of TAVI, documenting real-world application and outcomes for consecutive real-life patients treated in everyday clinical practice at both specialized and nonspecialized centers. Evidence from such a real-world setting is vital, and not only will document the current value of TAVI, but also may provide a solid foundation to guide future developments and clinical decision making along the path on which TAVI will proceed. So far, registry data on TAVI are sparse and only offer 30-day-outcome data for both the SAPIEN and Medtronic CoreValve device.10–12

Therefore, the results of the multicenter Italian experience with the third generation of the self-expandable Medtronic CoreValve device reported by Tamburino et al13 in the present issue of Circulation are important, and the authors are to be congratulated for providing relevant insights into their TAVI experience, including 1-year-follow-up data. In this prospective real-world registry, the authors evaluated the incidence and predictors of early (30 days) and late (30 days to 1 year) mortality after TAVI in 663 consecutive patients with severe aortic stenosis treated at 14 Italian TAVI centers beginning immediately after device commercialization in 2007.

Some important conclusions can be drawn from these registry data. To begin with, TAVI, already predominantly performed completely percutaneously under analgesic sedation (conscious sedation) rather than under general anesthesia with surgical access, appears to be safe and efficient in real-life clinical application. Procedural success, defined as implantation of a functioning prosthesis within the aortic annulus with stable hemodynamic conditions, absence of severe paravalvular regurgitation, and without intraproc-
The report by Tamburino et al\textsuperscript{13} also provides relevant data on the performance of the Medtronic CoreValve prosthesis up to 1 year. As already documented in previous studies, transaortic gradients were reduced dramatically, along with a marked increase in aortic valve area to $\sim1.6$ cm\textsuperscript{2} and remarkable clinical improvement, with most patients being in New York Heart Association class I or II after the procedure. These hemodynamic and clinical benefits were maintained throughout 1 year with no evidence of structural valve deterioration. Trace to mild paravalvular aortic regurgitation was found frequently after TAVI, but was obviously well tolerated. In contrast, moderate to severe postprocedural paravalvular regurgitation, after all found in 21\% of the patient population despite the use of intraprocedural countermeasures such as postdilation and valve-in-valve implantation, was an important predictor of late mortality. In this context, the German TAVI registry demonstrated that moderate to severe paravalvular aortic regurgitation is also associated with increased in-hospital mortality, a finding that was not replicated by Tamburino et al\textsuperscript{13} but that would fit into the authors’ concept that conditions that lead to hemodynamic instability negatively impact operative mortality.\textsuperscript{16} These findings are important and highlight the point that suboptimal procedural results should not be tolerated, and that the issue of paravalvular regurgitation with the CoreValve prosthesis must be addressed before its application is broaden to lower-risk patients. While the issue of a more controlled and precise placement to avoid malpositioning has been addressed recently by a new-generation delivery system (Accu-Trak; Medtronic), further technical developments with a focus on a repositionable and retrievable valve design promise to allow optimal placement and may thereby significantly reduce paravalvular aortic regurgitation related to malpositioning.

In summary, the results of the Italian multicenter TAVI experience presented by Tamburino et al\textsuperscript{13} in this issue of Circulation are encouraging and compare well with the recent results of expert operators at pioneering centers, demonstrating the safety and efficacy of TAVI in a large, real-world patient population. However, enthusiasm and caution must be carefully balanced. TAVI remains a complex and technically demanding procedure that requires advanced catheter skills and intensive training. Moreover, TAVI is still associated with some procedural complications that will need to be further reduced in the future to improve procedural outcome. Demonstrating that comorbidities largely account for late deaths after 30 days, the study by Tamburino et al\textsuperscript{13} also implies that TAVI might yield even better long-term results in lower-risk patients than in the current comorbid patient population. So, TAVI, quo vadis? It is most likely that with continuous technical refinements (eg, profile reduction, improved positioning that features repositionability and retrievability), procedural outcomes, operative mortality, and patient safety will further improve, justifying application of this emerging technology even in lower-risk patients. While randomized clinical trials are needed to evaluate whether the results of TAVI will indeed be competitive with those of surgical aortic valve replacement in lower-risk patients, the current registry data suggest that such clinical trials are

dural mortality, was 98\%, and intraprocedural mortality was only 0.9\% in a typical TAVI patient population with an estimated operative mortality of 23.0±13.7\%, as indicated by the logistic EuroSCORE. These data compare well with the recent results from the pioneering centers,\textsuperscript{5,14} with the industry-sponsored expanded evaluation registry 1 year after CE mark approval,\textsuperscript{10} and with recent data from the independent German Transcatheter Aortic Valve Interventions registry,\textsuperscript{12} as well as with the transfemoral group in the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry.\textsuperscript{11} The high rate of procedural success indicates that the advanced catheter skills needed to successfully perform TAVI with the Medtronic CoreValve prosthesis can be mastered, and that the procedure can be safely introduced into the real world by means of structured programs of training and proctorship. However, this report also shows that such intensive training programs covering the management of specific complications and adequate patient selection are, in fact, needed given the serious complications that are still observed, which importantly include malpositioning that requires valve-in-valve implantation, incomplete stent-frame expansion that requires postdilation, and major access site complications that necessitate vascular surgery or transcatheter repair, but also cardiac tamponade and valve embolization requiring conversion to surgery, as well as life-threatening arrhythmias. Interestingly, Tamburino et al\textsuperscript{13} also note that not only technical proficiency, but important progresses in postprocedural patient care are part of the inherent learning curve associated with the TAVI procedure, significantly improving operative mortality. This calls for additional education of the nursing staff, raising awareness of procedure-related complications (eg, the need for postprocedural pacemaker implantation) and of specific characteristics and needs in the postoperative care of the elderly, comorbid TAVI patient (eg, a short stay in the intensive care unit and an early mobilization).

Furthermore, the Italian registry data highlight the fact that different causes account for early (ie, operative) and late mortality, as already widely assumed but not convincingly proven because of the single-center design and small sample size of previous studies. Operative mortality was 5.4\%, and was mainly impacted by procedural complications and poor baseline conditions associated with hemodynamic instability, with multivariate analysis identifying conversion to open heart surgery, cardiac tamponade, major access site complications, reduced left ventricular function, prior balloon aortic valvuloplasty, and diabetes as key predictors. In comparison, late mortality was influenced primarily by comorbidities not related to the aortic valve disease (prior stroke, prior acute edema, chronic kidney disease), and by moderate to severe postprocedural paravalvular aortic regurgitation, which accounted for a cumulative incidence of 12.2\% at 6 months and 15.0\% at 1 year. As in previous studies, the logistic EuroSCORE showed only low discriminatory power to predict both early and late mortality, which implies the need for a TAVI-specific risk score and functional assessment scales, such as the recently proposed Karnofsky index, to better predict procedural success.\textsuperscript{15}
worthwhile. Meanwhile, TAVI should be restricted to appropriate carefully selected patients treated by a trained and dedicated multidisciplinary team.

**Disclosures**

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**References**


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