Medium Term Outcomes of Transapical Aortic Valve Implantation: Results From the Italian Registry of Trans-Apical Aortic Valve Implantation

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Background. Transcatheter aortic valve implantation (TAVI) has been proposed as a therapeutic option for high-risk or inoperable patients with severe symptomatic aortic valve stenosis. The aim of this multicenter study was to assess early and medium term outcomes of transapical aortic valve implantation (TA-TAVI).

Methods. From April 2008 through June 2012, a total of 774 patients were enrolled in the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA). Twenty-one centers were included in the I-TA registry. Outcomes were also analyzed according to the impact of the learning curve (first 50% cases versus second 50% cases of each center) and of the procedural volume (high-volume versus low-volume centers).

Results. Mean age was 81.0 ± 6.7 years, mean logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) I, EuroSCORE II, and The Society of Thoracic Surgeons risk score were 25.6% ± 16.3%, 9.4% ± 11.0%, and 10.6% ± 8.5%, respectively. Median follow-up was 12 months (range, 1 to 44). Thirty-day mortality was 9.9% (77 patients). Overall 1-, 2-, and 3-year survival was 81.7% ± 1.5%, 76.1% ± 1.9%, and 67.6% ± 3.2%, respectively. Thirty-day mortality of the first 50% patients of each center was higher when compared with the second half (p = 0.04) but 3-year survival was not different (p = 0.64). Conversely, 30-day mortality at low-volume centers versus high-volume centers was similar (p = 0.22). At discharge, peak and mean transprosthetic gradients were 21.0 ± 10.3 mm Hg and 10.2 ± 4.1 mm Hg, respectively. These values remained stable 12 and 24 months after surgery.

Conclusions. Transapical TAVI provides good results in terms of early and midterm clinical and hemodynamic outcomes. Thus it appears to be a safe and effective alternative treatment for patients who are inoperable or have high surgical risk.


Transcatheter aortic valve implantation (TAVI) represents a good therapeutic option for patients who have severe symptomatic aortic valve stenosis who are inoperable or who have serious comorbidities that generate a high surgical risk profile [1, 2]. TAVI can be accomplished through several access approaches: transfemoral, transaortic, transsubclavian (retrograde approach), and transapical (antegrade). The transapical approach, and transapical (antegrade). The transapical

Drs D’Onofrio, Cassese, Gerosa, and Tartara disclose financial relationships with Edwards Lifesciences.
approach is often considered a second choice access with respect to the transfemoral one because the latter can be carried out completely percutaneously and without general anesthesia or tracheal intubation. As a consequence, many centers adopt a “transfemoral first” policy, and transapical patients usually have a higher incidence of comorbidities and higher levels of preoperative risk prediction. Despite the higher risk profile, results of patients undergoing transapical TAVI (TA-TAVI) are similar to those of transfemoral patients [3, 4]. To date, the great majority of papers examine hospital and early results of TAVI and few papers focus their attention on transapical patients only. The aim of this prospective, multicenter study was to examine clinical and hemodynamic outcomes of patients undergoing TA-TAVI.

Patients and Methods

This study represents an update of our previously published paper with data from the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA) [5]. The I-TA registry is a prospective, independent, and spontaneous registry with the participation of the majority of Italian cardiac surgery centers who started a TA-TAVI program. All patients undergoing TA-TAVI at each center were enrolled in this registry. From April 2008 through June 2012, 774 patients underwent TA-TAVI at 21 centers. Details about the I-TA registry, investigators, and participating centers have already been described [5]. The Appendix shows the number of cases enrolled yearly in each center. Data collection was approved by the Ethics Committee, and patient informed consent was always obtained.

The dataset of the I-TA registry has been implemented according to the Valve Academic Research Consortium (VARC) updated definitions and endpoints (VARC-2) [6, 7]. The main indication for TA-TAVI was severe symptomatic aortic valve stenosis (aortic valve area <0.8 cm², mean transaortic gradient >40 mm Hg) associated with one or more of the following: (1) porcelain aorta; (2) high surgical risk (logistic European System for Cardiac Operative Risk Evaluation [EuroSCORE] I >20%, The Society of Thoracic Surgeons [STS] mortality score >10%); and (3) other serious comorbidities that advise against the surgical approach, such as severe pulmonary disease, previous total chest irradiation, hostile chest, and severe liver disease. The majority of centers that participate in the I-TA registry adopt a “transfemoral first” policy. The TA-TAVI procedures were performed usually under general anesthesia and the only implanted devices were the Sapien (Edwards Lifesciences, Irvine, CA) and, since mid 2010, the Sapien XT pericardial balloon expandable bioprosthesis (Edwards Lifesciences). Preoperative risk factors were defined according to the EuroSCORE [8]. The recently updated VARC definitions were used to report safety and efficacy endpoints, valve performance, and complications [7]. The impact of learning curve on patient outcomes was analyzed by comparing the overall survival of the first 50% versus the second 50% of patients for each center. The impact of case-volume on survival was analyzed by comparing survival of centers with more than 27 cases versus centers with less than 27 cases. We adopted 27 cases as the cutoff value as this was the median number of cases performed in the participating centers.

Patients underwent clinical and echocardiographic evaluation at their study site before the procedure, at discharge, between 2 and 6 months after TAVI, and 12 months thereafter. Patients who were not able to reach the study site for clinical evaluation received telephone interviews, and a copy of the most recent echocardiographic examination was collected. Follow-up was closed on June 30, 2012.

Statistical Analysis

Continuous data are expressed by mean and standard deviation or median and range as appropriate. Categorical data are summarized by reporting the percentages. Cumulative survival was estimated using the Kaplan-Meier method and we used the log rank test for comparison between groups. Categorical values were compared by the χ² or Fisher exact test, and continuous variables were compared by the t test. A stepwise logistic regression analysis was used to determine the independent predictive factors of VARC mortality. Variables for the multivariate analysis were selected because of recognized clinical importance or because they were significantly different at the univariate analysis. Statistical analyses were performed using SAS release 8.02 (SAS Institute, Cary, NC).

Results

Preoperative clinical variables of patients are listed in Table 1. Mean age was 81.0 ± 6.7 years, mean logistic EuroSCORE I was 25.6% ± 16.3%; EuroSCORE II, 9.4% ± 11.0%; and STS score, 10.6% ± 8.5%. New York Heart Association (NYHA) functional class III or IV was assigned to 621 patients (80.2%). Nearly 50% of patients had severe peripheral vascular disease. There were 167 patients (21.6%) who had already undergone cardiac surgery, and 139 patients (18.0%) who had percutaneous coronary angioplasty before TAVI. Sapien or Sapien XT valve size 23 mm was used in 279 patients (36.1%); 26 mm in 426 patients (55.0%); and 29 mm in 69 patients (8.9%). Device success was 95.9% (742 patients). Device success criteria were not met in 32 patients (4.1%) for the following reasons: suboptimal performance of the prosthetic heart valve in 19 patients (2.5%); 6 (0.8%) rescue “valve-in-valve”; 5 (0.6%) prosthesis embolization; and successful access failure in 2 patients (0.2%).

Incidence of permanent pacemaker implantation for complete atrioventricular block was 5.4% (42 patients). Incidence of disabling stroke was 0.6% (5 patients), and 5 other patients experienced minor stroke or transient ischemic attack. Incidence of acute myocardial infarction was 1.9% (15 patients); 6 patients (0.7%) required bailout percutaneous angioplasty for coronary ostia occlusion. Median stay in the intensive care unit was 2 days (interquartile range, 1 to 3) and median hospital stay was 8 days.

All-cause mortality at 30 days or during index procedure hospitalization (also in rehabilitation facilities) was
9.9% (77 patients). Cardiovascular mortality was 5.0% (39 patients); intraprocedural mortality occurred in 6 patients (0.7%); 21 (2.7%) died of heart failure; 7 (0.9%) of major ventricular arrhythmias; 3 (0.4%) died of ischemic stroke; and 2 (0.3%) had sudden death. Mortality was classified as noncardiac in 4.9% (38 patients); multiorgan failure in 13 (1.7%); sepsis in 12 (1.6%); respiratory failure in 7 (0.9%); severe hemorrhage in 3 (0.4%); and mesenteric ischemia in 2 (0.3%). There was 1 suicide (0.1%).

The combined early safety endpoint at 30 days, according to VARC-2 definitions, was met in 168 patients (21.7%), and 606 patients (78.3%) had an uneventful 30-day outcome. We observed 10 apex-related complications (1.2%); of these, 2 patients required the institution of cardiopulmonary bypass (1 with conversion to median sternotomy); the remaining 8 were successfully treated off pump through the minithoracotomy.
Follow-Up
Median follow-up was 12 months (range, 1 to 44). Overall Kaplan-Meier 1-year survival was 81.7% ± 1.5%, 2-year survival was 76.1% ± 1.9%, and 3-year survival was 67.6% ± 3.2% (Fig 1). One-year, 2-year, and 3-year freedom from cardiovascular mortality was 91.2% ± 1.1%, 87.4% ± 1.6%, and 83.1% ± 2.4%, respectively (Fig 2). There were no cases of structural valve deterioration nor of endocarditis of the aortic bioprosthesis during follow-up. The combined clinical efficacy endpoint at 1 year, according to VARC-2 definitions, was met by 207 patients (26.7%). Furthermore, we observed a significant improvement of NYHA functional class during follow-up: 574 patients (82.4%) were in class III-IV preoperatively versus 130 patients (18.6%) postoperatively (p < 0.001).

Learning Curve and Procedural Volume
We did not observe significant differences of survival at follow-up related to the learning curve. In fact, Kaplan-Meier analysis of survival found similar overall 3-year survival of the first 50% patients (66.9% ± 3.8%) versus the second 50% patients of each center (69.3% ± 5.0%; p = 0.64; Fig 3). However, 30-day VARC mortality was significantly higher among the first 50% patients (45 of 368 patients, 12.2%) than the second 50% (32 of 406 patients, 7.9%; p = 0.04). Thirty-day VARC mortality of low-volume centers was 12.2% (24 of 197 patients) whereas in high-volume centers it was 9.1% (53 of 577 patients); this difference was not significant (p = 0.22).

Echocardiographic Data
At discharge, no aortic regurgitation was found in 375 patients (53.8%); mild (1+/3+), moderate (2+/3+), and severe (3+/3+) aortic insufficiency was found in 261 (37.4%), 57 (8.2%), and 4 (0.6%), respectively. Peak and mean transaortic gradients at discharge were 21.0 ± 10.3 mm Hg and 10.2 ± 4.1 mm Hg, respectively; these values remained stable during follow-up. Figure 4 shows mean gradient and effective orifice area of Sapien/Sapien XT bioprosthesis at discharge and during follow-up by size.

Multivariate Analysis
Variables that were used in the multivariate analysis are shown in Table 1. The multivariate analysis identified as independent predictors of 30-day VARC mortality: chronic kidney failure, namely, serum creatinine ≥ 2 mg/dL or greater or dialysis (odds ratio [OR] 2.2, 95% confidence interval [CI]: 1.1 to 4.2; p = 0.02); neurologic dysfunction (OR 2.1, 95% CI: 1.0 to 4.3; p = 0.049); peripheral vascular disease (OR 2.0, 95% CI: 1.2 to 3.4; p = 0.008); critical preoperative state (OR 8.8; 95% CI: 4.0 to 19.6; p < 0.0001); and learning curve, second 50% (OR 0.57, 95 CI: 0.34 to 0.94; p = 0.02).

Comment
This study shows the results of transapical TAVI in a “real world” population. Our main findings are that transapical TAVI can be performed with an acceptable mortality rate, safety at 30 days, efficacy at 1 year, as well as 3-year survival and freedom from cardiovascular mortality, in particular if we consider the high surgical risk of these patients. All-cause mortality was 9.9%; this value is similar to that reported by other registries [9–11]. The 30-day combined
safety endpoint is a composite of patient-oriented endpoints (death, stroke, bleeding, kidney injury, myocardial infarction, vascular complications) together with a repeat procedure in the first 30 days to treat valve dysfunction (balloon valvuloplasty, valve-in-valve). Safety reflects the impact of TAVI on early hospital outcomes. In our study, 19.1% of patients met the safety endpoint; of these, 9.5% were deaths and the remaining 9.6% were complications. This value is consistent with that reported by other investigators [12]. However, efficacy at 1 year incorporates major clinical factors (death and failure of current therapy) and valve performance factors (prosthetic valve dysfunction like stenosis or regurgitation), thus reflecting the impact of TAVI on delayed outcomes (1 year or longer). In our study, the efficacy endpoint was met in 20% of patients. These values should be considered with caution as these are relatively new criteria, specifically developed for TAVI, and there are no studies that use these definitions to evaluate the performance of conventional aortic valve replacement [13]. A study focused on this issue would be important to compare the two procedures and validate these composite endpoints.

Another important aspect is that of the 19% of patients who met the safety endpoint, in 9.6% a severe complication occurred. The complications that are included in the composite safety endpoint are usually life-threatening, and that patients were able to survive such events highlights the importance of a multidisciplinary team approach to TAVI. In fact, a multidisciplinary team is able to carefully select patients, predict potential adverse events, and identify and treat complications in a timely and effective manner [14]. The TAVI procedure is a complex one that requires specific training, and consequently the learning curve may affect outcomes. We observed that patients who received TA-TAVI during the first half of the experience at each center had a significantly higher 30-day VARC mortality when compared with patients operated on during the following period. Nevertheless, survival at follow-up was similar, reflecting once again the importance of comorbidities. The learning curve is therefore crucial for patient selection and procedure performance (valve sizing, access, positioning, postdilation), and at the multivariate analysis it was identified as an independent predictor of 30-day mortality. However, procedural volume does not seem to have a significant impact on outcomes because 30-day mortality was similar between low-volume centers and high-volume centers. Medium term survival, up to 3 years, was 67.6% but freedom from cardiovascular mortality was 83.1%.

These data confirm that the impact of patient comorbidities play a major role in determining survival at follow-up [15] and show that, probably, the extension of indications toward a less compromised population could improve overall survival. Another aspect that is in favor of the indications for TAVI for younger patients is that we did not report any case of structural valve deterioration in the entire experience. Furthermore, we observed that the hemodynamic performance of the Sapien bioprosthesis is good, with low gradients and significant valve area improvement, and that it remains stable during follow-up. However, there is still an issue that causes caution and perplexity with regard to extension of indications for TAVI to younger or less compromised patients: postoperative aortic regurgitation. In this registry, 45% of patients had mild or moderate aortic regurgitation at hospital discharge. That should be taken into careful consideration since it has been demonstrated that even mild aortic insufficiency significantly reduces survival over time [16].

This study has several limitations: this is a transapical-only population that does not consider comparable transfemoral TAVI, transaortic TAVI, or conventional surgery. There is a not-homogeneous distribution of patients among the different centers. However, this is a common problem with multicenter registries and results reflect the real world nature of the study. We did not have a central core laboratory for echocardiographic examinations, and VARC adverse events were assigned by the referring center and not by an ad-hoc committee.
In conclusion, transapical TAVI provides good early and medium term (up to 3 years) clinical and hemodynamic results. Thus, it can be considered as a good therapeutic option for high-risk or inoperable patients with severe symptomatic aortic valve stenosis. In particular, the hemodynamic performance of the Sapien valve is good and is stable over time. Postoperative aortic insufficiency still represents a major issue, and should be solved with new generation devices to extend indications for TAVI. Chronic kidney failure, neurologic dysfunction, peripheral vascular disease, critical preoperative state, and learning curve were identified as independent predictors of VARC 30-day mortality.

References

Appendix. Number of Patients Enrolled Yearly in the Italian Registry of Trans-Apical Aortic Valve Implantation by Study Site

<table>
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<th>Site No.</th>
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<th>2012 (Jan–June)</th>
<th>Total</th>
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DISCUSSION

DR VINOD THOURANI (Atlanta, GA): I’d like to congratulate you on a great presentation. I have one question for you. Do you have any data for higher volume versus lower volume sites within the Italian registry? Because our sense is in the United States that earlier on even in the higher volume sites the mortality was relatively high; and as sites became on board, the mortality actually was much better. So do you have any data on low- versus high-volume sites?

DR D’ONOFRIO: We did not find any difference regarding 30-day VARC mortality of high-volume versus low-volume centers. So we had exactly the same results.

DR THOURANI: So the sites that were doing 10 or 12 cases were doing just as well as those sites that were doing 50 or 60 cases then?

DR D’ONOFRIO: Yes. We must consider that the first cases were done under a proctor supervision who is someone with a huge experience. So all centers at the beginning of their experience always had somebody that supervised the procedures and helped to select patients. This is the reason why I think we did not find any significant difference.

DR HERSH MANIAR (St. Louis, MO): It’s a fantastic review of the TA experience. Two questions: first, were these patients still considered a transfemoral access first and only transapical if they had peripheral vascular disease? Because I was surprised to see that only 50% of the total group had peripheral vascular disease. And then the second question is: you had good follow-up now going out beyond several years, did any of the echocardiographic data, particularly the paravalvular, which has been shown in some of the other registries, impact mortality either when it’s mild or certainly more than mild?

DR D’ONOFRIO: The great majority of these centers follow a transfemoral-first policy, so most of the centers that are included in this registry decide to perform a transapical procedure only if the patient is not suitable for transfemoral access. But the 50% of patients with peripheral vascular disease that I presented refer to EuroSCORE definitions so it doesn’t mean that only 50% has not vascular access. These data refer specifically to the EuroSCORE definitions of peripheral vascular disease. However, we know that peripheral vessels may not be suitable for transfemoral access even if they don’t meet exactly the EuroSCORE definitions. And I don’t have data in this registry regarding the impact of postoperative aortic regurgitation on survival, but we know from the PARTNER trial that even mild aortic regurgitation seems to have an important impact on survival.

DR JOSEPH FLACK (Springfield, MA): Did you look at stroke rate and did it vary over time? Did you look at the stroke rate of the population and what was the percentage of strokes and did it vary over time?

DR D’ONOFRIO: The percentage of stroke is around 1.5% in these cohort, and we did not observe any variation over time.

DR ADRIAN LEVINE (Stoke-on-Trent, United Kingdom): Have you got any data about how many people you had to use bypass on as rescue and was this temporally related with your learning curve?

DR D’ONOFRIO: In 22 of these cases, 22 of almost 800.

DR LEVINE: And was that in the first part of your learning curve? Was that in the first 50% of the early stage of your learning curve?

DR D’ONOFRIO: No, it is not statistically significant because we have small numbers, but there is not a big difference between the first part and the second part of the experience actually.