Early and Mid-Term Results of Rapid Deployment Valves: The Intuity Italian Registry (INTU-ITA)

EARLY AND MID-TERM OUTCOMES OF RAPID-DEPLOYMENT BIOPROSTHESES: THE ITALIAN REGISTRY OF INTUITY VALVE (INTU-ITA).

Intuity rapid-deployment aortic bioprostheses

A. D'Onofrio MD[1]; C. Tessari MD[1]; C. Filippini B.Sc[2]; L. Bagozzi[1] MD, M. Diena MD[3], F. Alamanni MD[4], M. Massetti MD[5], U. Livi MD[6], M. Di Eusanio MD[7], C. Mignosa MD[8], C. Russo MD[9], M. Rinaldi MD[2], R. Di Bartolomeo MD[10], L. Salvador MD[11], C. Antona MD[12], D. Maselli MD[13], R. De Paulis MD[14], G. Luzi MD[15], O. Alfieri MD[16], C.M. De Filippo MD[17], M. Portoghese MD[18], F. Musumeci MD[19], U. Bortolotti MD[20] and G. Gerosa MD[1]

From the departments of Cardiac Surgery of:

1. *University of Padova*
2. *University of Turin*
3. *San Gaudenzio Hospital, Novara*
4. *Monzino Hospital-University of Milan*
5. *Catholic University, Rome*
6. *S. Maria d. Misericordia Hospital-University of Udine*
7. *Ospedali Riuniti, Ancona*
8. *G.B. Morgagni Hospital, Catania*
9. *Niguarda Hospital, Milan*
10. *University of Bologna*
11. *San Bortolo Hospital, Vicenza*
12. *Sacco Hospital-University of Milan*
13. *S. Anna Hospital, Catanzaro*
14. *European Hospital, Roma*
15. *San Carlo Hospital, Potenza*
16. *San Raffaele University Hospital, Milan*
17. *Giovanni Paolo II Hospital, Campobasso*
18. *Santissima Annunziata Hospital, Sassari*
19. *San Camillo Hospital, Roma*
20. *University of Pisa*

ITALY

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Corresponding author:
Augusto D'Onofrio, MD, PhD
Division of Cardiac Surgery, University of Padova
Via Giustiniani, 2
35128, Padova, ITALY
adonofrio@hotmail.it
Tel: +390498212410
Fax: +390498212409

ABSTRACT

BACKGROUND. Rapid deployment bioprostheses (RDB) have been recently introduced into clinical practice for the treatment of severe aortic valve stenosis. Aim of this retrospective multicenter study was to assess early and mid-term clinical and hemodynamic outcomes of patients undergoing RDB implantation.

METHODS. Data from a National Registry that includes patients who underwent isolated or combined aortic valve replacement with RDB in Italy were analyzed. EuroSCORE definitions were used for preoperative variables and updated VARC definitions were used for postoperative outcomes assessment. Univariable and multivariable analysis were performed to identify independent predictors of mortality. Follow-up was carried out with clinical and echocardiographic examinations at each study site and, if this was not possible, through telephonic interviews. Kaplan-Meier method was used for survival analysis.

RESULTS. A total of 902 patients (December 2012-November 2017) from 20 national centers were included in the Registry. Device success was 95.9% and 30-day all-cause mortality was 2.8%. Postoperative pacemaker implantation was needed in 63 patients (6.9%). At discharge, peak and mean trans-aortic gradients were 19±7 mmHg and 11±4 mmHg, respectively. Mild and moderate aortic regurgitation were found in 71 (8.2%) and in 10 (1.2%) patients, respectively. Median follow-up time was 357 days (IQR: 103-638 days). Survival at 4 years was 86±1%. Preoperative conduction disturbances and history of previous myocardial infarction were independently associated with mortality.

CONCLUSIONS. Rapid deployment aortic bioprostheses provide good early and mid-term clinical and hemodynamic outcomes. These devices may be considered as a reasonable alternative to conventional bioprostheses especially in minimally invasive and combined operations.

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INTRODUCTION

Although transcatheter aortic valve replacement (TAVR) is rapidly growing and is now approved also in intermediate-risk patients (1), surgical aortic valve replacement (SAVR) is still the procedure of choice in low-risk patients and in those who need concomitant procedures (2, 3). Among the several aortic valve substitutes available for SAVR, rapid-deployment (RDB) and sutureless (SLB) bioprostheses have been recently introduced into clinical practice (4, 5) for the treatment of patients suffering from severe aortic valve stenosis with the aim of reducing aortic cross-clamp and cardiopulmonary bypass times and of facilitating minimally invasive procedures since they do not require the typical set of annular sutures to be implanted but they just need three guiding sutures at the nadir of each sinus for correct annular placement (6). After RDB implantation, the three guiding sutures are tied down and for this reason they cannot be truly defined as sutureless devices. The only commercially available rapid deployment device is the Intuity (and its evolution Intuity Elite) valve system (Edwards Lifesciences, Irvine, CA, USA). Aim of this multicenter retrospective study was to evaluate early and mid-term clinical and hemodynamic outcomes of patients undergoing rapid-deployment aortic valve replacement (RDAVR).

PATIENTS AND METHODS

The INTU-ITA registry

In this study, we analyzed data from the Italian Registry of the Intuity Valve (INTU-ITA). The INTU-ITA is a “real-world” “all-comers” independent multicenter registry that includes all patients who underwent isolated or combined RDAVR with the Edwards Intuity (and its evolution Intuity Elite) at participating centers. In particular, the INTU-ITA registry includes 902 patients from 20 Italian cardiac surgery institutions in a time period that goes from October 2012 through November 2017. The list of participating centers, the number of patients enrolled in each center and the enrollment period in shown in the Appendix. Since the Intuity valve is not approved for aortic insufficiency, all patients included in the registry underwent SAVR for severe aortic valve stenosis. Data were collected at each study site and then anonymously sent to the University of Padova (coordinating center) for storage and analysis. The study was approved by the ethic committee and patients’ informed consent for the procedure and for data collection for scientific purposes was always collected.

Surgical operation

All procedures were performed under general anesthesia through full sternotomy, ministernotomy (inverted T or J-shape) or right anterior thoracotomy according to the preference of implanting surgeons and to the policy of each single center. The Edwards Intuity aortic valve system is built on the Carpentier-Edwards Perimount platform (three bovine pericardial leaflets) with a subanular balloon-expandable skirt, similar to a transcatheter valve stent, that serves both for anchoring and sealing. The implanting technique has already been extensively described (6). Briefly, after aortic cross clamp and aortotomy the degenerated aortic valve was excised and the aortic annulus was decalcified. Then three guiding sutures (generally 2-0, braided) are passed at the nadir of each sinus and subsequently on the valve sewing ring. The valve is parachuted into the aortic annulus and stabilized using three tourniquets. Then the balloon is inflated for 10 seconds using the

manometer as a reference. The delivery system is then removed and the three guiding sutures are tied before closing the aortotomy. \

Definitions and Follow-up

Preoperative variables were defined according to the EuroSCORE definitions (7) and postoperative outcomes were defined according to the updated Valve Academic Research Consortium (VARC-2) definitions (8). We decided to use VARC definitions in order to allow easy comparison between these data and those of TAVR. Patients underwent clinical and echocardiographic assessment at the study site before the operation, at hospital discharge and then according to each center's protocol (that usually includes a clinical and echocardiographic assessment at the study site on a yearly basis), mainly with follow-up visits at the study site or using telephone interviews. The last census date is December 31st, 2017.

Statistical analysis

For continuous variables, data are reported as mean with standard deviation or as median and first and third quartile. For categorical variables, data are reported as frequency and percentage. A univariable analysis was performed to test which covariates would be considered in a further multivariable analysis. Comparison between groups for continuous variables was performed with t-test or Wilcoxon-Mann-Whitney according to type of distribution; comparison between groups for categorical variables was performed with Chi-square or Fisher exact test as appropriate; for paired categorical variables we use McNemar test. Clinical significant variables were then entered in the model; we chose the variables with a 0.2 significance level. Cox proportional hazard regression analysis was performed to identify independent predictors of mortality at follow-up, which are reported as hazard ratios (HRs), 95% confidence intervals (CIs), and *p* values. Cumulative survival was estimated using the Kaplan-Meier method. All statistical tests were 2-sided, and p values of 0.05 or less

were considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics, version 19 (SPSS, Inc, Chicago, IL).

RESULTS

Study population

The study population includes 902 patients enrolled in the INTU-ITA registry from October 2012 until November 2017. Preoperative variables are shown in Table 1. Mean age was 74±7.7 years, mean Logistic Euroscore, Euroscore II and STS-PROM scores were 8.0±8.1%, 3.0±3.1% and 2.4±1.8%, respectively. The New York heart Association (NYHA) functional class was III or IV in 433 (48%) patients. Baseline echocardiographic data are shown in Table 2; mean trans-aortic gradient was 49±15 mmHg.

Operative data

Operative data are listed in Table 3. The second generation Intuity Elite was implanted in the majority of patients (70.6%). A minimally invasive operation was performed in 40% of patients, mainly mini-sternotomy (37.9%). Combined procedures were done in 310 patients (34.4%) and of these the majority was coronary artery bypass grafting (CABG). In isolated AVR, median cardiopulmonary bypass (CPB) and aortic cross clamp (ACC) time was 83 and 64 minutes, respectively. Interestingly, median CPB and ACC duration was similar between full sternotomy (CPB: 81 minutes; ACC: 56 minutes) and mini-sternotomy (CPB: 82 minutes, ACC: 58 minutes) while patients undergoing mini-thoracotomy had longer median operative times: CPB: 116 minutes, ACC: 80 minutes. Intraoperative complications are listed in table 4. Device success was 95.9% (865 patients). Causes of no device success in 37 patients are listed in Table 4. Severe aortic regurgitation after Intuity deployment occurred in 18 patients (2%); in 12 patients, the RD valve was removed and a standard stented bioprosthesis was implanted; in 4 patients the Intuity valve was successfully repositioned and in 2 patients extra-stitches were positioned to close the leak. Immediate procedural mortality, defined according to VARC-2 definitions (8) as mortality occurring within 72 hours from the procedure, occurred in 8 patients (0.9%). Causes of immediate procedural mortality were: sudden cardiac death in 4 patients, multi-organ failure in two patients (one with acute

myocardial infarction, life-threatening bleeding and acute kidney injury in the immediate postoperative period; the other with stroke, bleeding and vascular complications), pneumonia in one patient and septic shock in one patient Out of 362 minimally invasive approaches, 10 patients (2.8%) were converted to full sternotomy due to the occurrence of an intraoperative complication.

Early postoperative clinical and hemodynamic outcomes

Early postoperative outcomes are shown in table 5. VARC all-cause mortality (within 30 days or during index procedure hospitalization if the postoperative length of stay is longer than 30 days) was 2.8% (25 patients) and cardiovascular mortality was 2.2% (20 patients). Causes of VARC mortality were: immediate procedural mortality in 8 patients (see “Operative data” section), multi-organ failure in 9 patients, respiratory insufficiency (including pneumonia) in 4 patients, low-output syndrome due to postoperative cardiac failure in 2 patients, stroke in one patient and sudden cardiac death in one patient. The incidence of acute myocardial infarction, stroke, life-threatening bleeding and severe acute kidney injury (AKI, stage 3) was 0.6%, 0.8%, 6%and 3.3%, respectively. A permanent pacemaker implantation for new-onset conduction disturbances was needed in 63 patients (6.9%). At discharge, peak and mean trans-aortic gradients were 19±7 mmHg and 11±4 mmHg, respectively. Mild and moderate aortic regurgitation were found in 71 (8.2%) and in 10 (1.2%) patients, respectively. Echocardiographic data at discharge are depicted in table 6 and echocardiographic data according to valve size are shown in Table 7.

Clinical and echocardiographic outcomes at follow-up.

Median follow-up time was 357 days (IQR: 103-638 days). We observed a low incidence (around 1%) of valve-related complications, as shown in Table 8. In particular, we recorded 4 prosthetic endocarditis (0.5%) with one reoperation and 3 reoperations for severe aortic regurgitation (0.3%). Kaplan-Meier survival at 4 years was 86±1% (Figure 1). We observed a

significant and stable reduction of mean aortic gradients as well as an increase of aortic valve area at follow-up, if compared to preoperative values (Figure 2). Out of the 71 patients with mild aortic regurgitation at discharge, 39 patients (54.9%) underwent echocardiographic control at one year that showed no changes in 20 patients (51.3%), no more aortic regurgitation in 18 patients (46.2%) and progression to moderate aortic regurgitation in 1 patient (2.5%). Out of the 10 patients with moderate aortic regurgitation at discharge, 3 patients underwent echocardiographic control at one year (30%) that showed no changes in 1 patient (33.3%), mild aortic regurgitation in 1 patient (33.3%) and progression to severe aortic regurgitation in 1 patient (33.3%). Furthermore, we observed a significant improvement in NYHA functional class at follow up when compared to the preoperative period (Figure 3). The multivariable analysis identified as independent predictors of mortality at follow-up the following variables: preoperative conduction disturbances (HR: 2,9, 95%CI: 1.027-8.002; p: 0.0444) and history of previous myocardial infarction (HR: 5.129; 95%CI: 1.487-17.895; p: 0.0097).

DISCUSSION

After the introduction into clinical practice of SLB and of RDB the portfolio of aortic valve substitutes available for the treatment of patients with severe aortic valve stenosis has now a new option that enables to implant an aortic valve prosthesis through a surgical access but with no need for annular sutures. The two available prostheses are the SLB Perceval (Livanova, London, UK) and the RDB Intuity. The former is made of a self-expanding nitinol stent with bovine pericardial leaflets, the latter is built on the Perimount Magna Ease valve platform with a subanular balloon-expandable stent derived from the Sapien TAVR device. Although these two prostheses have a different design and a slightly different implantation technique, the ultimate goal of both devices is to reduce surgical time (especially during combined operations) and to facilitate minimally invasive procedures. This study is based on data from the INTU-ITA Italian National registry and, to the best of our knowledge, to date is the study with the highest number of enrolled patients undergoing Edwards Intuity RDB implantation worldwide. When talking about RDB there are mainly three aspects that are worth discussing: 1) surgical times; 2) hemodynamic performance (gradients and paravalvular leaks); 3) pace-maker implantation rate. Durability of course is another crucial aspect but it's definitely too early since longer follow-up times are needed to obtain reliable data about the Intuity valve. In our study population, 40% of patients underwent minimally invasive aortic valve replacement due to the rapidity and ease of valve deployment; of these the great majority (37.9%) were done through mini-sternotomy and just a few through right anterior thoracotomy. Surgical times were similar between full and mini-sternotomy but they were significantly longer in mini-thoracotomy. In our analysis, median aortic cross-clamp time and cardiopulmonary bypass times for isolated RDAVR through full sternotomy were 56 and 81 minutes, respectively. These values are shorter than those reported in the STS database (9) for conventional surgical AVR (78 and 106 minutes, respectively) but are longer than those reported in other studies with the Intuity valve. In fact, in the TRITON trial (6) cross clamp and CPB times were 41 and 66 minutes, respectively and in the TRANSFORM trial (10) they were 44 and 69 minutes, respectively. This difference, around 10-15 minutes, may

be due to the “real world” “all comers” and observational nature of this study as well as to the variability of the number of patients enrolled in each center. Another possible explanation is that 40% of the participating centers of our registry are teaching institutions with residents and fellows. Under the hemodynamic point of view our data show a good performance of all sizes of RDB (see Appendix). Overall mean trans-valvular gradient at discharge was 11 mmHg with an indexed aortic valve area of 1.12 cm2/m2. Looking at small valve sizes, 19 mm and 21 mm, we found at discharge a mean gradient of 14 mmHg and 11 mmHg, respectively. These values are consistent with those reported in the TRITON trial (6) and also by Theron et al (13) who reported mean gradients at 30 days for the 19 mm and the 21 mm RDB of 15 mmHg and 12 mmHg, respectively. We also found a good stability of hemodynamic parameters during follow up confirming the 5-year data analysis from the TRITON trial (14) that, although no splitting according to valve size was done, showed no variance of hemodynamic behavior of the Intuity valve over time. Furthermore, Martin and coll. (REF 15) found significant lower gradients in the Intuity valve if compared to its stented version, the Magna Ease valve (16 mmHg vs. 14 mmHg, p=0.025). A possible explanation of the improved hemodynamics with the rapid-deployment valves is the lack of pledget material obstructing the left ventricular outflow tract (LVOT) together with the LVOT expansion due to the ballon-expandable skirt. Since the Intuity valve has an anchoring and sealing system similar to that of the balloon-expandable transcatheter aortic valve, one of the main concerns regards the incidence of paravalvular leak (PVL). In fact, PVL has been demonstrated to have a significant impact on patients’ survival in TAVR populations (16). In our analysis, we observed significant intraoperative PVL that required repositioning of the RDB in 4 cases and implantation of a new device in 12 cases. In our experience, one of the most common causes of severe PVL after Intuity implantation is wrong valve sizing: a smaller valve will not provide a proper annular sealing, a bigger valve will not fit into the annulus and consequently pop-up towards the ascending aorta with the three tied guiding sutures that prevent it from true embolization. At discharge, we observed mild and moderate PVL in 8.2% and in 1.2% of patients, respectively. These PVL rates are lower than those reported for TAVR. In the

Sapien-3 high risk cohort of the PARTNER-2 trial authors report mild and moderate PVL rate of 29.1% and 2.7%, respectively (17) while data from the Sapien-3 European approval study report mild and moderate PVL in 17.2% and 1.1% of patients, respectively (18). The implantation technique of RDB includes leaflet removal and complete decalcification of the aortic annulus together with annular sizing under direct vision, exactly as for a conventional stented aortic bioprosthesis. Therefore, this is a possible explanation for the low rate of PVL detected after Intuity implantation. Furthermore, the possibility to intraoperatively check valve function and positioning with trans-esophageal echocardiography and to intervene in case a significant PVL is found, as demonstrated by our registry, is a potential advantage of RDB over TAVR. The Intuity balloon-expandable stent that inflates into the left ventricular outflow tract generates high radial forces that may interfere with the conduction tissue generating rhythm disturbances after surgery. Our data show the need for a permanent pace-maker implantation in 6.9% of patients. This rate is consistent to the 7% found in the TRITON trial (6) but lower than the 11% reported in the TRANSFORM trial (10). In patients undergoing surgical aortic valve replacement the pace-maker rate ranges between 3% and 11% (19); in the surgical cohort of the PARTNER 2A trial, in patients at intermediate risk undergoing SAVR, the incidence of postoperative pace-maker implantation was 7.9% (20). Therefore, the real impact of RDB on postoperative conduction disturbances requiring the implantation of a pace-maker should be still assessed. However, the postoperative need for a pace-maker after Intuity implantation compares favorably with TAVR that has a reported rate that ranges between 6% and 30% (21-23). This can be easily explained by the complete decalcification of the aortic annulus with consequent no dislodgment of bulky calcification during stent expansion (that happens during TAVR) and also because there is no need for valve oversizing in RDB implantation with consequently less compression on the left ventricular outflow tract.

Limitations

The limitations of this study are mainly related to its retrospective nature. The number of patients operated on at each center was heterogeneous, ranging from 4 to 189. There is no Adverse Event Adjudication Committee nor echo core-lab, therefore adverse events were self-adjudicated. Echocardiographic examinations were done by different physicians using different machines.

Conclusions

Rapid deployment bioprostheses are a useful tool in the already rich portfolio of devices available for the treatment of patients suffering from severe symptomatic aortic valve stenosis. According to the INTU-ITA registry data, the Intuity valve provides good early and mid-term outcomes in terms of survival, device success, valve-related adverse events and hemodynamic performance. Preoperative conduction disturbances and a history of previous myocardial infarction were identified as independent predictors of mortality.

DISCLOSURES

Dr. Augusto D'Onofrio is a physician TAVR proctor for Edwards Lifesciences and for Symetis

REFERENCES

1. Wahlers TCW, Haverich A, Borger MA, et al. Early outcomes after isolated aortic valve replacement with rapid deployment aortic valve. J Thorac Cardiovasc Surg 2015;151:1639-1647.

2. Thourani VH, Suri RM, Gunter RL, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg 2015;99:55-61.

3. Nishimura RA, Otto CM, Bonow RO, et al.; American College of Cardiology; American College of Cardiology/American Heart Association; American Heart Association. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary. Circulation. 2014;129:1-96.

4. Borger MA, Moustafine V, Conradi L, et al. A randomized multicenter trial of minimally invasive rapid deployment versus conventional full sternotomy aortic valve replacement. Ann Thorac Surg 2015;99:17-25.

5. Shrestha M, Folliguet T, Meuris B, et al. Sutureless Perceval S aortic valve replacement: a multicenter, prospective pilot trial. J Heart Valve Dis 2009;18:698-702.

6. Kocher AA, Laufer G, Haverich A, et al. One-year outcomes of the surgical treatment of aortic stenosis with a next generation surgical aortic valve (TRITON) trial: a prospective multicenter study of rapid-deployment aortic valve replacement with the EDWARDS INTUITY Valve System. J Thorac Cardiovasc Surg 2013;145:110-116.

7. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734-744.

8. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endopoint definitions for transcatheter aortic valve implantation: The Valve Academic research Consortium-2 consensus document. J Thorac Cardiovasc Surg 2013;145:6-23.

9. Phan K, Tsai YC, Niranjan N, et al. Sutureless aortic valve replacement: a systematic review and meta-analysis. Ann Cardiothorac Surg 2015;4:100-111

10. Barnhart GR, Accola KD, Grossi EA, et al., on behalf of the TRANSFORM Trial Investigators. TRANSFORM (Multicenter Experience With Rapid Deployment Edwards INTUITY Valve System for Aortic Valve Replacement) US clinical trial: performance of a rapid deployment aortic valve. J Thorac Cardiovasc Surg. 2016;153:241-251.

11. Salis S, Mazzanti VV, Merli G, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. J Cardiothorac Vasc Anesth 2008;22:814-822.

12. Al-Sarraf N, Thalib L, Hughes A, et al. Cross-clamp time is an independent predictor of mortality and morbidity in low- and high-risk cardiac patients. Int J Surg 2011;9:104-109.

13. Theron A, Garoboldi V, Grisoli D, et al. Rapid deployment of aortic bioprosthesis in elderly patients with small aortic annulus. Ann Thorac Surg 2016;101:1434-1442.

14. Laufer G, Haverich A, Andreas M, et al. Long-term outcomes of a rapid deployment aortic valve: data up to 5 years. Eur J Cardiothorac Surg 2017;52:281-287.

15. Andreas M, Wallner S, Habertheuer A, et al. Conventional versus rapid-deployment aortic valve replacement: a single-centre comparison between the Edwards Magna valve and its rapid-deployment successor. Interact Cardiovasc Thorac Surg. 2016;22:799-805.

16. Kodali SK, Williams MR, Smith CR, et al.; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366:1686-1695.

17. Herrmann HC, Thourani VH, Kodali SK, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. Circulation 2016;134:130-140.

18. Vahanian A, Urena M, Walther T, et al. Thirty-day outcomes in patients at intermediate risk for surgery from the SAPIEN 3 European approval trial. Eurointervention 2016;12:e235-e243.

19. Matthews IG, Fazal IA, Bates MG, Turley AJ. In patients undergoing aortic valve replacement, what factors predict the requirement of permanent pacemaker implantation? Interact Cardiovasc Thorac Surg 2011;12:475-479.

20. Thourani VH, Forcillo J, Szeto WY, et al. Outcomes in 937 intermediate-risk patients undergoing surgical aortic valve replacement in PARTNER 2A. Ann Thorac Surg 2017 doi: 10.1016/j.athoracsur.2017.10.062.

21. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohn-Ioser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. J Cardiovasc Electrophysiol 2012;23:391-397.

22. Ledwoch J, Franke J, Gerckens U, Kuck KH, Linke A, Nickenig G, et al. Incidence and predictors of permanent pacemaker implantation following transcatheter aortic valve implantation: analysis from the German transcatheter aortic valve interventions registry. Catheter Cardiovasc Interv. 2013;82:e569-e577.

23. Siontis GC, Jünu P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. J Am Coll Cardiol 2014;64:129-140.

TABLES

Table 1, Preoperative variables

Variables	Patients (n= 902)
Gender	
Females,n(%)	454(50.3)
Males,n(%)	448(49.7)
Age, years	74±7.7
Arterial Hypertension,n(%)	717(79.5)
Dyslipidemia,n(%)	450(49.9)
Diabetes Mellitus,n(%)	202(22.3)
Insulin dependent,n(%)	56(6.2)
Serum creatinine, mg/dl	1.04±0.72
Serum creatinine ≥ 2 mg/dl,n(%)	16(1.8)
Glomerular Filtration Rate (ml/min/1.73)	68.4±25.4
Glomerular Filtration Rate ≤ 50 ml/min/1.73,n(%)	168(18.6)
Chronic Dialysis,n(%)	4(0.4)
Peripheral Vascular Disease,n(%)	143(15.9)
Chronic Obstructive Pulmonary Disease,n(%)	115(12.8)
Neurological Dysfunction,n(%)	24(2.7)
Previous Cardiac Surgery n(%)	47(5.2)
Aortic valve replacement,n(%)	21(2.3)
CABG,n(%)	9(1.0)
Mitral replacement/repair,n(%)	(0.8)
Aortic valve and root replacement,n(%)	3(0.3)
Valve-sparing,n(%)	2(0.2)
Ascending aortic replacement,n(%)	1(0.1)
Subaortic membrane resection,n(%)	1(0.1)
Aortic valve and ascending aortic replacement,n(%)	1(0.1)
Aortic valve replacement and CABG,n(%)	1(0.1)
Balloon aortic valvuloplasty,n(%)	1(0.1)

Previous Acute Myocardial Infarction	28(3.1)
< 90 days,n(%)	49(5.4)
≥ 90 days,n(%)	
History of Coronary Artery Disease,n(%)	315(34.9)
Cardiac Rhythm	
Sinus Rhythm,n(%)	757(83.9)
Permanent Atrial Fibrillation,n(%)	88(9.8)
Paroxysmal Atrial Fibrillation,n(%)	27(3.0)
Pace-maker,n(%)	30(3.3)
New York Heart Association Functional Class	
Class I,n(%)	69(7.6)
Class II,n(%)	400(44.4)
Class III,n(%)	395(43.8)
Class IV,n(%)	38(4.2)
Logistic EuroScore	8.0±8.1
EuroScore II	3.0±3.1
STS-PROM	2.4±1.8

Table legend: CABG = coronary artery bypass grafting; STS-PROM: The Society of Thoracic Surgeons-Predicted Risk of Operative Mortality

Table 2. Preoperative echocardiographic data

Variable	Patients- (n = 902)
Peak aortic gradient, mmHg	78±24
Mean aortic gradient, mmHg	49±15
Indexed aortic valve area, cm^2/m^2	0.43±0.12
Aortic regurgitation	
Mild,n(%)	276(30.6)
Moderate,n(%)	134(14.9)
Severe,n(%)	60(6.7)
Left ventricle ejection fraction,%	59±10

Table 3. Operative variables

Variables	Patients (n = 902)
Prosthesis type	
Intuity,n(%)	265(29.4)
Intuity Elite,n(%)	637(70.6)
Prothesis diameter	
19 mm,n(%)	127(14.1)
21 mm,n(%)	283(31.4)
23 mm,n(%)	271(30.0)
25 mm,n(%)	169(18.7)
27 mm,n(%)	52(5.8)
Surgical access	
Full-sternotomy,n(%)	540(59.9)
Mini-sternotomy,n(%)	342(37.9)
Mini-thoracotomy n(%)	20(2.2)
Combined procedures,n(%)	310(34.4)
CABG,n(%)	208(23.1)
Mitral replacement/repair,n(%)	32(3.5)
Ascending aortic replacement,n(%)	15(1.7)
Others,n(%)	55(6.1)
Cardiopulmonary bypass time, minutes	90(70-120)
Isolated AVR	83(65-103)
Full-sternotomy	81(65-100)
Mini-sternotomy	82(64-102)
Mini-thoracotomy	116(90-158)
Combined procedures	120 (90-145)
Aortic cross-clamping time, minutes	64(50-95)
Isolated AVR	57(45-73)
Full-sternotomy	56(45-71)
Mini-sternotomy	58(45-73)
Mini-thoracotomy	80(68-112)
Combined procedures	86(67-108)

Table legend. AVR = aortic valve replacement; CABG = coronary artery bypass grafting.

Table 4. Intraoperative complications

Intraoperative complications	Patients (n = 902)
VARC Device Success,n(%)	865(95.9)
No device success	37(4.1)
Immediate procedural mortality (≤ 72 hours from the procedure)	8(0.9)
Not correct positioning of a single prosthesis (without death)	16(1.8)
Not intended performance of the prosthetic valve	13(1.4)
Moderate PVL	10(1.1)
Mean gradient >20 mmHg	3(0.3)
Significant paravalvular regurgitation,n(%)	18(2.0)
PVL closure with extra annular stitches	*2(0.2)*
Prosthesis repositioning	*4(0.5)*
Prosthesis replacement,n(%)	*12(1.3)*
New Intuity prosthesis,n(%)	*2(0.2)*
Stented prosthesis,n(%)	*10(1.1)*
Full-sternotomy conversion,n(%)	10(2.8)
(362 minimally invasive approaches)	
IABP,n(%)	3(0.3)
ECMO,n(%)	1(0.1)
Aorto-ventricular junction rupture,n(%)	*1(0.1)*
Brachiocephalic artery lesion,n(%)	*1(0.1)*
Aortic root injury and urgency right coronary CABG n(%)	*1(0.1)*
Left atrial lesion,n(%)	*1(0.1)*

Table legend. CABG = coronary artery bypass grafting; ECMO = extra-corporeal membrane oxygenation; IABP = intra-aortic balloon pump; PVL= Paravalvular regurgitation; VARC = valve academic research consortium.

Table 5. Postoperative outcomes

Variables	Patients (n = 902)
ICU stay, hours	48(24-72)
Hospital stay, days	8(7-11)
VARC all-cause mortality,n(%)	25(2.8)
VARC cardiovascular mortality,n(%)	20(2.2)
VARC acute myocardial infarction,n(%)	5(0.6)
VARC major stroke,n(%)	7(0.8)
VARC life-threatining bleeding,n(%)	54(6.0)
Pace-maker implantation,n(%)	63(6.9)
New onset atrial fibrillation,n(%)	268(29.7)
VARC Acute kidney injury,n(%)	58(6.4)
Stage 1,n(%)	10(1.1)
Stage 2,n(%)	18(2.0)
Stage 3,n(%)	30(3.3)

Table legend: ICU = intensive care unit; VARC = valve academic research consortium.

Table 6. Echocardiographic data at discharge

Variables	Patients discharged with Intuity prosthesis (n=869)
Peak aortic gradient, mmHg*	19±7
Mean aortic gradient, mmHg**	11±4
Indexed aortic valve area (cm^2/m^2)***	1.12±0.34
Patient-prosthesis mismatch (EOAi ≤0.85)***	57(18.4%)
Severe patient-prosthesis mismatch (EOAi <0.65)***	7(2.3%)
Aortic regurgitation	
mild	71(8.2)
moderate	10(1.2)
severe	0(0)
Left ventricle ejection fraction, %	59±10

*745 patients

**789 patients

***310 patients

Table 7. Echocardiographic data according to valve size

	19 mm (n =127)	**21 mm (n = 276)**	**23 mm (n = 268)**	**25 mm (n = 169)**	**27 mm (n = 52)**
Indexed aortic valve area, cm^2/m^2					
Baseline(n=621)	0.43±0.12	0.43±0.11	0.43±0.11	0.43±0.12	0.43±0.12
Discharge(n=310)	0.83±0.14	0.98±0.27	1.16±0.36	1.20±0.33	1.32±0.33
1-year follow-up(n=146)	0.84±0.20	0.96±0.22	1.10±0.31	1.27±0.36	1.24±0.26
2-year follow-up(n=25)	1.00±0.05	1.09±0.23	1.29±0.48	1.27±0.45	1.21±0.23
3-year follow-up(n=59)	1.00±0.16	1.07±0.26	1.10±0.22	1.20±0.24	1.10±0.25
4-year follow-up(n=40)	1.01±0.21	1.11±0.19	1.05±0.25	1.23±0.12	-
Mean transvalvular gradient, mmHg					
Baseline(n=853)	50±15	50±16	48±16	46±13	45±16
Discharge(n=789)	14±5	11±4	10±4	9±3	9±3
1-year follow-up(n=323)	13±4	10±4	10±4	8±3	8±3
2-year follow-up(n=74)	11±5	9±3	9±5	9±3	6±1
3-year follow-up(n=74)	11±4	8±4	7±2	8±3	8±4
4-year follow-up(n=45)	9±4	9±5	6±2	5±2	-
Peak transvalvular gradient, mmHg					
Baseline(n=820)	83±25	82±25	76±22	74±21	70±26
Discharge(n=745)	24±8	20±7	18±7	16±6	16±5
1-year follow-up(n=308)	22±7	19±6	18±6	15±5	15±6
2- year follow-up(n=72)	20±9	15±5	17±8	17±5	11±3
3-year follow-up(n=73)	19±5	14±5	12±4	16±6	17±5
4-year follow-up(n=40)	16±5	13±4	12±4	12±5	

Table 8. Clinical outcomes at follow-up

Variables	Patients (n = 877)
All-cause late mortality	50(5.7)
Cardiovascular mortality	31(3.5)
Hemorrhage	3(0.3)
Thrombo-embolism	7(0.8)
Stroke	5(0.6)
Acute myocardial infarction	5(0.6)
Heart failure	13(1.5)
Arrhythmia	10(1.1)
Endocarditis	4(0.5)
Reoperation for endocarditis	1(0.1)
Reoperation for aortic regurgitation	3(0.3)
Late pace-maker implantation	11(1.3)

FIGURE LEGEND

Figure 1: Kaplan-Meier survival of the INTU-ITA population

Figure 2: Indexed aortic valve area and mean gradients trends according to valve size

Figure 3: NYHA class before surgery and at follow-up