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Transcatheter Aortic Valve Implantation in Patients with Age ≤70 Years: Experience from Two Leading Structural Heart Disease Centers

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ABSTRACT

BACKGROUND: Transcatheter aortic valve implantation (TAVI) is emerging a an appealing management strategy for patients with severe aortic stenosis at intermediate, high or exceedingly high risk, but its risk-benefit profile in younger patients is less certain. We aimed at exploring the outlook of patients aged 70 years or less and undergoing TAVI at 2 high-volume Italian institituions.

METHODS: We retrospectively collected baseline, imaging, procedural and outcome features of patients with age ≤70 years in whom TAVI was attempted at participating centers between 2012 and 2021. Non-parametric tests and bootstrap resampling were used for inferential purposes.

RESULTS: A total of 39 patients were included, out of >3,000 screened with heart team involvement and >1,500 receiving TAVI. Most common or relevant indications for TAVI were reduced life expectancy (eg cardiogenic shock or severe left ventricular systolic dysfunction), chronic obstructive pulmonary disease, morbid obesity, active or recent extra-cardiac cancer, porcelain aorta, neurologic disability, cirrhosis, or prior surgical aortic valve replacement, as well as extreme cachexia, and Hutchinson-Gilford progeria. At least two contemporary high-risk features were present in most cases. Transapical access was used in 5 (12.8%) cases, and a sheathless approach in 15 (38.5%). A variety of devices were used, including both balloon- and self-expandable devices. Clinical outcomes were satisfactory, despite the high risk profile, at both short- and mid-term, with no in-hospital death, and 5.1% (95% confidence interval 0-12.8%) mortality at a median follow-up of 15 months (minimum 1; maximum 85). Notably, no case of significant valve deterioration requiring reintervention occurred.

CONCLUSIONS: In carefully selected patients with 70 years or less of age and prohibitive risk for surgery or reduced life expectancy, TAVI represents a safe option with a favorable mid-term survival and low rate of adverse events.

KEY-WORDS

Age; Aortic stenosis; Transcatheter aortic valve implantation; Transcatheter aortic valve replacement

ABBREVIATIONS

AR: Aortic regurgitation

AS: Aortic stenosis

COPD: Chronic Obstructive Pulmonary Disease

ECMO: Extracorporeal membrane oxygenator

EuroSCORE: European System for Cardiac Operative Risk Evaluation

LVEF: Left ventricular ejection fraction

NYHA: New York Heart Association

RCT: Randomized controlled trial

SAVR: Surgical aortic valve replacement

TAVI: Transcatheter aortic valve implantation

TAVR: Transcatheter aortic valve replacement

THV: Transcatheter heart valve

VARC-3: Valve Academic Research Consortium-3

INTRODUCTION

Transcatheter valve technology is an area of uniquely intense research and clinical implementation, also given the prevalence of valve disease, such that its management has been revolutionized in the last two decades, thanks for instance to the introduction of transcatheter aortic valve implantation (TAVI), also labelled transcatheter aortic valve replacement (TAVR), and transcatheter mitral valve repair (TMVR).the most advanced innovation of cardiovascular surgery and it has rapidly evolved to become a standard of care for patients affected by aortic valve disease.(1-4)

While TAVI was first conceived and tested as a means to treat patients with prohibitive surgical risk, it eventually proved risk- and cost-equivalent (if not beneficial) also in carefully selected patients at high or intermediate surgical risk.(2,4-10) Evidently, TAVI is associated with lower morbidity in comparison to surgical aortic valve replacement (SAVR), but it is fraught with an increased risk of residual aortic regurgitation (mainly due to paravalvular leak) and permanent pacemaker implantation.(11-12) Most importantly, there is uncertainty on the long-term durability of TAVI, as available studies are limited to early generation devices or have follow-up reaching 10 years or less.(1) Accordingly, the risk-benefit and effectiveness profile of TAVI in younger patients is a matter of intense debate.

In patients in whom SAVR with a biological prosthesis is envisioned, the equipoise between TAVR and SAVR appears possibly more likely, despite the paucity of data on TAVI in younger patients, with most reports stemming from TAVI units.(13-14) Actually, Expanding the transcatheter solution to low-risk patients poses the great challenge of the treatment of young patients with aortic stenosis. Furthermore, there is still lack of international and high-quality (ie stemming from randomized trials) evidence regarding the use of TAVI strategy in patients aged less than 70 years old, given that the mean age of patients enrolled in available clinical trials is typically well over 70 years.(15-16)

Thus, we aimed to report the early and late outcome of our institutional experience regarding the clinical application of TAVI in patients aged 70 years or less, highlighting the most common and

appropriate clinical scenarios, as well as the decision-making process to safely and efficiently carry out TAVI in such unique patient subset.

METHODS

Patients with 70 years or less of age undergoing TAVI at our institutions between 2012 and 2021 were retrospectively identified from our institutional databases. Ethics committee approval was obtained as appropriate, as was written informed consent.

Baseline features were adjudicated with particular focus on reasons for high or prohibitive surgical risk, as well as absolute contraindications to surgery. These potentially included severe obesity or cachexia, myelodysplasia, cancer, end-stage pulmonary failure due to chronic obstructive pulmonary disease (COPD), advanced cirrhosis in waiting list for liver transplant, progeria, or prohibitive results at quantitative estimation of surgical risk.(17) Baseline imaging was performed as per institutional expertise, collecting systematically details on aortic valve gradients and regurgitation, as well as left ventricular ejection fraction (LVEF). In addition, details on baseline pharmacologic therapy were sought from all patients.(18) Notably, indications were based on thorough appraisal of surgical and procedural risk, as well as subsequent life expectancy, factoring also procedural details and planning.(19-20) Both EuroSCORE II and Society (STS) scores were computed.(21)

Procedures were performed by either transfemoral or transapical access, using any of the locally and commercially available devices for TAVI as per pertinent time period. While balloon-expandable TAVI devices (eg Sapien, Edwards Lifesciences, Irvine, CA, USA) were preferentially used in one institution, self-expandable devices were preferentially used on the other center (most commonly Evolut, Medtronic, Minneapolis, MN, USA, and Portico, Abbott Vascular, Santa Clara, CA, USA), but also Acurate (Boston Scientific, Natick, MA, USA).(22-23) Hemostasis was achieved with either Prostar XL or Perclose Proglide (Abbott Vascular).

Clinical follow-up was performed as per routine practice at each participating institution, with in person visits or phone contacts, as well as periodic (every 1-6 months) transthoracic echocardiography, with serial assessments for LVEF, aortic valve gradients, aortic regurgitation,

and ancillary findings. Clinical and imaging outcomes were formally adjudicated according to currently sanctioned definitions.(24)

In particular, as endpoints of interest we collected details on death, stroke, myocardial infarction, bleeding (distinguished in type 1, 2, 3, and 4), reintervention (balloon aortic valvuloplasty, repeat TAVI or SAVR), access site complication (distinguished as major vascular complication, minor vascular complication, major non-vascular complication, and minor non-vascular complication), permanent pacemaker implantation, and New York Heart Association (NYHA) class.

Descriptive analysis was based on median (minimum; maximum), and count (%). Inferential analysis was based on percentile boostrapping (1000 replications), providing eventually 95% confidence intervals. Computations were performed with Stata 13 (StataCorp, College Station, TX, USA).

RESULTS

Out of a total of >3,000 screened patients and >1,500 TAVI cases, 39 subjects aged 70 years or less underwent TAVI between 2012 and 2021 (Table 1)(Figure 1). Specifically, there were 20 (51.3%) women, and the most common indication was severe aortic stenosis. Several absolute or relative contraindications to surgery were evident in most patients, even when standard surgical risk score appeared uninformative. Indeed, main reasons that influenced heart team decision beyond the risk score mortality estimation included cardiogenic shock (with two patients undergoing TAVI during extracorporal membrane oxygenation support), severe left ventricular dysfunction, severe chronic obstructive pulmonary disease, morbid obesity, active or recent extra-cardiac cancer, end-stage cirrhosis waiting transplantation, and rare disease as Hutchinson-Gilford progeria. Notably, at least two contemporary factors were present in most case, and in some patients several multiple contraindications were present.

Bicuspid aortic valve disease was recognized in 2 (5.1%) subjects (Table 2), with severe aortic or mitral regurgitation in, respectively, 4 (10.3%) and 2 (5.1%). Transfemoral access was chosen in 34 (87.2%) cases, with transapical access being preferred in 5 (12.8%), mainly in the early TAVI experience of one institution, and for two cases of genetic vasculopathy (Marfan disease and progeria). A variety of devices was used, ranging, in decreasing order, from Portico/Navigator to Sapien/Sapien 3/Sapien 3 Ultra, Evolut/Evolut R/Evolut Pro, and Acurate. Eventually, procedural success was achieved in all patients (with device success in all but 1 case which required intra-procedural valve-in-valve), with a median length of stay of 6 days, and no in-hospital death.

Clinical and imaging follow-up was available in all patients, with a median of 15 months (minimum 1; maximum 85)(Table 1). Death occurred in two patients (5.1% [95% confidence interval: 0-12.2%]), with cardiovascular death in one (2.6% [0-7.6%]). Non-fatal complications were uncommon, and were limited to one major acces-site vascular complication (2.6% [0-7.6%]), 6 permanent pacemaker implantations (15.4% [4.1%-26.7%]), and one rehospitalization (2.6% [0-7.6%]). Imaging follow-up confirmed, as expected, the favorable results achieved acutely, including

appraisal of LVEF, aortic valve gradients, mitral regurgitation, and systolic pulmonary artery pressure.

DISCUSSION

Despite ongoing refinements and favorable early and long-term data, the still uncertain on the very long-term durability of transcatheter aortic valve prostheses, as well as the implications of the high incidence of new pacemaker implantation and the possible need to to coronary arteries.(25) Thus, these and other issues still concern most practitioners envisioning the expansion of TAVI to younger and lower risk subjects, such that these are highly relevant argument during heart team discussions, and when weighing feasibility and futility.(26-27) Recent European and American guidelines recommend to consider TAVI over SAVR in intermediate or high-risk patients with advanced age, but for younger patients SAVR still remains the preferred therapy.(28-30) This is useful input, but still patients and decision-makers need to recognize the lack of high-quality evidence stemming from randomized trials focusing on young patients with severe aortic stenosis who are not at increased surgical risk.

Indeed, the aim of the present analysis was to report our experience in the treatment of patients aged less than 70, in order to clarify the clinical scenario that is associated with the therapeutic indication and reporting early and late outcome. We collected data from a relatively ample cohort of 39 patients who were denied for surgery by the local heart teams, and underwent TAVI over almost 10 years. Our results showed optimal early safety of the TAVI procedure with durable clinical and echocardiographic results over time. Most interestingly, in our experience the risk estimation through the conventional scores had to be complemented by a comprehensive and multidisciplinary clinical evaluation of each patient by the heart team, as well as ancillary specialists. Notably, clinical factors such as porcelain aorta, cardiogenic shock, active or recent cancer, liver disease, severe chronic obstructive pulmonary disease, severe obesity or presence of rare genetic disease played a special role in the therapeutic indication.(31) Indeed, most of our patients had a low surgical risk score at face value, but they were anyhow judged not operable for associated factors demonstrating that there is often a significant discordance between heart team assessment and conventional risk scoring in these young individuals.

Focusing on external validity, to the best of our knowledge, a limited number reports of the current medical literature analyzed this patient population, and very few focusing on Italy. For instance, Tarantini and coauthors recently reported the factors influencing decision making and the outcome of patients younger than 80 years old from the OBSERVANT Study.(32) Out 4801 patients included in the sub-study, 4318 were treated by SAVR vs 483 by TAVI. In this study, a subgroup of 23 TAVR patients were aged less than 65. These patients exhibited the highest preoperative risk profile and showed an increased all-cause mortality at 5 years when compared either with conventional surgery or with TAVI in other ages groups (65-74 or 75-79). In consistence with the results presented in our series, the main predictors of indication for TAVI were previous cardiac surgery, porcelain aorta, oxygen dependency, need for dialytic treatment, and moderate– severe frailty score.

The AQUA registry compared with a propensity matched analysis 1388 pairs of patients treated with SAVR and TAVI in the age span from 65 to 74 years old.(33) In a propensity matched analysis, rates of in-hospital mortality, stroke/transient ischemic attack, and myocardial infarction were not different after TAVI or SAVR. Yet, postoperative delirium was more frequent after SAVR, while the need for permanent pacemaker implantation was higher after TAVI. Notably, frailty, high surgical risk, limited life expectancy, malignancy porcelain aorta, and patient preferences were the main factors associated with heart team decision to select TAVI in this work as well as in similar ones.(34-35)

In light of our work and similar ones, we can infer that the application of TAVI even in younger patients is reasonable and safe with encouraging results at mid-term follow-up. We observed an extremely low rate of perioperative adverse events even though this factor may be associated with the small patient population. Moreover, data from our study explained once again that heart team evaluation represents a key step in the decision-making process and that conventional risk scores calculator are still not enough to classify a patient in a realistic risk profile. Furthermore, our work reinforces the need to consider both TAVI and SAVR in a continuum of care, with the provision of

intensive and aggressive medical therapy (including a post-procedural rehabilitation program), crucial to achieve excellent early and long-term outcomes.(TAKAGI_MCA_2021)

Despite these encouraging results, longer term data are necessary, as well as larger observational studies. Moreover, it is crucial to secure funding and conduct one or more large multicenter randomized trials capable of testing formally the early as well as the long-term safety and effectiveness of TAVR in comparison to SAVR and/or conservative management in young patients (with evidently the latter favored as comparator of interest when surgical risk is prohibitive). While awaiting the peer-reviewed publication of the results of such studies, we can expect a slow but progressive expansion of TAVI to relatively younger patients at prohibitive surgical risk (at first), and then to subjects at high as well as, possibly, intermediate risk. The key question is whether low surgical risk patients should ever be offered, when, and how, TAVI instead of SAVR with a biological prosthesis. Indeed, another piece of the puzzle is the continuous evolution of devices and procedures, for both TAVI and SAVR, such that what holds true now may not be valid in 3-5 years (and this argument is even more valid if inferences stem from data from the distant past) (17) .

This two-center series, while promising, has many limitations, including the small size, limited follow-up, and, evidently, lack of a comparator. Furthermore, clinical and imaging endpoints were analyzed based on hospital and ambulatory chart review, without exploiting standardized case forms, external core labs, or blinded adjudication forms. Accordingly, further works are needed to confirm our findings, notwithstanding that even larger observational studies would have limited inferential impact.

In conclusion, even if surgery remains the gold standard for patients aged <75 years with severe aortic stenosis, we can state that according to our data TAVI may be considered when specifical conditions are present and after thorough heart team discussion and involvement of patients and referring physicians. Clearly, larger series and randomized data are mandatory to confirm these findings, clarify indications and refine patient selection criteria.

KEY MESSAGES

- Transcatheter aortic valve implantation may be recommended after heart team appraisal in patients with severe aortic valve disease in roughly 1% of total cases
- Most of these patients will have two or more major contraindications to cardiac surgery
- Irrespectively, in carefully selected patients with 70 years or less of age and prohibitive risk for surgery or reduced life expectancy, TAVI represents a safe option with a favorable mid-term survival and low rate of adverse events

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Table 1. Baseline features.

Feature	Median or count (%)	Minimum	Maximum
Patients	39 (100%)	-	-
Age (years)	68	23	70
Age ≤65 years	11 (28.2%)	-	-
Female sex	20 (51.3%)	-	-
Weight (kg)	80	20	130
Height (cm)	165	138	176
Body mass index (kg/m^2)	29	11	42
Body surface area (m^2)	1.93	0.91	2.41
Indication			
Severe aortic stenosis	26 (66.7%)	-	-
Severe aortic regurgitation	4 (10.3%)	-	-
Mixed aortic disease	9 (23.1%)	-	-
Surgical risk			
Intermediate	13 (33.3%)	-	-
High	16 (41.0%)	-	-
Inoperable	10 (25.6%)	-	-
Hostile chest	3 (7.7%)	-	-
Neurologic disability	6 (15.4%)		
Cancer	4 (10.3%)		
Cirrhosis	5 (12.8%)		
Chronic renal failure	5 (12.8%)		
Chronic obstructive pulmonary disease	11 (28.2%)	-	-
Porcelain aorta	2 (5.1%)		
Genetic syndrome	2 (5.1%)		
Diabetes mellitus	10 (25.6%)	-	-
Dyslipidemia	22 (56.4%)	-	-
Hypertension	31 (79.5%)		
Peripheral artery disease	11 (28.2%)	-	-
Coronary artery disease	4 (10.3%)		
Prior myocardial infarction	4 (10.3%)	-	-
Prior stroke or transient ischemic attack	2 (5.1%)	-	-
Prior cardiac surgery	4 (10.3%)		
Prior coronary artery bypass grafting	2 (5.1%)		
Prior aortic valve surgery	3 (7.7%)		
EuroSCORE II	2.1	0.9	49.0
STS score	2.2	0.7	20.0
Hemoglobin (g/dL)	11.9	7.1	16.1
Serum creatinine (mg/dL)	1.1	0.6	5.3
Estimated glomerular filtration rate (mL/min/1.73 m^2)	63	12	104
New York Heart Association class			
I	0	-	-
II	17 (43.6%)	-	-
III	19 (48.7%)	-	-
IV	3 (7.7%)	-	-

Table 2. Imaging and procedural features.

Feature	Median or count (%)	Minimum	Maximum
Patients	39 (100%)	-	-
Left ventricular ejection fraction (%)	55	20	65
Bicuspid aortic valve disease	2 (5.1%)	-	-
Aortic valve area (cm^2)	0.58	0.40	0.84
Peak gradient (mm Hg)	75	27	100
Mean gradient (mm Hg)	45	10	97
Aortic regurgiation			
None, trace or mild	26 (66.7%)	-	-
Moderate or moderate-severe	9 (23.1%)	-	-
Severe	4 (10.3%)	-	-
Mitral regurgitation			
None, trace or mild	10 (25.6%)	-	-
Moderate or moderate-severe	27 (69.2%)	-	-
Severe	2 (5.1%)	-	-
Systolic pulmonary artery pressure (mm Hg)	48	35	60
Access			
Transapical	5 (12.8%)	-	-
Transfemoral	34 (87.2%)	-	-
Sheathless procedure	24 (61.5%)	-	-
Predilation	20 (51.3%)	-	-
Device type			
Accurate	1 (2.6%)	-	-
Evolut, Evolut R, Evolut Pro	11 (28.2%)	-	-
Portico, Navitor	14 (35.9%)	-	-
Sapien, Sapien 3, Sapien 3 Ultra	13 (33.3%)	-	-
Device size (mm)	26	20	29
Postdilation	14 (35.9%)	-	-
Device success	38 (97.4%)		
Procedural success	39 (100%)		
Total length of stay (days)	6	3	60

Table 3. Clinical and imaging follow-up.

Feature	Median or count (%)	Minimum	Maximum
Patients	39 (100%)	-	-
Follow-up	6	1	85
Death	2 (5.1%)	-	-
Cardiac death	1 (2.6%)	-	-
Stroke	0	-	-
Myocardial infarction	0	-	-
Bleeding			
Any	0	-	-
Type 1 bleeding	0	-	-
Type 2 bleeding	0	-	-
Type 3 bleeding	0	-	-
Access-site complication			
Any		-	-
Major access-site vascular complication	1 (2.6%)	-	-
Minor access-site vascular complication	0	-	-
Major access-site non-vascular complication	0	-	-
Minor access-site non-vascular complication	0	-	-
Amputation	0	-	-
Permanent pacemaker implantation	6 (15.4%)	-	-
Repeat transcatheter aortic valve replacement	0	-	-
Surgical aortic valve replacement	0	-	-
Rehospitalization	1 (2.6%)	-	-
New York Heart Association class			
I	14 (35.9%)	-	-
II	22 (56.4%)	-	-
III	3 (7.7%)	-	-
IV	0	-	-
Left ventricular ejection fraction (%)	57	30	65
Peak gradient (mm Hg)	14	6	34
Mean gradient (mm Hg)	10	3	23
Aortic regurgitation			
None, trace or mild	37 (94.9%)	-	-
Moderate or moderate-severe	2 (5.1%)	-	-
Severe	0	-	-
Para-valvular leak			
None, trace or mild	38 (97.4%)	-	-
Moderate or moderate-severe	1 (2.6%)	-	-
Severe	0	-	-
Mitral regurgitation			
None, trace or mild	18 (46.2%)	-	-
Moderate or moderate-severe	18 (46.2%)	-	-
Severe	3 (7.7%)	-	-
Systolic pulmonary artery pressure (mm Hg)	35	23	87

Figure 1. Graphical summary of key baseline, procedural, and outcome features among 39 patients undergoing transcatheter aortic valve implantation (TAVI). BE=balloon-expandable; PM=pacemaker implantation.

Authors contribution section

Marco Russo, Nicola Corcione, Antonio Giovanni Cammardella, Federico Ranocchi were responsible for study protcol and wrote the paper. Antonio Lio, Guglielmo Saitto, Francesca Nicolò, Amedeo Pergolini, Vincenzo Polizzi, Paolo Ferraro, Alberto Morello, Michele Cimmino, Michele Albanese, Luisa Nestola, were deputy for data collection and patient'sfollow-up. Giuseppe Biondi-Zoccai, Martino Pepe, Luca Bardi were supervisor and reviewed statistical analsysis. Arturo Giordano, Francesco Musumeci, were senior supervisor, reviewed the draft and perfomed conceptualization.

All authors read and approved the present paper.

TAVI IN PATIENTS WITH AGE ≤70 YEARS

Patient factors	Operative factors
Age	Expertise
Comorbidities	Technique
Risk scores	Device size
Life expectancy	Availability
Preferences	Reimbursement