Five-year outcome in 18,010 patients from the German Aortic Valve Registry

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One-sentence summary: TAVI patients are older and less healthy than sAVR patients, and even after taking these factors into account they have a higher 5-year mortality rate than sAVR patients.

Abstract

Aims: The 5-year outcome in patients undergoing isolated transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (sAVR) was evaluated from the German Aortic Valve Registry (GARY).

Methods and Results: Allocation to TAVI or sAVR was performed after a heart team decision. Eligible patients with TAVI and sAVR were matched using propensity scores in a nearest-neighbour approach.

A total of 18,010 patients treated in 2011 and 2012 were included (n=8,942 TAVI and n=9,068 sAVR). Patients with repeat procedures or unequivocal indication for one treatment option (e.g. frailty) were excluded (n=4,785 for TAVI and n=2 for sAVR). This led to 13,223 patients (4,157 TAVI and 9,066 sAVR) as an unmatched subcohort. TAVI patients were significantly older (80.9±6.1 versus 68.5±11.1 years, p<0.001), had a higher Society of Thoracic Surgeons (STS) score (6.3±4.9 versus 2.6±3.0, p<0.001) and a higher 5-year all-cause mortality (49.8% versus 16.5%, p<0.0001). There was no major difference in in-hospital stroke, in-hospital myocardial infarction, or temporary and chronic dialysis.

In the propensity score-matched group (n=3,640), there were 763 deaths (41.9%) among 1,820 TAVI patients compared with 552 (30.3%) among 1,820 treated with sAVR during the 5-year follow-up (HR 1.51; 95%CI 1.35-1.68; p<0.0001). New pacemaker implantation was performed in 448 patients (24.6%) after TAVI and in 201 (11.0%) after sAVR (p<0.0001).

Conclusion: The 5-year follow-up data show that TAVI patients were significantly older and had a higher STS score than sAVR patients. After propensity score matching, TAVI with early-generation prothesis was associated with significantly higher 5-year all-cause mortality than sAVR.

Keywords: Transcatheter aortic valve implantation • Surgical aortic valve replacement • Five-year follow-up • GARY • Low risk

Introduction

Transcatheter aortic valve implantation (TAVI) is one of the most important developments in cardiovascular medicine during recent years. Previous randomized controlled trials (RCTs) showed an advantage of TAVI in inoperable patients (1) and survival rates that were similar to those of high-risk patients treated by surgical aortic valve replacement (sAVR) (2). Further studies have evaluated the prognosis of patients with intermediate risk who underwent either TAVI or sAVR (3,4). Most recently, 1-year follow-up results from prospective RCTs comparing TAVI with sAVR in low-risk patients have been published (5,6), and, in parallel, 1-year all-comers registry data from GARY comparing TAVI with sAVR showed similar 1-year survival rates (7).

Despite the increasing use of TAVI worldwide, long-term outcome data from larger numbers of patients are not yet available, even though they are becoming more and more important for guiding heart team decisions. Data from prospective RCTs demonstrate that 5-year mortality after TAVI and sAVR are similar in patients with intermediate and high risk (5,8).

Whereas RCTs usually include highly selected patients, all-comers registry data may provide a better overview of daily clinical practice. Recently, 5-year outcomes of the Italian OBSERVANT study (9) were published for a real-world population of patients with severe aortic stenosis and low or intermediate risk. Higher rates of pacemaker implantation have been reported following TAVI than after sAVR (10), and a lower survival rate after 5 years in high-risk patients after TAVI than after sAVR has been published (9,11).

The aim of our study was to analyse 5-year outcome data from GARY for patients treated in 2011 and 2012. In addition to a descriptive characterization, we performed propensity score matching to compare long-term outcomes after TAVI versus sAVR in a selected subgroup. To the best of our knowledge, this is the largest reported series of the two treatment modalities with a 5-year follow-up.

Methods

GARY database

GARY was initiated in 2010 as a prospective, multicentre registry to enable data acquisition across a large patient population (12) with voluntary participation of each individual patient. Lack of informed consent by the patient is the only exclusion criterion. (For further details see Supplementary Appendix).

Study population and procedures

The study population consisted of 18,010 patients treated in 2011 or 2012 by TAVI (8,942) or isolated sAVR (9,068) at 92 sites in Germany with an in-hospital mortality of 5.3% or 1.9% (HR[95%CI] = 3.43% [2.88% to 3.97%]; p<0.0001), respectively. Excluded from the present analyses were patients with first-line indications for TAVI (and who were not eligible for sAVR) such as frailty, re-do procedure, very high risk, prognosis-limiting secondary disease, porcelain aorta, and incurable malignancy, resulting in an unmatched cohort of 13,223 patients (Figure 1). Surgical and transcatheter procedures were carried out according to practice that was standard for 2011/2012.

Clinical endpoints

Survival at 5 years was the primary endpoint. Periprocedural complications, including in-hospital stroke, in-hospital myocardial infarction (MI), and the need for temporary or chronic dialysis or new pacemaker implantation were defined as secondary endpoints. (For further details see Supplementary Appendix)

Ethical considerations

The study complies with the Declaration of Helsinki. Subjects included in the registry gave informed consent, and an ethics body at participating institutions approved the use of patient data for research purposes.

Statistical methods

A total of 3,640 patients (20.2%) with isolated aortic valve procedures were matched according to propensity score (n=1,820 in each group). The propensity scores were constructed using a conventional logistic regression model, and the propensity score was the fitted value from the model for the subject likelihood of undergoing TAVI on the logit scale. Subjects were matched using a nearest-neighbour approach with a tight calliper (0.01 on the logit scale) and the gmatch macro (13). (For further details see Supplementary Appendix)

Results

Unmatched patient population

A total of 4,157 TAVI and 9,066 sAVR patients were analysed according to the preoperative characteristics. There were significant differences in all baseline characteristics. TAVI patients were significantly older (80.9 ± 6.1 versus 68.5 ± 11.1 years, p<0.0001) and had a higher Society of Thoracic Surgeons (STS) score (6.3 ± 4.9 versus 2.6 ± 3.0, p<0.0001). The prevalence of cardiac and non-cardiac comorbidities was much higher among TAVI patients than sAVR patients. Further baseline characteristics are given in Table 1. Of the 4,157 TAVI patients, 3,031 (72.9%) were treated by the transfemoral and 1,059 (25.5%) by the transapical route.

There were no major differences in the rate of major in-hospital complications. In the TAVI group 66 patients had a stroke (1.6%), 18 had an MI (0.4%), and 108 patients needed permanent dialysis (2.6%). In the sAVR group the incidence of stroke (N=97, 1.1%), MI (N=38, 0.4%), and permanent dialysis (N=110, 1.2%) was similar. The rate of new pacemaker implantation was significantly higher (p<0.0001) for TAVI (N=1,165, 28.0%) than for sAVR (N=594, 6.6%) patients.

In the unmatched group, both in-hospital mortality of TAVI (5.1%, 212/4,157) vs. sAVR patients (1.9%, 169/9,066), and the 5-year mortality of TAVI (49.8%, 2,074/4,157) vs. sAVR patients (16.5%, 1,494/9,066) showed a significant difference (p< 0.0001).

Matched patient cohort

Propensity score matching of 4,157 TAVI and 9,066 sAVR patients resulted in an excellent match of 1,820 patients in each group (20.2% of the entire study population). Table 1 shows the baseline characteristics of the patient cohorts (total and matched), and Table S1 shows the characteristics of the patients for whom a match was not achieved. All baseline characteristics were candidate explanatory variables in the propensity score matching procedure. Within the matched cohort, 94.1% (1,712/1,820) of TAVI patients and 95.6% (1,741/1,820) of sAVR patients completed 4 years and 11 months of follow-up, and only 1.6% (57/3,640) were followed up for less than 2 years.

All variables were highly significantly different in the unmatched cohorts (Table 1). After performing the propensity score matching, there was a good matching of all the variables between the 1,820 paired patients in each group, including for age and for important prognostic markers such as the STS score, left ventricular ejection fraction, mitral and tricuspid regurgitation >2°, and previous ICD/pacemaker. There was further no difference between in-hospital mortality, in-hospital stroke, in-hospital MI, or temporary or chronic dialysis for TAVI and sAVR patients (Table 2). A total of 329 (18.1%) patients treated with TAVI needed new permanent pacemaker implantation, whereas 83 (4.6%) needed a new permanent pacemaker among those treated with sAVR (P<0.0001). Pacemaker implantation, regardless of underlying treatment, was associated with an increase in risk of death in univariate analysis (HR 1.35, 95%CI 1.18 to 1.54; p<0.0001). The pacemaker implantation rate was compared for the propensity score-matched TAVI and sAVR patients according to the type of TAVI device implanted (Table S2). Overall TAVI procedures carried a higher pacemaker implantation rate as compared to sAVR.

In-hospital mortality for TAVI vs. sAVR patients was 4.1% vs. 3.7% (p=0.669; Table 2). During the 5-year follow-up, there were 763 deaths (41.9%) among those treated with TAVI compared with 552 (30.3%) deaths after sAVR, with a hazard ratio (HR) of 1.51 (95%CI 1.35 to 1.68; p<0.0001) (Table 3, Figure 2). There was a significant interaction between STS score and outcome (Table 3). The higher risk of death associated with TAVI was greatest in those within the lowest quartile of STS score (STS <2.35), i.e. those with the lowest likelihood based upon their baseline characteristics to be selected for TAVI. However, the risk of death was significantly higher among patients undergoing TAVI compared with sAVR for all quartiles of the score. The difference in mortality risk for TAVI versus sAVR was somewhat lower in 2012 compared with 2011, although the difference was not significant (Figure S1).

In the 2011-2012 cohort, CoreValve™, Sapien™, and SapienXT™ were the three most commonly used TAVI prostheses (Table S3). In the sAVR group, Perimount™ was the most frequently used prosthesis, followed by Hancock™, Trifecta™, and Epic™ (Table S3).

Discussion

GARY offers the unique opportunity to evaluate the largest 5-year, real-world dataset of TAVI and sAVR patients to date, comprising 18,010 patients who underwent isolated aortic valve procedures in 2011 and 2012.

Unmatched TAVI cohort

Differences in baseline characteristics were highly significant between the two treatment groups, even after excluding those patients with a specific, reported reason for allocating them directly for TAVI. TAVI patients were more often female, >12 years older (80.9 years), and had an STS score (6.3%) that was almost 2.5-fold higher. The prevalence of cardiac and non-cardiac comorbidities, in particular, was higher among TAVI patients. These results underline that, in general, heart team decisions were guiding patients toward the correct treatments.

In GARY, 5-year mortality was within the expected range (49.8%) in TAVI patients. This corresponds very well to data relating to death by any cause/disabling stroke (47.9%) of the TAVI cohort in the randomized controlled PARTNER 2A trial, where the STS score was slightly lower (5.8%) and age was slightly higher (81.5 years) (8). In the OBSERVANT study, 5-year mortality of the TAVI group was 48.3% (9). However, the risk profile of the OBSERVANT patients was lower than that of GARY patients. Five-year data are also available from the smaller Nordic Aortic Valve Intervention (NOTION) Trial (14). This trial randomized low-risk (STS-PROM 3.0 +/- 1.7%) patients aged >70 years with isolated severe aortic valve stenosis to TAVI (n=145) or sAVR (n=135) in Denmark and Sweden. After 5 years, TAVI all-cause mortality was markedly lower (27.6%) than that of GARY patients, but mean age (79.2 years) and STS score (2.9%) were also much lower (14).

Unmatched sAVR cohort

In GARY the vast majority of the 9,066 sAVR patients can be classified in the low-risk category (mean age 68.5 years, STS score 2.6%). The prevalence of cardiac and non-cardiac comorbidities was low compared with the TAVI cohort. Long-term outcomes were excellent, with a 5-year mortality of 16.5%. In comparison to the results from RCTs (8,14,15), survival rates were much higher in GARY.

Matching

In contrast to the selection method in an RCT, patients from GARY were allocated to one of the treatment options on the basis of a decision made by the heart team. In the years 2011 and 2012 older patients and those at greater risk were much more likely to be treated with TAVI, whereas younger patients with fewer comorbidities underwent surgery. In order to make a meaningful comparison in the long-term outcome between these vastly different groups of patients, propensity score matching was performed for n=1,820 in each group, resulting in a total of 3,640 matched patients (20.2% of the entire 2011-2012 cohort).

The incidence of periprocedural stroke was not different between the two matched groups. The incidence of in-hospital MI was low in both groups (0.5 to 0.7%) and not significantly different despite the 39% incidence of coronary artery disease in both groups. In TAVI patients there was a substantially higher need for permanent pacemaker implantation in both unmatched and matched cohorts, and patients who received these devices were at a significantly elevated long-term risk of death (univariate analysis HR 1.35; 95%CI 1.18 to 1.54; $p<0.0001$).

In GARY, TAVI conducted in 2011 and 2012 was associated with a higher 5-year all-cause mortality than sAVR. This is similar to the data from other registries in low- and intermediate-risk (9) and high-risk patients (11), but is in contrast to the results of RCTs. Five-year follow-up data from the PARTNER 2A trial (8) showed no significant differences in TAVI and sAVR regarding the primary endpoint (death or disabling stroke). Furthermore, 5-year mortality was similar in PARTNER 1 (15) and in the CoreValve U.S. Pivotal High Risk Trial in high-risk patients (16). In contrast, registry data has uniformly shown higher mortality rates among TAVI patients. The reasons for the discrepancy between the results of registries and RCTs remain speculative. As mentioned above, as is common in registries, GARY patients were allocated to one of the treatment options on the basis of the decision made by a heart team. Although we used a very sophisticated propensity score matching, we cannot exclude unknown confounders that were not documented in GARY. In addition, TAVI technology and interventional knowledge in 2011 is not comparable to the current situation, as devices implanted in these previous years and the clinical skills have improved over time.

The differences in the predictive factors included in the propensity score to create tightly matched cohorts for each time period, in particular the importance of diabetes and age/surgical risk, indicate the changing decision-making processes for TAVI during the study period. Among the 4,157 patients included as potential subjects for matching who underwent TAVI in the 2011-2012 cohort of patients followed up for 5 years, some 3,128 (75.3%) had an STS score between 3% and 15%, which was one of the inclusion criteria for the SURTAVI trial (4). The fact that long-term mortality was higher, but in-hospital mortality very similar, suggests that other variables play a role that were not captured by the matching process; therefore, it has to be emphasized that competent decision-making in the interdisciplinary heart team is of central importance.

Future implications

TAVI has become established as a routine therapy for treating elderly and higher-risk patients with acquired aortic stenosis. In addition, short-term outcomes in lower-risk patients have been shown to be favourable in selected patient populations. Routine clinical use of TAVI in younger and lower-risk patients, however, should only be considered when the longer-term outcomes of these patient populations are available. In RCTs TAVI prosthesis function was demonstrated to be excellent after 5 years; however, valid data from a 10-year follow-up are not yet available. Before TAVI prostheses are implanted routinely in a larger number of low-risk, younger patients, many potential implications for outcomes need to be investigated in long-term studies with a 10-year follow-up.

Study limitations

The present analysis of the GARY cohort utilizes a sophisticated propensity score-matching approach that achieves a very high degree of matching between groups. While this approach has advantages, in particular excluding patients from the analyses who are not considered suitable candidates for both treatment options, the propensity score approach is not a perfect instrument to address bias. In addition, we cannot exclude confounders that are not reflected by the data collected. Conversely, the data may be interpreted as demonstrating good clinical decisions for those patients at higher risk, since there is no evidence for substantial prostheses dysfunction that may explain a higher mortality.

Data from GARY are not adjudicated, and the data reported in this manuscript are limited to the clinical analyses. The current findings at 5 years strongly encourage re-examination at later time points. In addition, primarily first-generation TAVI and earlier-generation sAVR prostheses were used in the years 2011-2012 when the patients were included in this study.

Conclusions

Patients treated in a real-world setting with TAVI or sAVR in 2011 and 2012 had a good outcome at 5 years that is comparable to that observed in an RCT. In the entire patient population there was a significant difference in the need for new pacemaker implantation between the TAVI and sAVR groups. In a smaller, propensity-matched subset (20%) of patients treated with early-generation TAVI devices, a higher 5-year all-cause mortality was observed. Longer follow-up and re-evaluation with newer prostheses types is mandatory to ensure patients are not disadvantaged.

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Disclosure:

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Figure Legends

Figure 1: Study flowchart of cohort 2011-2012

Figure 2: Survival probability by treatment for 2011-2012 matched cohort.

Appendices

See supplementary material

Tables

Table 1. Baseline, unmatched and matched characteristics in 2011-2012 cohort

Variable	**Total sAVR n=9,066**	**Total TAVI n=4,157**	**Unmatched p**	**Included in PS**	**Matched sAVR n=1,820**	**Matched TAVI n=1,820**	**Matched p**	**SD**
Age, y	68.51 (11.13)	80.89 (6.06)	<0.0001	1	78.03 (5.09)	77.96 (6.1)	0.697	0.012
BMI, kg/m^2	28.3 (5.01)	27.38 (4.99)	<0.0001	1	28.14 (4.94)	28.09 (5.26)	0.785	0.010
PMean AV, mmHg	46.93 (18.63)	43.9 (16.09)	<0.0001	1	46.06 (16.52)	45.42 (16.69)	0.287	0.039
PMax AV	74.13 (28.53)	70.87 (25.06)	<0.0001		73.32 (25.51)	72.28 (25.52)	0.272	0.041
STS Valve score 2008	2.62 (3.02)	6.31 (4.93)	<0.0001	1	4.58 (3.79)	4.46 (3.27)	0.301	0.034
AVA, mm^2	0.75 (0.23)	0.69 (0.1)	<0.0001	1	0.72 (0.21)	0.72 (0.22)	0.959	0.000
Male sex	5438 (60.0%)	1949 (46.8%)	<0.0001	1	884 (48.6%)	872 (48.9%)	0.715	0.013
NYHA III/IV	5540 (61.1%)	3451 (82.9%)	<0.0001	1	1413 (77.6%)	1412 (77.6%)	1.000	0.001
Coronary artery disease	1789 (19.7%)	2208 (53.0%)	<0.0001	1	711 (39.1%)	702 (38.6%)	0.786	0.010
Previous MI	464 (5.1%)	682 (16.4%)	<0.0001	1	198 (10.9%)	198 (10.9%)	1.000	0.000
Previous PCI	763 (8.4%)	1178 (28.3%)	<0.0001	1	325 (17.9%)	328 (18.0%)	0.931	0.004
Previous cardiac surgery	795 (8.8%)	977 (23.5%)	<0.0001	1	313 (17.2%)	297 (16.4%)	0.506	0.024
Arterial vascular disease	1388 (15.3%)	1246 (30.0%)	<0.0001	1	403 (22.2%)	422 (23.2%)	0.452	0.025
Peripheral vascular disease	419 (4.6%)	703 (16.9%)	<0.0001	1	189 (10.4%)	191 (10.5%)	0.914	0.004
COPD	569 (6.3%)	529 (12.7%)	<0.0001	1	206 (11.3%)	200 (11.0%)	0.792	0.010
Pulmonary hypertension	787 (8.7%)	1164 (28.2%)	<0.0001	1	315 (17.4%)	322 (17.8%)	0.760	0.010

Variable	Total sAVR n=9,066	Total TAVI n=4,157	Unmatched p	Included in PS	Matched sAVR n=1,820	Matched TAVI n=1,820	Matched p	SD
Arterial hypertension	7258 (80.8%)	3685 (89.7%)	<0.0001	1	1605 (89.1%)	1587 (87.9%)	0.274	0.030
Diabetes	2165 (23.9%)	1430 (34.4%)	<0.0001		629 (34.6%)	606 (33.3%)	0.441	0.027
Creatinine >2 mg/dl	131 (1.4%)	226 (5.4%)	<0.0001	1	61 (3.4%)	64 (3.5%)	0.856	0.009
Dialysis	207 (2.3%)	222 (5.3%)	<0.0001	1	75 (4.1%)	76 (4.2%)	1.000	0.003
Diabetes with insulin	755 (8.6%)	588 (14.1%)	<0.0001		239 (13.1%)	255 (14.0%)	0.468	0.026
Atrial fibrillation	847 (9.3%)	1211 (29.1%)	<0.0001	1	371 (20.4%)	368 (20.2%)	0.934	0.004
Previous ICD/pacemaker	401 (4.4%)	571 (13.7%)	<0.0001	1	167 (9.2%)	174 (9.6%)	0.733	0.013
LVEF			<0.0001	1			0.940	
<30%	248 (2.7%)	351 (8.4%)		1	92 (5.1%)	88 (4.8%)		0.010
30-50%	1808 (19.9%)	1216 (29.2%)		1	463 (25.4%)	469 (25.8%)		0.008
>50%	7010 (77.3%)	2597 (62.4%)		1	1265 (69.5%)	1263 (69.4%)		0.002
Mitral regurgitation ≥2°	799 (9.2%)	1034 (25.5%)	<0.0001	1	289 (16.4%)	304 (17.2%)	0.529	0.022
Tricuspid regurgitation ≥2°	304 (3.6%)	656 (16.5%)	<0.0001	1	147 (8.6%)	137 (8.0%)	0.536	0.020
Emergency	138 (1.5%)	36 (0.9%)	0.0017	1	25 (1.4%)	22 (1.2%)	0.769	0.015
CCF 4	97 (1.1%)	112 (2.7%)	<0.0001	1	44 (2.4%)	40 (2.2%)	0.741	0.015
Immunotherapy	279 (3.1%)	121 (3.0%)	0.702	1	55 (3.1%)	53 (3.0%)	0.846	0.006
Prior stroke	120 (1.3%)	130 (3.1%)	<0.0001	1	48 (2.6%)	42 (2.3%)	0.594	0.021
Bicuspid aortic valve	38 (0.5%)	150 (3.8%)	<0.0001	1	23 (1.4%)	30 (1.8%)	0.407	0.032
CVD	522 (5.8%)	523 (12.6%)	<0.0001		182 (10.0%)	196 (10.8%)	0.447	0.025

Data shown as mean (standard deviation) or as n (%).

Abbreviations: AVA, aortic valve area; BMI, body mass index; CCF 4, congestive cardiac failure stage 4; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PMax AV, maximal pressure aortic valve; PMean AV, mean pressure aortic valve; sAVR, surgical aortic valve replacement; SD, standard deviation; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation

Table 2. Periprocedural complications for 2011-2012 propensity score-matched cohort

Event	**sAVR n=1,820**	**TAVI n=1,820**	**P**
In-hospital mortality	74 (4.1%)	68 (3.7%)	0.669
In-hospital stroke	29 (1.6%)	26 (1.4%)	0.786
In-hospital myocardial infarction	12 (0.7%)	9 (0.5%)	0.663
Temporary dialysis	38 (2.1%)	38 (2.1%)	1
Chronic dialysis	37 (2.0%)	38 (2.1%)	1
Pacemaker implantation	83 (4.6%)	329 (18.1%)	<0.0001

Table 3. Hazard ratio by primary endpoint (survival), STS quartile, restricted to age and BMI within IQR of 2011-2012 cohort

Comparison	**Hazard Ratio**	**Lower 95%CI**	**Upper 95%CI**	**P**	**Total**	**Deaths**
Survival	1.508	1.352	1.683	<0.0001	3640	1315
Interaction with STS score				0.0004		
STS ≥75% (4.81)	1.328	1.105	1.596	0.0025	907	461
STS ≥50% (3.24) and <75% (4.81)	1.6	1.288	1.988	<0.0001	908	337
STS ≥25% (2.35) and <50% (3.24)	1.328	1.048	1.682	0.0187	907	278
STS <25% (2.35)	2.118	1.62	2.769	<0.0001	918	239
Age 75 to 82 (IQR)	1.723	1.485	1.999	<0.0001	2074	730
BMI 24.61 to 30.86 (IQR)	1.568	1.329	1.851	<0.0001	1708	578

Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; STS, Society of Thoracic Surgeons