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Quality of Life After Transcatheter Aortic Valve Replacement

Prospective Data From GARY (German Aortic Valve Registry)

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ABSTRACT

OBJECTIVES This study sought to analyze health-related quality-of-life (HrQoL) outcomes of patients undergoing transcatheter aortic valve replacement (TAVR) based on data from GARY (German Aortic Valve Registry).

BACKGROUND Typically, patients currently referred for and treated by TAVR are elderly with a concomitant variable spectrum of multiple comorbidities, disabilities, and limited life expectancy. Beyond mortality and morbidity, the assessment of HrQoL is of paramount importance not only to guide patient-centered clinical decision-making but also to judge this new treatment modality in this high-risk patient population.

METHODS In 2011, 3,875 patients undergoing TAVR were included in the GARY registry. HrQoL was prospectively measured using the EuroQol 5 dimensions questionnaire self-complete version on paper at baseline and 1 year.

RESULTS Complete follow-up EuroQol 5 dimensions questionnaire evaluation was available for 2,288 patients (transvascular transcatheter aortic valve replacement [TAVR-TV]: n = 1,626 and transapical TAVR [TAVR-TA]: n = 662). In-hospital mortality was 5.9% (n = 229) and the 1-year mortality was 23% (n = 893). The baseline visual analog scale score for general health status was 52.6% for TAVR-TV and 55.8% for TAVR-TA and, in parallel to an improvement in New York Heart Association functional class, improved to 59.6% and 58.5% at 1 year, respectively ($p < 0.001$). Between baseline and 1 year, the number of patients reporting no complaints increased by 7.8% (TAVR-TV) and by 3.5% within the mobility dimension, and by 14.1% (TAVR-TV) and 9.2% within the usual activity dimension, whereas only moderate changes were found for the self-care, pain or discomfort, and anxiety or depression dimensions. In a multiple linear regression analysis several pre- and post-operative factors were predictive for less pronounced HrQoL benefits.

CONCLUSIONS TAVR treatment led to improvements in HrQoL, especially in terms of mobility and usual activities. The magnitude of improvements was higher in the TAVR-TV group as compared to the TAVR-TA group. However, there was a sizable group of patients who did not derive any HrQoL benefits. Several independent pre- and post-operative factors were identified being predictive for less pronounced HrQoL benefits. (J Am Coll Cardiol Intv 2016;9:2541–54)

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

EQ-5D = EuroQol 5 dimensions questionnaire

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HrQoL = health-related quality of life

KCCQ = Kansas City Cardiomyopathy Questionnaire

NYHA = New York Heart Association

SAVR = surgical aortic valve replacement

SF-12/36 PCS = 12/36-Item Short Form Health Survey physical component score

TAVR = transcatheter aortic valve replacement

TAVR-TA = transapical transcatheter aortic valve replacement

TAVR-TV = transvascular transcatheter aortic valve replacement

VAS = visual analog scale

The increasing prevalence of aortic valve stenosis correlates with a widespread increase in life expectancy in the Western world. Once symptomatic, severe aortic valve stenosis has a very poor prognosis. If left untreated, severe, symptomatic aortic valve stenosis carries a high mortality of about 25% to 50% per year (1,2).

In patients with aortic valve stenosis, progressive and rapid symptom deterioration leads to an impairment of functional status and compromised health-related quality of life (HrQoL). Transcatheter aortic valve replacement (TAVR) was introduced as an alternative, less-invasive treatment modality for those patients who are at high risk for surgical aortic valve replacement (SAVR) or inoperable. TAVR has gained rapid clinical acceptance and has quickly become the standard of care in the treatment of appropriately selected individuals with inoperable aortic valve stenosis during recent years. Typically, patients currently referred for and treated by TAVR are elderly, with a concomitant variable spectrum of multiple comorbidities, disabilities, and limited life expectancy. For these patients, the primary goal is not solely longevity, but rather the restoration of comfort in daily life, functional mobility, and independent status. Therefore, beyond mortality and morbidity, an HrQoL assessment is of paramount importance not only to guide patient-centered clinical decision-making, but also to judge the efficacy of this treatment modality (3).

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The aim of the present study was to analyze HrQoL outcomes of patients undergoing TAVR on the basis of data from GARY (German Aortic Valve Registry) with a focus on a comparison between transapical and transvascular treatment approaches.

METHODS

THE GARY REGISTRY. The GARY registry is a nationwide registry that was inaugurated by the German Society of Thoracic and Cardiovascular Surgery and the German Society of Cardiology in July 2010. The aim of the GARY registry is to evaluate the current practice of treatment of aortic valve diseases in Germany. The registry's responsible body is a nonprofit organization. The GARY registry seeks to collect reliable data on short- and long-term outcomes and to provide information on a real-world, all-comers basis for patients undergoing the complete spectrum of transcutaneous and conventional surgical aortic valve interventions.

The GARY registry protocol has been previously described in detail (4). The responsible societies and the BQS Institute are independent organizations by virtue of their constitutions from both legal and scientific viewpoints. The GARY registry receives financial support in the form of unrestricted grants by medical device companies (Edwards Lifesciences; Medtronic; Symetis; JenaValve Technology; LivaNova, formerly Sorin Group; St. Jude Medical; Direct Flow Medical), the German Heart Foundation, the German Society of Cardiology and the German Society of Thoracic and Cardiovascular Surgery, none of which have access to data or any influence on its publication.

EuroQol QUESTIONNAIRE. HrQoL was assessed by applying the EuroQol 5 dimensions questionnaire (EQ-5D) self-complete version on paper (EQ-5D-3L) pre-operatively and 1-year post-operatively. The EQ-5D is a 5-domain generic health state classification system providing a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care and in population

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health surveys. The EQ-5D is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, hospitals, and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. The EQ-5D consists of 5 domains of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is divided into 3 levels: no problems (level 1), some or moderate problems (level 2), and severe problems (level 3). Based on the responses to these classifications, a single index value is estimated using a general population-based algorithm. The standardized extended version of EQ-5D uses a visual analog scale (VAS) for the self-rating of health status. Patients estimate their own health on a visual analog scale, with numeric values from 0 to 100 and with the endpoints labeled best imaginable health state at the top and worst imaginable health state at the bottom (5,6) (Online Figure 1).

EQ5D-INDEX. EQ-5D-3L health states, defined by the EQ-5D descriptive system, yielding 243 (or 3^5) possible health states, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e., state 11,111). The EQ-5D index has an upper bound equal to 1 that indicates full health (indicated by "no problem" in all domains). Changes in the EQ-5D index score may arise from different patterns of impairment across individual dimensions. Negative values may occur, and the lower bound varies depending on the country-specific value set used. Initially only available in the United Kingdom, over the last decade, several country-specific value sets have been estimated using time trade-off methods and regression analysis. Value sets and coefficients for the German population were used for the estimation of an individual's EQ-5D index value (7).

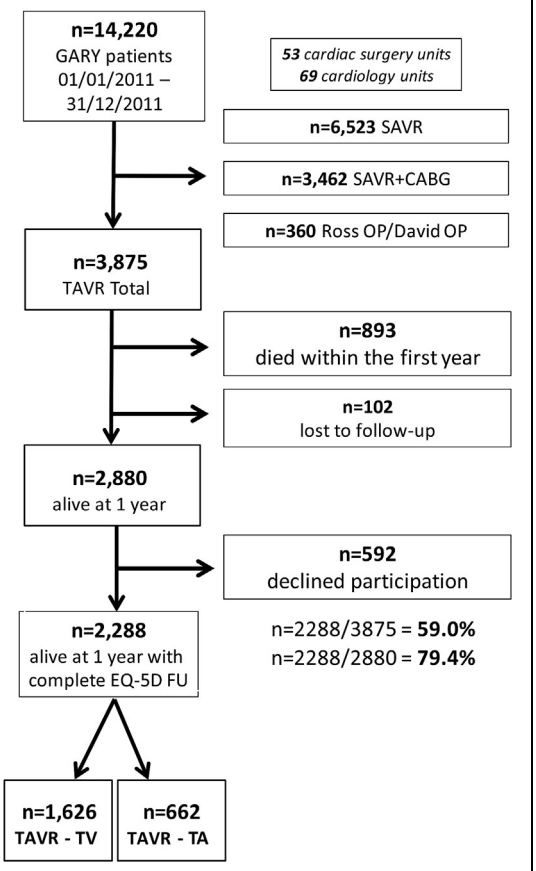
STATISTICS. Categorical variables are presented as percentages and values, and continuous data are expressed as mean ± SD. A comparison of baseline values among the subgroups was performed using a Mann-Whitney *U* test for continuous variables. Categorical variables were compared by means of the chi-square test and Fisher's exact test where applicable. Paired sample *t* tests were used to analyze the difference between pre-operative and 1-year follow-up VAS scores within the subgroups. Statistical significance was 2-sided tested with an alpha level of 5%. Multiple linear regression models with stepwise variable selection was used to identify independent risk factors for deviations in quality of life, starting with all variables showing a p value of <0.2 in previous univariate analyses.

All statistical analyses were performed using the SPSS statistical package version 19.0.0 (IBM, Armonk, New York). Data management and statistical analyses were performed by the BQS Institute for Quality and Patient Safety (Düsseldorf, Germany).

RESULTS

PATIENT CHARACTERISTICS. From 14,220 patients recruited for the GARY registry, 3,875 patients

FIGURE 1 Study Population



Flowchart of included patients in GARY (German Aortic Valve Registry) between January 1, 2011, and December 31, 2011, and the final study population. CABG = coronary artery bypass grafting; EQ-5D = EuroQol 5 dimensions questionnaire; FU = follow-up; SAVR = surgical aortic valve replacement; TAVR-TA = transapical transcatheter aortic valve replacement; TAVR-TV = transvascular transcatheter aortic valve replacement.

underwent transvascular (TAVR-TV) or transapical (TAVR-TA) TAVR in 2011. Complete pre-operative and 1-year follow-up HrQoL evaluations assessed by the EQ-5D-3L questionnaire were available for 2,288 patients (participants) representing 59% of the initial 3,875 patients treated by TAVR and 79% of patients who were alive at 1 year. Of the initial patients, 1,485 (38.3%) patients did not complete a questionnaire at baseline or after 1 year. Of these, 893 (23%) patients (nonparticipants or nonsurvivors) died within the first year after implantation. A total of 592 (15.3%) patients (nonparticipants or survivors) declined participation or were unavailable for a 1-year follow-up. For 102 (2.6%) patients, survival and HrQoL statuses were unknown due to a loss to follow-up, resulting in a final study population of 2,288 patients (**Figure 1**).

A comparison of pre-, intra-, and post-operative characteristics between participants and nonparticipants revealed that nonsurvivors showed significantly more comorbidities and a lower general health status, suggesting a higher pre-operative risk (see Online Tables 1 to 3). These results may lead to an overestimation of the HrQoL status within the study population due to a selection bias because patients who died during follow-up could not be included in our study (nonparticipants or nonsurvivors). In contrast, a comparison of participants and surviving nonparticipants revealed only a few variables, such as sex, presence of arterial and peripheral arterial vascular disease, and the respective logistic European System for Cardiac Operative Risk Evaluation score (EuroSCORE) and German aortic valve score, were significantly different (detailed information is given in Online Tables 1 to 3). All other baseline parameters were comparable between both groups.

In the group of participants, 1,626 patients underwent TAVR-TV, and 662 patients underwent TAVR-TA. A comparison of pre-operative characteristics between both groups revealed a significantly higher rate of previous cardiac surgery (29.4% vs. 18.3%), renal replacement therapy (5.7% vs. 3.6%), arterial vascular disease (37.9% vs. 24.4%), and peripheral vascular disease (23.4% vs. 14.2%), respectively, in the TAVR-TA group. Patients in the TAVR-TV group underwent significantly more urgent or emergent procedures (19.8% vs. 12.1%) and had suffered more often from cardiogenic shock within the last 48 h (3.1% vs. 1.5%). Furthermore, patients in the latter group exhibited significantly higher logistic EuroSCORE (23.9 ± 17.0 vs. 21.2 ± 14.3) and German aortic valve scores (7.6 ± 7.9 vs. 6.5 ± 5.9).

The mean procedure time was significantly longer for TAVR-TA (96 ± 47 min) compared to that for TAVR-TV (88 ± 47 min). For the TAVR-TA group, 94.1% of patients were treated under general anesthesia compared to only 45.9% of the TAVR-TV group. Patients undergoing TAVR-TA showed a significantly higher rate of a new onset need for dialysis, whereas the rate of pacemaker insertion (22.3% vs. 9.7%) was significantly higher for the TAVR-TV group. Intensive care unit stay (2.8 ± 3.4 days vs. 3.4 ± 4 days) and in-hospital stays (10.8 ± 6.8 days vs. 12.3 ± 8.2 days) were significantly longer for the TAVR-TA group compared to the TAVR-TV group. During the first year after TAVR, repeated hospitalization was necessary in 40% of TAVR-TV and 45% of TAVR-TA patients ($p = 0.03$). Procedure-related complications necessitated rehospitalization in 4.1% of patients undergoing TAVR-TV compared to 7.9% in the TAVR-TA group ($p < 0.001$).

Detailed information on pre-, intra-, and post-operative characteristics, as well as 1-year outcomes, for both groups is given in **Tables 1 to 4**.

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS AND EQ-VAS SCORE. Pre-operatively, more than 83% of TAVR patients were in New York Heart Association (NYHA) functional classes III or IV (TAVR-TA: 83.4%; TAVR-TV: 84.1%). This difference between the groups was not statistically significant ($p = 0.66$). One year after the procedure, 68.9% of TAVR patients (TAVR-TA: 69.1%; TAVR-TV: 68.6%) reported an increase in NYHA functional class compared to their pre-operative evaluation. **Figure 2** shows the parallel NYHA functional class shift, from NYHA functional classes class III and IV to NYHA functional class I and II, in patients undergoing either TAVR-TV or TAVR-TA.

In line with NYHA functional class improvements, the VAS score also improved after 1 year. The VAS score increased significantly from 52.6% to 59.6% for the TAVR-TV group and from 55.8% to 58.5% for the TAVR-TA group at 1-year follow-up, respectively (**Figure 3**). The VAS score difference between baseline and at 1 year was 7.01% for the TAVR-TV group and 2.75% for the TAVR-TA group. This difference in the improvement of the VAS score between both treatment modalities was statistically significant ($p < 0.001$) (**Figure 3**).

EQ-5D-3L. The EQ-5D measures 5 quality-of-life dimensions each divided into 3 levels, ranging from no and mild complaints to severe complaints within individual dimensions. For the TAVR-TV group, the pre-operative values ranged from 33.4% to 64.8% for level 1 (no complaints), 31.5% to 63.4% for level 2 (mild complaints), and 3.2% to 9.8% for level 3 (severe complaints) within the 5 dimensions.

TABLE 1 Pre-Operative Patient Characteristics of EQ-5D Participants Undergoing TAVR-TV or TAVR-TA

	EQ-5D Participants (n = 2,288)		EQ-5D Participants (TAVR-TV) (n = 1,626)		EQ-5D Participants (TAVR-TA) (n = 662)		p Value
	n or n/N	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	(TAVR-TV vs. TAVR-TA)
Age, yrs	2,285	80.6 ± 6.1	1,623	80.9 ± 6.1	662	79.9 ± 6.1	**0.001**
Female	1,288	56.3	973	59.8	315	47.6	**<0.001**
BMI, kg/m^2	2,250	27.2 ± 4.9	1,597	27.1 ± 4.9	653	27.5 ± 4.9	0.112
BMI <22 kg/m^2	255/2,250	11.3	188/1,597	11.8	67/653	10.3	0.341
NYHA functional class III–IV	1,920	83.9	1,368	84.1	552	83.4	0.661
CAD	1,213	53.0	856	52.6	357	53.9	0.580
Previous MI	385/2,282	16.9	271/1,622	16.7	114/660	17.3	0.758
Previous PCI	626	27.4	452	27.8	174	26.3	0.470
Previous cardiac surgery	489/2,275	21.5	296/1,618	18.3	193/657	29.4	**<0.001**
Atrial fibrillation	580	25.3	401	24.7	179	27.0	0.244
LVEF							**0.037**
Normal	1,450	63.4	1,043	64.1	407	61.5	
30%–50%	667	29.2	452	27.8	215	32.5	
<30%	171	7.5	131	8.1	40	6.0	
Cardiogenic shock/decompensation within 48 h prior to admission	60/2,273	2.6	50/1,615	3.1	10/658	1.5	**0.042**
Renal replacement therapy	96	4.2	58	3.6	38	5.7	**0.021**
Chronic renal replacement therapy	55	2.4	36	2.2	19	2.9	0.368
Neurodysfunction (central or peripheral)	282/2,285	12.3	195/1,624	12.0	87/661	13.2	0.441
Arterial vascular disease	648/2,287	28.3	397/1,625	24.4	251/662	37.9	**<0.001**
Peripheral arterial vascular disease	386/2,286	16.9	231/1,625	14.2	155/661	23.4	**<0.001**
EOA, cm^2	2,150	0.68 ± 0.22	1,543	0.69 ± 0.22	607	0.68 ± 0.20	0.995
Pmean, mm Hg	2,039	46.5 ± 17.4	1,500	47.4 ± 17.7	539	44.1 ± 16.2	**0.001**
Pmax, mm Hg	1,905	74.5 ± 26.4	1,416	75.5 ± 26.8	489	71.5 ± 24.9	**0.004**
Mitral insufficiency ≥2°	586/2,257	26.0	431/1,606	26.8	155/651	23.8	0.152
Log EuroSCORE	2,199	23.1 ± 16.3	1,560	23.9 ± 17.0	639	21.2 ± 14.3	**0.010**
German AV score	2,169	7.3 ± 7.4	1,538	7.6 ± 7.9	631	6.5 ± 5.9	**<0.001**
Urgent/emergent treatment	402	17.6	322	19.8	80	12.1	**<0.001**

Bold values indicate statistical significance with $p < 0.05$.

AV = aortic valve; BMI = body mass index; CAD = coronary artery disease; EOA = effective orifice area; EQ-5D = EuroQol 5 dimensions questionnaire; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TAVR-TA = transapical transcatheter aortic valve replacement; TAVR-TV = transvascular transcatheter aortic valve replacement.

TABLE 2 Procedural Data of EQ-5D Participants Undergoing TAVR-TV or TAVR-TA

	EQ-5D Participants (n = 2,288)		EQ-5D Participants (TAVR-TV) (n = 1,626)		EQ-5D Participants (TAVR-TA) (n = 662)		p Value
	n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	(TAVR TV vs. TAVR TA)
General anesthesia	1,369	59.8	746	45.9	623	94.1	**<0.001**
Procedure time, min	2,288	90 ± 48	1,626	88 ± 47	662	96 ± 50	**<0.001**
Radiation, min	2,082	14.9 ± 11.1	1,523	17.5 ± 10.7	559	8.1 ± 9.0	**<0.001**
Contrast, ml	2,115	161 ± 85	1,550	176 ± 87	565	118 ± 64	**<0.001**
Balloon dilation	2,043	89.3	1,415	87.0	628	94.9	**<0.001**
Rapid pacing for implant	1,547	67.6	956	58.8	591	89.3	**<0.001**
Conversion to open heart surgery	25	1.1	17	1.0	8	1.2	0.825
CPB used	43	1.9	17	1.0	26	3.9	**<0.001**

Bold values indicate statistical significance with $p < 0.05$.

CPB = cardiopulmonary bypass.

TABLE 3 Post-Operative In-Hospital Patient Characteristics of EQ-5D Participants Undergoing TAVR-TV or TAVR-TA

	EQ-5D Participants n = 2,288		EQ-5D Participants (TAVR-TV) n = 1,626		EQ-5D Participants (TAVR-TA) n = 662		p Value
	n or n/n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	(TAVR-TV vs. TAVR-TA)
In-hospital mortality	0	0.0	0	0.0	0	0.0	
TIA	35	1.5	29	1.8	6	0.9	0.136
Stroke	17	0.7	13	0.8	4	0.6	0.791
Myocardial infarction	3	0.1	1	0.1	2	0.3	0.203
New onset atrial fibrillation	94/1,708	5.5	61/1,225	5.0	33/483	6.8	0.157
New PM/ICD implantation (pre-operative SR)	279/1,489	18.7	238/1,067	22.3	41/422	9.7	**<0.001**
Dialysis (new onset)							**0.024**
Temporary	27/2,192	1.2	14/1,568	0.9	13/624	2.1	
Chronic	3/2,192	0.1	1/1,568	0.1	2/624	0.3	
Bleeding							**<0.001**
1 RBC unit	112/2,284	4.9	75/1,624	4.6	37/660	5.6	
2-3 RBC units	390/2,284	17.1	250/1,624	15.4	140/660	21.2	
≥4 RBC units	162/2,284	7.1	83/1,624	5.1	79/660	12.0	
Number unknown but ≥1 U	26/2,284	1.1	22/1,624	1.4	4/660	0.6	
Post-operative in-hospital stay, days	2,285	11.2 ± 7.2	1,624	10.8 ± 6.8	661	12.3 ± 8.2	**<0.001**
Post-operative intensive care, days		3.0 ± 3.6		2.8 ± 3.4		3.4 ± 4.0	**0.001**

Bold values indicate statistical significance with $p < 0.05$.
ICD = implantable cardioverter-defibrillator; PM = pacemaker; RBC = red blood cell; SR = sinus rhythm; TIA = transient ischemic attack; other abbreviations as in Table 1.

For TAVR-TA, the pre-operative values were 35.5% to 74.6%, 21.8% to 58.5%, and 1.8% to 8.2% for levels 1, 2, and 3, respectively (Figure 4).

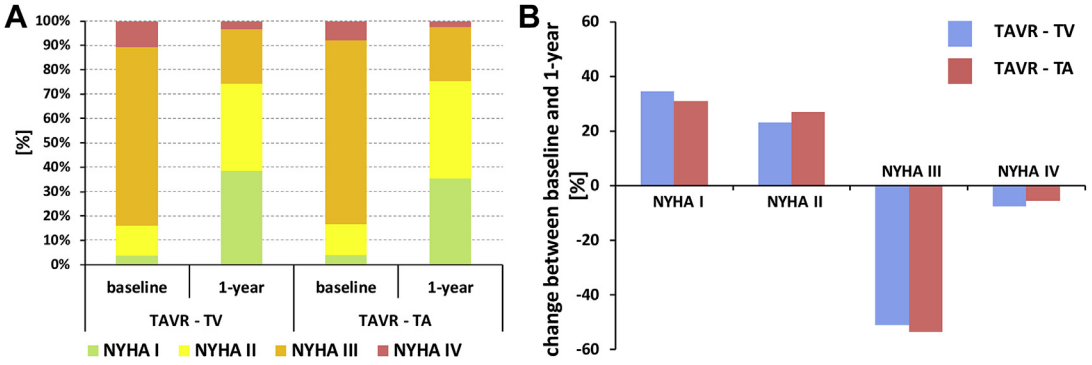
When comparing the number of patients within level 1 at baseline and after 1 year, improvements in all 5 dimensions within the TAVR-TV group were noted, with the highest increase for the usual activity dimension. In parallel, the number of patients at level 2 decreased for all dimensions. Notably, the number of patients at level 3 also increased (reflecting a worsening of quality of life) for all dimensions except mobility. This effect was most pronounced for the pain/discomfort dimension (Figure 5A). A slightly different picture was found in the TAVR-TA group. Patient numbers at level 1 increased for mobility and usual activity, and only slightly for pain/discomfort, but decreased for the self-care and depression/anxiety dimension. Comparable to the TAVR-TV group, the number of patients at level 2 decreased for all dimensions except for self-care,

TABLE 4 1-Year Outcome of EQ-5D Participants Undergoing TAVR-TV or TAVR-TA

	EQ-5D Participants (n = 2,288)		EQ-5D Participants (TAVR-TV) (n = 1,626)		EQ-5D Participants (TAVR-TA) (n = 662)		p Value
	n or n/N	%	n or n/N	%	n or n/N	%	(TAVR-TV vs. TAVR-TA)
TIA total	55	2.4	43	2.6	12	1.8	0.292
Stroke total	38	1.7	27	1.7	11	1.7	1.000
Myocardial infarction total	12	0.5	8	0.5	4	0.6	0.753
New onset PM/ICD implantation total	445/2,004	22.2	362/1,425	25.4	83/579	14.3	**<0.001**
Repeat hospital stay	949	41.5	651	40.0	298	45.0	**0.031**
Repeat hospital stay for complications of the procedure	119	5.2	67	4.1	52	7.9	**0.001**
Repeat hospital stay for cardiovascular problems	365	16.0	255	15.7	110	16.6	0.572
PCI after discharge	38	1.7	28	1.7	10	1.5	0.857
CABG after discharge	5	0.2	2	0.1	3	0.5	0.149

Bold values indicate statistical significance with $p < 0.05$.
CABG = coronary artery bypass grafting; other abbreviations as in Tables 1 and 3.

FIGURE 2 NYHA Functional Class



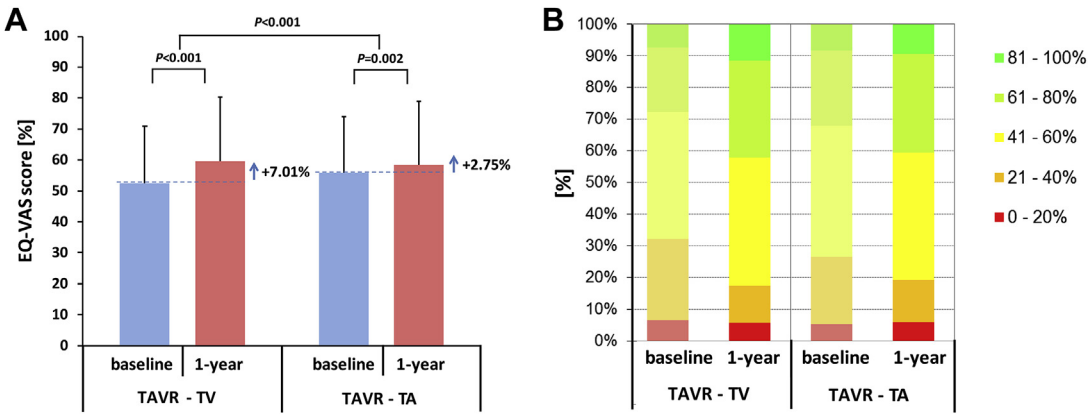
New York Heart association (NYHA) functional class at **(A)** baseline and 1-year follow-up and **(B)** changes are depicted showing a clear shift from NYHA functional class III or IV to NYHA functional class I or II in both treatment modalities. Abbreviations as in Figure 1.

which showed almost no change. Also comparable to patients undergoing TAVR-TV, patient numbers at level 3 increased in all dimensions with, again, the most distinct increase seen for pain/discomfort (Figure 5B).

The number of patients at each level for all dimensions does not reflect individual changes between pre-operative and 1-year follow-up quality of life. Therefore, we analyzed EQ-5D level changes (Figure 6). For the TAVR-TV group, the majority of patients (41.6% to 64.7%, depending on dimension) described equal EQ-5D levels at a 1-year follow-up when compared to baseline. The same was found for the TAVR-TA group, with 41.7% to 69.9% of patients describing an equal level at baseline and at a 1-year follow-up. An increase in EQ-5D levels was seen, from 18.9% to 29.5%, within the TAVR-TV group and from 12.4% to 24.8% for the TAVR-TA group. Interestingly, a substantial proportion of patients in the TAVR-TV (15.7% to 33.8%) as well as in the TAVR-TA group (17.7% to 35.8%) reported a decrease in EQ-5D levels, especially for the pain/discomfort dimension.

For the whole study population (independent of the access route) several independent risk factors

FIGURE 3 EQ-VAS Score



Mean visual analog scale (VAS) scores in the TAVR-TV and the TAVR-TA groups pre-operatively and **(A)** at 1-year and **(B)** the respective percentiles. The mean VAS score improvement between baseline and 1 year was more pronounced in the TAVR-TV group. EQ-VAS = EuroQol 5 dimensions questionnaire visual analog scale; other abbreviations as in Figure 1.

FIGURE 4 Percentage of Patients in Each of the 3 EQ-5D Levels at Baseline and 1 Year

Percentage of patients in each of the 3 EQ-5D levels across each EQ-5D dimension at baseline and at 1 year for the TAVR-TV and TAVR-TA groups. Abbreviations as in Figure 1.

were identified by multiple regression analysis to be predictive for less pronounced or absent quality-of-life improvements (age, female sex, body mass index [BMI], NYHA functional class III or IV, neurodysfunction, renal replacement therapy, pre- or post-operative), peripheral arterial vascular disease, mitral insufficiency ≥2°, post-operative transient ischemic attack or stroke, post-operative hospitalization). For patients in the TAVR-TV group, age, female sex, BMI, NYHA functional class III or IV, neurodysfunction, renal replacement therapy, peripheral arterial vascular disease or post-operative hospitalization whereas for the group of patients that were treated via the transapical access route (TAVR-TA), female sex, atrial fibrillation, neurodysfunction, chronic pre-operative renal replacement therapy or post-operative transient ischemic attack or stroke were found to be independent risk factors for a nonresponder status (for details see Tables 5 and 6).

DISCUSSION

An exponential increase in the use of TAVR has been witnessed over recent years. With accumulating evidence of feasibility and safety, as well as reduced rates for early mortality and post-operative morbidity, additional outcome parameters such as HrQoL are of paramount importance to judge the treatment efficiency of TAVR (8-10).

To date, with a total of 2,288 patients, the present study is the largest nonrandomized series to report on HrQoL outcomes in patients undergoing TAVR. The PARTNER (Placement of Aortic Transcatheter Valve-Trial) randomized controlled trial had previously reported on HrQoL outcomes in 328 patients. Beyond this, only observational reports exist with fewer patients.

At baseline, more than 80% of patients within our study population were in NYHA functional class III or IV. After 1 year, more than two-thirds of patients exhibited an improvement in their NYHA functional class, a finding comparable with data reported in the literature. In 56 observational studies summarized by Kim et al. (11), an average of 81% of patients (range 54% to 100%) exhibited NYHA functional class III or IV symptoms at baseline. After 1 year, the majority of patients showed NYHA functional class I or II symptoms. On average, an improvement of at least 1 NYHA functional class was reported up to 36 months after TAVR (11). Most TAVR studies report NYHA functional class as a measure of symptom severity and functional limitations. However, whether NYHA functional class alone—because of its subjective nature and poor correlation with objectively measured exercise capacity—is sensitive enough to capture the overall effect of treatment on patients' quality of life and ability to perform routine daily activities has been questioned. Therefore, it has been claimed that NYHA functional class should be supplemented with other validated instruments of functional status and quality of life (11).

The HrQoL of patients, as determined using the EQ-5D assessment tool, significantly improved a year after TAVR when compared to baseline measurements. In parallel to the observed improvements in NYHA functional class, the VAS score, a measure of self-evaluated health status, also improved significantly for both TAVR-TA (+2.7%) and TAVR-TV groups (+7.0%). The magnitude of

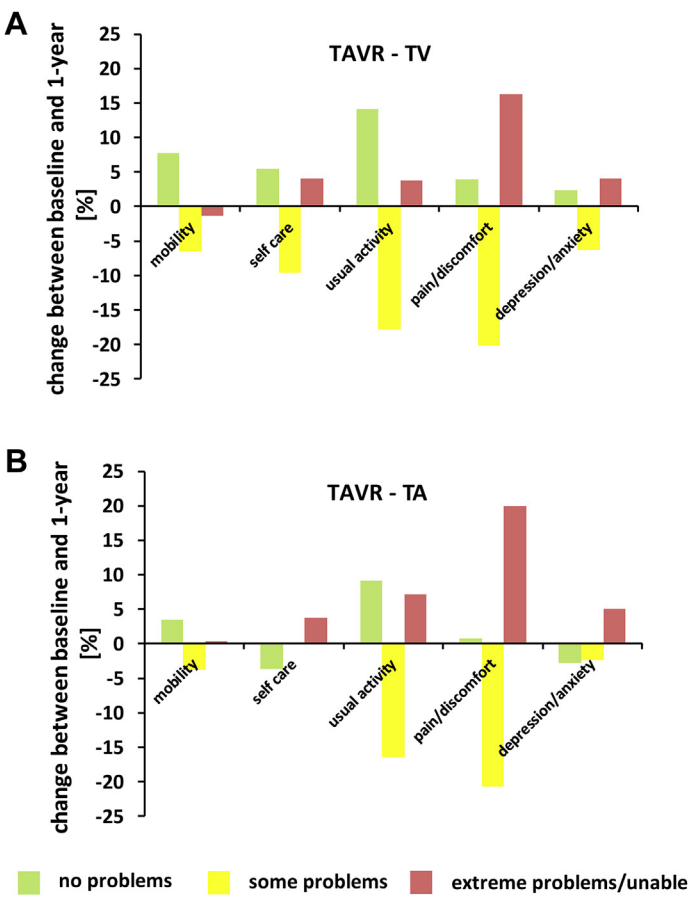
improvement was significantly higher for the TAVR-TV group.

When looking at the EQ-5D subdomains, an increased patient number at the no problems level was seen for each dimension within the TAVR-TV group, whereas for the TAVR-TA group, an increased patient number at the same level was only detected for the mobility usual activity, and, to a lesser extent, for the pain/discomfort dimensions. Interestingly, a substantial proportion of patients described a worsening of their HrQoL for the pain/discomfort and depression/anxiety dimensions reflected by an increase in patient numbers for the extreme problems category for both treatment modalities. Overall, the majority of patients (40% to 60%) reported an equal HrQoL between baseline and 1-year follow-up as reflected by the absence of changes within the 3 levels for individual patients.

Accumulating evidence in the literature indicates that similar to improvements seen in the NYHA functional class, TAVR is associated with clinically important benefits in physical function. Clinically important improvements post-TAVR have been observed with disease-specific or physical functional measures such as the 12- or 36-item Short Form Health Survey physical component score (SF-12/36 PCS), the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Minnesota Living With Heart Failure Questionnaire, or the 6-min walk test. Most studies used the SF-12/36 for HrQoL assessments. On average, the PCS score improved from 6 to 11 months and 12 months. The improvements were less consistent and often smaller than what was considered clinically important in general health measures (EQ-5D) and in a psychological dimension (SF-12/36 PCS). The observed changes in mental component scores ranged from as low as 1.0 to 8.9 points. However, it remains speculative why TAVR patients do not benefit mentally as much as they do physically (11). Perhaps, the follow-up period of 12 months is too short to translate into an improvement in mental health measures.

For 102 patients undergoing TAVR, Fairbairn et al. (12) evaluated their HrQoL by means of 2 generic health questionnaires (SF-12, EQ-5D) at baseline, 30 days, 6 months, and 1 year. Patients' HrQoL significantly improved over 1 year, becoming comparable to age-adjusted U.S. population norms. The greatest change was observed from baseline to 30 days, with further significant improvements observed after 6 months. However, an insignificant decline occurred between 6 months and a year, which was also reported by other groups (13).

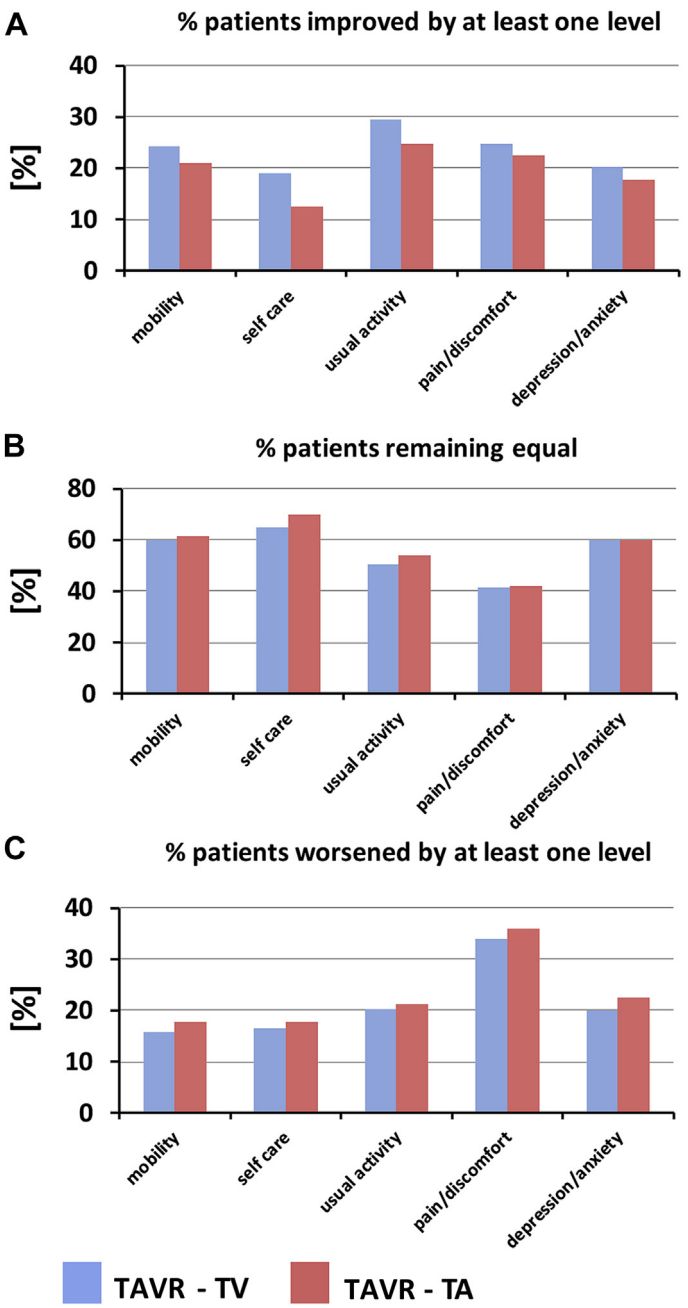
FIGURE 5 Within Level EQ-5D Percentage Changes



Percentage change in each of the 3 EQ-5D levels across all EQ-5D dimensions between baseline and at 1 year for the **(A)** TAVR-TV and **(B)** TAVR-TA groups. Abbreviations as in Figure 1.

When comparing HrQoL outcomes of TAVR patients treated via either a transvascular or a transapical approach, improvements were less pronounced for the TAVR-TA group. In the PARTNER trial (cohort A), patients eligible for transfemoral TAVR demonstrated significant HrQoL benefits at 1 month when compared to conventional SAVR. In contrast, patients treated via the transapical approach demonstrated no benefits over conventional SAVR at any time point. EQ-5D utilities increased by 0.08 to 0.10 at 6 and 12 months, with both TAVR and AVR, respectively, for the transfemoral cohort; for the TA cohort, the increase in EQ-5D scores was slightly less but nonetheless significant for both treatment modalities (14). The reduced HrQoL benefits for our TAVR-TA group might be partly explained by the fact that greater repeat hospital admissions were necessary for these patients. The results observed in our study are in

FIGURE 6 Patient Individual Description of EQ-5D Level Changes



Percentage of individual patients having changed, with **(A)** improvement or **(C)** worsening by 1 or 2 levels or **(B)** not having changed their level within the different EQ-5D dimensions between baseline and at 1 year in the TAVR-TV and TAVR-TA groups. Abbreviations as in Figure 1.

contrast to a recent report published by Bona et al. (15). In a prospective study including 264 consecutive patients receiving transfemoral or transapical TAVR, HrQoL was assessed using the EQ-5D questionnaire. TAVR-TA patients reported lower overall health status domains and significantly more problems in mobility, self-care, and usual activities prior to treatment. Although the improvement in HrQoL at 30 days was more pronounced in the transfemoral cohort than in the transapical cohort, this difference was no longer evident at 1 year (15). The higher 1-year mortality rate in the TAVR-TA group suggests that TAVR-TA patients represented a sicker group of patients. However, in our study, TAVR-TA patients reported fewer problems at baseline, rendering a comparison of results obtained by us and by Bona et al. (15) difficult.

In the European PARTNER study, 78.1% of TAVR-TA patients and 84.8% of transfemoral TAVR patients experienced significant improvements in NYHA functional class. In this study, 73.9% and 72.7% showed improved KCCQ scores, respectively. However, an evaluation of the EQ-5D data revealed only marginal improvements at 1 year post-intervention. The difference between baseline and 1-year results did not reach statistical significance. There was no difference between transfemoral TAVR and TAVR-TA. However, this study included only 51 patients with complete EQ-5D follow-up at 1 year (16).

The extent to which functional recovery following TAVR is affected by patient- and procedure-related factors remains poorly understood. Hence, our ability to accurately distinguish between patients who will most likely derive a functional benefit from TAVR and those who will not, remains limited. Notably, a considerable proportion of patients in the present study reported a worsening of HrQoL of at least 1 level within the respective domain. Except for mobility the proportion of patients reporting extreme problems within the subdomains usual activities, self-care, anxiety/depression, and pain/discomfort increased, ranging from 3.9% to 17.3%. This suggests that a considerable number of patients did not benefit from TAVR. Similarly, within the PARTNER trial, one-third of all patients treated had a poor outcome at 6 months according to a conservative definition (death, KCCQ score <45 [comparable to NYHA functional class IV], or decrease of ≥10 points in the KCCQ score), and one-half of patients had a poor outcome at 1 year using an expanded definition (death, KCCQ score <60, or decrease of ≥10 points in the KCCQ score) (17). This shows that there remains a sizable group of patients who either die or who do not derive HrQoL benefits after TAVR (18).

The extent to which functional recovery following TAVR is affected by patient- and procedure-related

TABLE 5 Univariate Linear Regression Analysis (Adjusted for the EQ-5D-Index at Baseline)

	All Patients			TAVI-TV			TAVI-TA		
	Regression Coefficient (β)	Standard Error	p Value ($p < 0.2$)	Regression Coefficient (β)	Standard Error	p Value ($p < 0.2$)	Regression Coefficient (β)	Standard Error	p Value ($p < 0.2$)
Pre-operative characteristics									
Age (yrs)	−0.002	0.001	**0.032**	−0.003	0.001	**0.011**	−0.001	0.002	0.794
Female	−0.074	0.013	**<0.001**	−0.072	0.016	**<0.001**	−0.092	0.025	**<0.001**
BMI	−0.003	0.001	**0.011**	−0.003	0.002	**0.057**	−0.004	0.003	**0.097**
BMI <22	−0.008	0.021	0.703	−0.010	0.024	0.670	−0.002	0.041	0.957
NYHA functional class III or IV	−0.051	0.018	**0.004**	−0.071	0.021	**0.001**	−0.005	0.033	0.892
CAD	0.002	0.013	0.896	−0.007	0.015	0.635	0.024	0.025	0.334
Previous MI	0.003	0.017	0.874	−0.003	0.021	0.900	0.015	0.033	0.637
Previous PCI	−0.005	0.015	0.717	0.010	0.017	0.575	−0.047	0.028	**0.092**
Previous cardiac surgery	0.041	0.016	**0.010**	0.053	0.020	**0.008**	0.032	0.027	0.244
Atrial fibrillation	−0.005	0.015	0.731	0.017	0.018	0.347	−0.053	0.028	**0.056**
LVEF									
30%–50%	0.012	0.014	0.416	0.013	0.017	0.433	0.013	0.026	0.622
<30%	0.012	0.025	0.627	0.027	0.028	0.334	−0.045	0.052	0.381
Cardiogenic shock/decompensation within 48 h prior to admission	−0.030	0.041	0.464	−0.020	0.045	0.653	−0.118	0.101	0.243
RRT	−0.095	0.033	**0.004**	−0.116	0.041	**0.005**	−0.052	0.053	0.324
Chronic RRT	−0.122	0.043	**0.004**	−0.102	0.052	**0.052**	−0.158	0.074	**0.033**
Neurodysfunction	−0.080	0.020	**<0.001**	−0.076	0.024	**0.001**	−0.086	0.036	**0.019**
Arterial vascular disease	−0.023	0.015	**0.113**	−0.037	0.018	**0.041**	0.014	0.025	0.579
Peripheral arterial vascular disease	−0.046	0.017	**0.008**	−0.052	0.022	**0.018**	−0.026	0.029	0.376
EOA	0.030	0.031	0.332	0.024	0.036	0.496	0.038	0.065	0.562
Pmean	0.001	0.399×10^{-3}	**0.180**	0.356×10^{-3}	0.455×10^{-3}	0.434	0.001	0.001	0.295
Pmax	0.234×10^{-3}	0.272×10^{-3}	0.388	0.096×10^{-3}	0.308×10^{-3}	0.756	0.001	0.001	0.337
Mitral insufficiency ≥2°	−0.034	0.015	**0.022**	−0.029	0.017	**0.100**	−0.054	0.029	**0.064**
Post-operative characteristics									
New onset RRT	−0.094	0.057	**0.101**	−0.194	0.080	**0.016**	0.016	0.082	0.844
Post-operative TIA or stroke	−0.153	0.044	**<0.001**	−0.125	0.048	**0.010**	−0.278	0.101	**0.006**
New onset atrial fibrillation	0.036	0.033	0.286	0.070	0.041	**0.088**	−0.030	0.057	0.605
New PM/ICD	−0.003	0.021	0.875	−0.002	0.023	0.930	−0.021	0.053	0.689
Bleeding ≥2 U	−0.041	0.015	**0.007**	−0.039	0.019	**0.042**	−0.034	0.026	**0.199**
Post-operative hospitalization	−0.004	0.001	**<0.001**	−0.005	0.001	**<0.001**	−0.001	0.002	0.429
Post-operative ICU	−0.003	0.002	**0.107**	−0.004	0.002	**0.095**	−0.001	0.003	0.834

Bold values indicate statistical significance with $p < 0.05$.

ICU = intensive care unit; LVEF = left ventricular ejection fraction; RRT = renal replacement therapy; other abbreviations as in Tables 1 and 3.

factors remains poorly understood and our ability to accurately identify patients who will most likely derive a benefit from TAVR (utility) is limited. In the context of the different studies investigating HrQoL after TAVR, both patient characteristics and procedural complications have been described to influence post-procedural recovery. However, predictive factors for the extent of HrQoL changes identified by available studies have been inconsistent. Goncalves et al. (19) showed that patients with peripheral vascular disease had less benefit in the extent of HrQoL improvement as shown by a lower enhancement in Minnesota Living With Heart Failure Questionnaire physical dimension score. Fairbairn et al. (12) showed that female sex and vascular complications were independent predictors of lower HrQoL improvements at 1 year. In contrast, procedure-related multiple small cerebral infarcts occurring in 77% of their patients were not associated with an altered health status (20). In a prospective study performed at our center, involving 106 patients completing a 1-year follow-up, a mitral valve regurgitation degree of greater than mild was predictive of lower HrQoL improvements. Only, at 3 months this difference reached statistical significance. Likewise, in accordance with Fairbairn et al. (12), female sex was also associated with less HrQoL improvements at 3 months (13). Although Taramasso et al. (21) observed no association between either patient demographics or baseline comorbidities and the degree of post-TAVR functional improvement, residual moderate to severe paravalvular leak and

TABLE 6 Multiple Linear Regression Analysis (Adjusted for the EQ-5D-Index at Baseline)

	Regression Coefficient (β)	Standard Error	Standardized Regression Coefficient (β)	p Value
All patients (corrected $R^2 = 0.254$)				
Constant	0.877	0.109		<0.001
Age (yrs)	-0.002	0.001	-0.042	0.031
Female	-0.071	0.014	-0.100	<0.001
BMI	-0.004	0.001	-0.055	0.004
NYHA functional class III or IV	-0.038	0.018	-0.039	0.035
Neurodysfunction	-0.082	0.020	-0.077	<0.001
RRT (pre- or post-operative)	-0.090	0.029	-0.058	0.002
Peripheral arterial vascular disease	-0.050	0.018	-0.053	0.004
Mitral insufficiency ≥2°	-0.031	0.015	-0.039	0.036
Post-operative TIA or stroke	-0.115	0.043	-0.049	0.008
Post-operative hospitalization	-0.002	0.001	-0.047	0.012
Pre-operative EQ-5D index (adjustement factor)	-0.702	0.027	-0.498	<0.001
TAVR-TV (corrected $R^2 = 0.269$)				
Constant	1.029	0.129		<0.001
Age (yrs)	-0.004	0.001	-0.062	0.006
Female	-0.071	0.016	-0.099	<0.001
BMI	-0.005	0.002	-0.062	0.006
NYHA functional class III or IV	-0.062	0.021	-0.064	0.003
Neurodysfunction	-0.084	0.023	-0.077	<0.001
RRT (pre- or post-operative)	-0.115	0.037	-0.067	0.002
Peripheral arterial vascular disease	-0.056	0.022	-0.055	0.013
Post-operative hospitalization	-0.004	0.001	-0.066	0.002
Pre-operative EQ-5D index (adjustement factor)	-0.717	0.031	-0.514	<0.001
TAVR-TA (corrected $R^2 = 0.211$)				
Constant	0.461	0.046		<0.001
Female	-0.097	0.024	-0.139	<0.001
Atrial fibrillation	-0.069	0.027	0.088	0.012
Neurodysfunction	-0.079	0.036	-0.077	0.027
Chronic RRT—pre-operative	-0.193	0.072	-0.093	0.008
Post-operative TIA or stroke	-0.272	0.099	-0.095	0.006
Pre-operative EQ-5D index	-0.644	0.051	-0.440	<0.001

Abbreviations as in Tables 1, 3, and 5.

periprocedural stroke were each associated with less substantial improvements in the SF-36 PCS. Stortecky et al. (22) observed that patients with preoperative chronic renal failure (defined as a serum creatinine >2.0 mg/dl) and obesity (defined as a BMI >30 kg/m^2), despite a significant improvement of HrQoL, had lower SF-36 PCS at follow-up if compared to patients without these comorbidities.

STUDY LIMITATIONS. Currently, the EQ-5D is the most well-known and commonly used generic measure of health status. However, the EQ-5D questionnaire has been criticized as a non-disease-specific instrument for HrQoL evaluation. Whilst in many applications the EQ-5D has been shown to be a valid and reliable measure of patient health, it has also been argued that in some contexts the 3-level version of the EQ-5D may lack sensitivity or fail to capture important aspects of health in certain disease areas (23). As for now, specific HrQoL assessment tools for aortic stenosis do not exist. However, the EQ-5D was chosen because it is cognitively simple and takes only a few minutes to complete, both aspects being important in this elderly patient population. Moreover, the EQ-5D has been widely employed as a generic HrQoL assessment tool in cardiovascular patients, involving populations affected by coronary artery disease, heart failure, or following heart transplantation (24–26). However, HrQoL improvements seen in studies using other generic and disease-specific assessment tools appear more prominent and consistent than improvements measured by the EQ-5D (11).

Of the original study population, 2.6% was lost to follow-up. However, a lost-to-follow-up rate of <10% is considered low and acceptable (11). Given the typical high 1-year mortality within the study population of 23% (20.7% for the TAVR-TV group and 28.0% for the TAVR-TA group, respectively), the proportion of patients with available data diminished over time. As expected, and depicted in Online Table 1, baseline characteristics of patients who died during follow-up and who were consequently not available for analysis (nonparticipants or nonsurvivors) showed significantly more comorbidities (log EuroSCORE 31.0 ± 20.5 vs. 23.1 ± 16.3; German aortic valve score 11.2 ± 11.5 vs. 7.3 ± 7.4) and more often underwent emergent procedures compared to participating survivors. Therefore, depicted HrQoL data are based on patients with a better general health status. In the current study, a group of patients that had not been treated invasively was not available for comparison. However, in the PARTNER study an excessively high mortality rate of 50% within 1 year was observed in patients receiving medical treatment alone. Hence, the results of the present investigation suggest that TAVR alleviates symptoms and improves physical function and quality of life compared with noninvasive treatment. Unfortunately, a total of 592 surviving patients rejected study participation. As depicted in Online Table 1, baseline characteristics of patients who survived but were not available for final data analysis as compared to the group of participants were comparable. However, significantly higher log EuroSCORE and German aortic valve scores were found: log EuroSCORE 23.1 ± 16.3 (participants) versus 26.3 ± 17.7 (surviving nonparticipants) and German aortic valve score (7.3 ± 7.4 vs. 8.5 ± 8.1), limiting the generalizability of results. Finally, 2,288 patients were available for data analysis representing 79.4% of patients that were alive after 1 year (n = 2,880), which can be considered a high percentage for this specific patient population. This

response rate was comparable to the PARTNER trial (cohort A) (14).

A drawback is that the study population is from 2011. Several important variables have changed, including newer generation devices, smaller and friendlier delivery systems, greater experience in appropriate patient selection, and procedural performance. However, we think the study population is representative for a high-risk patient TAVR population. The investigation of outcomes over time and outcomes in lower risk patients will be subject of future investigations.

CONCLUSIONS

TAVR was associated with HrQoL improvements after 1 year when compared to baseline, with pronounced changes observed for mobility and usual activity dimensions, whereas only moderate changes were found for self-care, pain/discomfort, and anxiety/depression. The magnitude of improvements was higher for the TAVR-TV group as compared to the TAVR-TA group. There was a sizable group of patients who did not derive HrQoL benefits. Several independent risk factors could be identified being predictive for a negative impact on quality of life 1 year after TAVR.

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PERSPECTIVES

WHAT IS KNOWN? Several previous studies have demonstrated that TAVR treatment significantly improves HrQoL in high-surgical risk patients with severe aortic valve stenosis with sustained effects up to 2 years when compared with optimal medical care and demonstrates comparable benefits relative to SAVR. The extent to which HrQoL following TAVR is affected by patient- and procedure-related factors remains poorly understood and our ability to accurately identify patients who will most likely derive a benefit from TAVR or not is limited.

WHAT IS NEW? To date, with a total of 2,288 included patients providing complete follow-up, the present study is the largest prospective nonrandomized series reporting on HrQoL outcomes in patients having undergone TAVR. HrQoL was prospectively measured using the EQ-5D-3L questionnaire at baseline and 1 year. In parallel to improvements in NYHA functional class, TAVR was associated with HrQoL improvements after 1 year when compared to baseline, especially in terms of mobility and usual activities. The magnitude of improvements was higher in the TAVR-TV group as compared to the TAVR-TA group. However, there was a sizable group of patients who did not derive any HrQoL benefits. Several independent pre- and post-operative factors could be identified being predictive for less pronounced HrQoL benefits.

WHAT IS NEXT? HrQoL assessment should continue to be an important component of TAVR-related trials. The effect of newer generation devices, smaller and friendlier delivery systems, greater experience in appropriate patient selection and procedural performance on HrQoL outcomes, and the inclusion of lower-risk patients warrant future investigations.

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APPENDIX For supplemental tables and a figure, please see the online version of this article.