



Cardiac rehabilitation and mid-term follow-up after transcatheter aortic valve implantation

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Abstract

Background Evaluation of patient outcomes following transcatheter aortic valve implantation (TAVI) has usually been based on survival and clinical improvement. Studies on quality of life are limited, and data from comprehensive assessments after the procedure are lacking. **Methods** Sixty patients referred for cardiac rehabilitation after TAVI underwent in-hospital and after-discharge multidimensional assessments to evaluate clinical, functional, and nutritional statuses, degree of autonomy, cognitive impairment, depression and quality of life. **Results** On admission to rehabilitation, approximately half of the patients had severe functional impairment and dependence for basic activities of daily living. During their hospital stay, one-third of the patients suffered significant clinical complications and two had to be transferred to the implantation center. Despite this, the overall outcome was very good. All of the remaining patients were clinically stable at discharge and functional status, autonomy and quality of life were improved in most. During a mean follow-up of 540 days (range: 192–738 days), five patients died from noncardiac causes, three were hospitalized for cardiac events, and nine for non cardiac reasons. Functional status and autonomy remained satisfactory in the majority of patients and most continued to live independently. **Conclusions** Patients referred for rehabilitation after TAVI are often very frail, with a high grade of functional impairment, dependence on others and high risk of clinical complications. During a rehabilitation programme, based on a multidimensional assessment and intervention, most patients showed significant improvement in functional status, quality of life, and autonomy, which remained stable in the majority of subjects during mid-term follow-up.

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1 Introduction

Transcatheter aortic valve implantation (TAVI) has become the standard of care for patients with severe symptomatic aortic stenosis who are considered unsuitable for conventional surgery and may be a valid alternative to surgery in selected high-risk surgery patients.^[1–5]

Clinical trial and registry data have shown a high rate of procedural success and favourable mid- to long-term outcomes after TAVI, including an improved survival rate compared with standard therapy, sustained clinical, hemodynamic and functional benefits, and optimal valve durabil-

ity.^[6–14] Three studies assessing health-related quality of life (HRQOL) in these patients using different questionnaires showed significant improvements of HRQOL, which were maintained for at least one year.^[15–17] The necessity of assessing HRQOL is supported by the valve academic research consortium (VARC-2) consensus document because improvement of quality of life may be as important as survival benefit in an elderly population with multiple chronic comorbidities.^[18] The VARC-2 consensus document also stresses the need to assess patient frailty, which is a syndrome resulting from a multisystem reduction in reserve capacity, typical in the elderly. It increases vulnerability to stress and is associated with an adverse health outcome, dependency, institutionalization, and mortality.^[19,20] Frailty is a multidimensional concept covering individual factors such as cognition, wasting and malnutrition, functional ability, and loss of independence in addition to psychosocial factors such as depression, poverty, and isolation. These variables should be assessed both in the initial risk stratifi-

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cation and during the post-procedure phase in older patients who are candidates for TAVI in order to tailor early intervention and long-term care to the individual patient. Recently, multidimensional geriatric assessment has been shown to predict mortality, cardiovascular events, and functional decline after TAVI.^[21,22]

The aim of the present study was to perform comprehensive assessment, intervention and mid-term follow-up of patients referred for cardiac rehabilitation after TAVI in order to determine the in-hospital and mid-term outcomes of these patients.

2 Methods

2.1 Patients and study design

This study was a prospective, single-center, one-arm study involving 60 patients who underwent TAVI at the 'A. De Gasperis' Cardiology and Cardiac Surgery Department, Niguarda Ca' Granda Hospital in Milan and were then referred to the Cardiac Rehabilitation Center of Istituti Clinici di Perfezionamento Hospital in Milan between September 2009 and June 2012. At least six months of follow-up was required to be eligible for enrolment. We limited enrolment into this study to patients sent by this high-volume center because we were asked to participate in the follow-up. The study was approved by the institution's research Ethics Committee and all patients gave written, informed consent.

Rehabilitative intervention was tailored to each patient based on individual diagnoses and needs. The goal was to achieve clinical stability and optimize pharmacological therapy, functional status, and autonomy. After discharge, patients underwent a follow-up program at our center after 6–12 months (T1) and 18–24 months (T2).

2.2 Measurement of health status

Initial assessment during the in-hospital phase included history taking, clinical evaluation and trans-thoracic echocardiography. All patients able to perform it were given a 6 min walking test (6MWT).^[23,24] Multidimensional assessment was based on the validated instruments described below.

Multimorbidity was quantified according to the Cumulative Illness Rating Scale (CIRS), a validated instrument used in geriatrics and rehabilitation, which measures the clinical burden of multiple medical problems in an individual patient.^[25]

The risk of protein-energy malnutrition and need for nutritional support was assessed by dietitians and nurses using the Malnutrition Universal Screening Tool (MUST) and a 3-day food diary obtained after admission.^[26]

The Modified Barthel index was used to assess independence of patients in relation to personal care and mobility. It measures the ability of a person to execute 10 basic activities of daily living, giving a quantitative estimate of the patient's level of dependency.^[27]

Cognitive impairment was assessed by the Mini Mental State Examination (MMSE), a validated and extensively used tool that tests five areas of cognitive function: orientation, memory, attention and concentration, language, and spatial ability.^[28]

To identify depression, we used the Geriatric Depression Scale (GDS), a tool designed specifically for rating depression in the elderly.^[29]

Health-related quality of life was assessed using the EuroQol Questionnaire (EQ-5D).^[30,31] It is a standardized generic measure of health applicable to a wide range of health conditions and consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

During each follow-up visit, patients underwent clinical and echocardiographic evaluation, the 6MWT, assessment of cognitive function, depression, autonomy, quality of life and living conditions. Patients unable to undergo complete multidimensional evaluation at our centre because they lived in different regions or in a geriatric residence were assessed by a telephone interview during which they (or their caregivers) were asked to give information on their clinical status, living conditions, quality of life and grade of autonomy.

2.3 Multidimensional intervention

The main purposes of the in-hospital rehabilitation programme were: (1) optimization of drug therapy in order to achieve clinical stabilization, titrate drug dosages, and treat periprocedural complications. (2) Nutritional evaluation and intervention. For patients with moderate or high risk of malnutrition, a careful analysis of common risk factors, such as eating dependency, dislike of the food provided, oral, dental, and swallowing disorders, depression or cognitive impairment, and persistent nausea or severe constipation, was made to tailor intervention to each individual. When indicated, a nutritional support was implemented early in the rehabilitation process. (3) Functional recovery and disability treatment. The exercise program was tailored to each patient on the basis of the clinical condition, result of the preliminary 6MWT, and disability grade. Patients unable to perform 6MWT and/or with dependence in basic activities underwent a personalized program based on bed exercises, sitting callisthenics and ambulatory training aimed at improving musculoskeletal flexibility and strength, movement coordination and the ability to perform activities of daily

living. In patients with mild disability and/or moderate reduction of functional capacity during the 6MWT, treatment with interval or steady-state aerobic training with cicloergometer or treadmill and callisthenics was used. Patients were treated six days a week. Psychological support and, in some cases, therapy with antidepressants were given in case of persistent or severe depression.

2.4 Statistical analysis

Continuous variables are presented as mean \pm SD (or range for follow-up length) and categorical variables as counts and percentages.

Changes of study variables during rehabilitation were assessed by using the paired *t*-test (continuous variables) or the McNemar test (proportions). Finally, changes over time in continuous variables (multiple time-points) were analyzed by generalized linear regression models for repeated measures, adopting the Bonferroni corrections for multiple pairwise comparisons. Statistical analysis was carried out using SPSS software. For all analyses, a value of $P < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics of patients

The main clinical and demographic characteristics of the study population are shown in Table 1. Mean age was 83.5 ± 5.0 years (range, 70–92) and more than half of the study

Table 1. Baseline characteristics ($n = 60$).

Age, yrs	83.5 \pm 5.0
Females	32 (53%)
Body mass index, kg/m ²	25.2 \pm 4.5
Logistic EuroSCORE, %	22 \pm 13
Cumulative Illness Rating Scale	3.75 \pm 1.5
Previous ACS or critical coronary stenosis	31 (52%)
Chronic renal failure	22 (37%)
Chronic obstructive pulmonary disease	17 (28%)
Diabetes	8 (13%)
Previous TIA/stroke	7 (12%)
Transfemoral approach	42 (70%)
Transaortic approach	18 (30%)
Aortic mean gradient before TAVI, mmHg	51.7 \pm 12.0
Aortic mean gradient after TAVI, mmHg	10.7 \pm 3.4
Days between TAVI and referral to rehabilitation	10.6 \pm 3.4
Days in cardiac rehabilitation stay	18.3 \pm 5.6

Values are mean \pm SD or n (%); ACS: acute coronary syndrome; TAVI: transcatheter aortic valve implantation; TIA: transient ischemic attack.

participants were women. The mean body mass index was 25.2 ± 4.5 . The mean logistic EuroSCORE and the comorbidity index of CIRS were high. In addition to the most significant comorbidities reported in Table 1, there were 36 patients with peripheral arterial disease, eight with serious vertebral column or knee arthrosis, seven with a history of neoplasms, six with chronic anaemia and three with chronic thrombocytopenia. The majority of patients ($n = 55$) were given a Medtronic CoreValve. Four patients were given a Direct Flow valve and one patient an Edwards SAPIEN valve. In 70% of the patients, a transfemoral approach was used. In patients with unfavourable peripheral access (30%), the TAVI procedure was performed with a direct aortic approach through a right anterior mini thoracotomy. The reduction of aortic gradient after TAVI was remarkable in each patient. The mean interval between procedure and referral to our rehabilitation center was 10.6 ± 3.4 days, and the mean length of cardiac rehabilitation was 18.3 ± 5.6 days.

3.2 Clinical complications after TAVI and during rehabilitation

Table 2 summarizes the main clinical complications observed in our patients both in the periprocedural phase and during in-hospital rehabilitation. In the early periprocedural phase, 23 patients required multiple blood transfusions for major bleeding due to vascular complications (12 patients), massive pericardial (two patients) and/or pleuric haematic effusions (four patients), and macrohaematuria (five pa-

Table 2. Main clinical complications after transcatheter aortic valve implantation.

Peri-procedural	
Anemia with blood transfusion	23 (38%)
Permanent pacemaker implantation	16 (27%)
Vascular complications	12 (20%)
Massive pleuric or pericardial effusion	6 (10%)
Myocardial infarction	1 (2%)
Cardiac perforation	1 (2%)
During cardiac rehabilitation	
Heart failure	7 (12%)
Anemia with blood transfusion	6 (10%)
Pneumonia	4 (7%)
Thrombocytopenia	3 (5%)
Massive pleuric effusion	1 (2%)
Severe respiratory failure	1 (2%)
Severe kidney failure	1 (2%)
Fracture of the pelvis	1 (2%)

Data are presented as n (%).

tients). Implant-related new and/or worsened conduction disturbances required permanent pacemaker implantation in 16 patients. A case of cardiac perforation required conversion to open heart surgery. None of the patients referred to our centre had stroke or acute stage three kidney injury in the periprocedural phase.

During in-hospital rehabilitation, the most frequent complications were heart failure (seven patients), drop in haemoglobin level requiring transfusion of ≥ 2 units of packed red blood cells (six patients), pneumonia (four patients), and thrombocytopenia leading to dual antiplatelet therapy withdrawal (three patients). One patient had a pelvic fracture due to an accidental fall, one was transferred for unresponsive respiratory failure, and another for severe pancytopenia. No patient died during in-hospital rehabilitation. Overall, 22 patients had clinical complications during rehabilitation and their mean in-hospital stay was significantly longer than that of patients without complications (21.5 ± 6.8 days vs. 17.1 ± 3.3 days) ($P = 0.001$).

3.3 Comprehensive assessment during in hospital rehabilitation

The parameters selected for a multidimensional assessment of the patients are presented in Table 3. Risk of mal-

Table 3 Comprehensive assessment during in hospital rehabilitation.

Parameter	Admission	Discharge	P
Malnutrition risk moderate	8 (22%)		
Malnutrition risk high	3 (8%)		
6MWT	210 \pm 87	275 \pm 97	< 0.001*
NYHA class	1.8 \pm 0.4	1.6 \pm 0.4	NS
EQ VAS	54 \pm 14	75 \pm 11	< 0.001*
Barthel index	84 \pm 21	95 \pm 10	< 0.001*
Autonomy (Barthel 91–100 points)	32 (53%)	45 (75%)	
Partial dependence (Barthel 65–90 points)	18 (30%)	13 (22%)	< 0.001 [†]
Dependence (Barthel < 65 points)	10 (17%)	2 (3%)	
Moderate cognitive impairment (MMSE 18–23 points)		19 (33%)	
Severe cognitive impairment (MMSE 10–17 points)		7 (12%)	
Moderate depression (GDS 11–17 points)		10 (18%)	
Severe depression (GDS 18–30 points)		7 (13%)	

Values are mean \pm SD or *n* (%). *According to *t*-test for paired data comparison; [†]According to McNemar test for paired proportions comparison. EQ VAS: EuroQol visual analogic scale; GDS: geriatric depression score; MMSE: mini mental state examination; NS: not significant; NYHA: New York Heart Association; 6MWT: 6-min walking test.

nutrition was assessed on admission to cardiac rehabilitation. High risk was found in eight subjects (22%) and moderate risk in three patients (8%). The 3-day alimentary diary confirmed a nutrient intake < 50% of calculated requirements in six patients with three patients requiring temporary oral nutritional support.

The mean distance walked at 6MWT at discharge was significantly higher than that at the admission, and corresponds to the $64\% \pm 23\%$ of the predicted vs. $49\% \pm 21\%$ in the admission test. With the exception of the patient who incurred a pelvis fracture, all patients could undergo a final 6MWT. On admission, six were unable to perform the test. Assessing only the 35 patients without performance-limiting motor problems, the mean value of distance walked was 328 ± 86 m, corresponding to the 73% of the predicted value.

The mean value of EQ VAS improved significantly during rehabilitation, as did the mean value of the Barthel index. At discharge 75% of the patients had good autonomy (vs. 53% at admission), 22% were partially dependent (vs. 30% at admission), and only 3% were dependent (vs. 17% at the admission).

Twelve percent of the patients had severe cognitive impairment, and 13% had severe depression at discharge.

3.4 Follow-up data

The mean follow-up was 540 days (range, 192–738 days). No patients were lost to follow-up. Fifty-four out of 58 patients discharged from rehabilitation had a complete comprehensive assessment at T1 and of the 42 patients evaluated at T2 (76% of the survivors), 38 were evaluated at our centre. Patients unable to reach our centre (four at T1 and four at T2) were reached by telephone to collect data as previously described in the methods section.

Two patients died in the first year after TAVI (one of medullary aplasia and one of progressive worsening of multiple comorbidities), and three died during the second year (two of cancer and one of respiratory failure).

Among survivors, 12 had new hospitalization [one for pleural decortication due to recurrent effusions after TAVI, three for cardiovascular causes (one acute coronary syndrome, one heart failure, and one ICD replacement), four for orthopaedic causes (femoral or vertebral fractures), two for transient ischemic attacks, and two for internal problems].

Of the 55 survivors at last follow-up, 52 were living at their own home and three in a geriatric residency [16 lived alone and 36 with a caregiver (most often a family member)].

Table 4 presents the results of the echocardiographic and multidimensional evaluation at T1 and T2. No cases of structural valve deterioration were observed. Mean trans-

Table 4. Follow up data.

	Rehabilitation	Follow-up		P
	discharge n = 58	T1 n = 56	T2 n = 42	
All cause mortality		2 (3)	5 (8)	
Rehospitalization		5 (8)	12 (20)	
Trans-aortic mean gradient, mmHg	10.7 ± 5.2	9.3 ± 3.9	10.8 ± 4.9	NS
Mild periprosthetic leak	14 (24)	11 (20)	11 (26)	
Moderate periprosthetic leak	4 (7)	2 (4)	2 (5)	
6MWT, m	275 ± 77	281 ± 88	265 ± 77	NS
EQ VAS	75 ± 11	71 ± 14	66 ± 16 [†]	0.007*
Barthel index	95 ± 10	91 ± 16	88 ± 18 [#]	0.04*
Autonomy (Barthel 91–100 points)	43 (75)	41 (73)	25 (60)	
Partial dependence				
65–90 points	13 (22)	13 (23)	11 (26)	
< 65 points	2 (3)	2 (4)	6 (14)	
Depression (GDS)				
Moderate (11–17 points)	11 (19)	12 (21)	9 (21)	
Severe (18–30 points)	8 (14)	4 (7)	7 (17)	
Cognitive impairment (MMSE)				
Moderate (18–23 points)	19 (33)	17(30)	11(26)	
Severe (< 18 points)	7 (12)	8(14)	6(14)	

Values are mean ± SD or n (%). EQ VAS: EuroQol visual analogic scale; GDS: geriatric depression score; MMSE: mini mental state examination; 6MWT: 6-min walking test; T1: 6–12 months follow-up; T2: 18–24 months follow-up. *For within-subjects effect according to generalized linear regression model for repeated measures; P values for pairwise comparisons (Bonferroni's corrected) are indicated as follows: [†]P < 0.002 vs. rehabilitation discharge; [#]P < 0.05 vs. rehabilitation discharge.

aortic gradient and the frequency of moderate periprosthetic leak remained unchanged during the period of observation.

Mean distance walked at 6MWT did not change significantly, but the number of patients unable to perform the test increased during follow-up: three at T1 and seven at T2.

The trend towards a decline in functional status in some patients was confirmed by a decrease in autonomy as reflected by the mean value of the Barthel index and by the statistically insignificant increase in the number of dependent patients over time. These findings are consistent with the significant reduction of the mean EQ VAS score observed during follow-up (Figure 1). However, we must emphasize that the mean EQ VAS value of our study population compared with the general population over 80 years of age was not significantly different both at rehabilitation discharge (R2) and at T1 and was only slightly lower at T2.

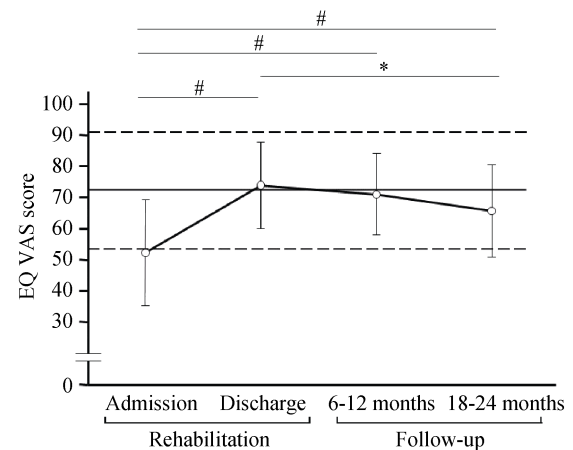


Figure 1. EuroQol visual analogue scale (EQ VAS) score in cardiac rehabilitation and during follow up. Data are reported as mean ± SD and graphically compared to the values of a general population survey of subjects aged 80 years. For pairwise comparison according to general linear regression model for repeated measures: [#]P < 0.001; *P < 0.05.

The percentages of patients with severe depression and severe cognitive impairment did not change over time.

4 Discussion

To our knowledge, this is the first study reporting the short-term and mid-term outcome of patients referred to cardiac rehabilitation for comprehensive assessment, intervention, and follow-up after TAVI.

The early post-procedural outcome of a significant number of patients was characterized by clinical problems due to haemodynamic instability, need for pacemaker implantation, vascular complications and anemia with multiple blood transfusions. This may have resulted in prolonged bed rest and deconditioning and increased the risk of malnutrition, functional decline, and progressive dependence. At admission to our rehabilitation program, many patients in the cohort were very frail: 30% were at risk of malnutrition, 47% were dependent for basic activities of daily living, 10% were unable to undergo 6MWT, 52% were “slow walkers” (< 200 m), 45% had moderate to severe cognitive impairment and 31% had moderate to severe depression. In addition, during in-hospital rehabilitation, approximately one-third of the patients had clinical complications that interfered with the rehabilitation programme and prolonged the hospital stay. Despite this, the overall outcome was good because, with the exception of the two patients requiring transfer, all patients were discharged in stable condition and most of them improved their functional status, autonomy and quality of life.

Prosthetic valve performance during follow-up was excellent. The mean transaortic gradient remained stable and the frequency of moderate paravalvular leaks was very low. Only five patients died during follow-up. This mortality rate is slightly lower than the rate recently reported by the Italian CoreValve registry, but the modest size of our cohort and the limited duration of follow up do not allow valid comparison.^[10] It is probable that the low mortality found in our study is not due to patient selection because, usually, the most complex patients are sent to cardiac rehabilitation. In addition, our findings are consistent with the very favourable in-hospital outcome of our patients.

As in the Italian CoreValve registry, deaths that occurred during follow-up were not related to cardiovascular events; similarly only three out of 12 post-rehabilitation hospitalizations were due to cardiac causes.^[10]

Among patients able to undergo the 6MWT, performance remained stable but the number of patients decreased over time. The functional status of a minority of patients worsened, mainly for orthopaedic reasons causing them to become partially or total dependent. This may have contributed to the significant worsening of quality of life observed at T2. Considering that frailty and disability have been found to be predictive of mortality and cardiovascular events after TAVI, it could be argued that, in selected patients, a rehabilitative intervention designed to prevent progression toward dependence could improve autonomy, quality of life and prognosis.^[21,22]

In addition to the mid-term favourable functional status found in the majority of patients, this prospective cohort study documents that, after TAVI, most patients continued to live independently in their home, alone or with the aid of their family or other caregiver.

In conclusion, the current study showed that on admission to rehabilitation after TAVI, many patients present with complex geriatric syndromes mainly due to deconditioning, dependence for basic activities of daily living, risk of malnutrition and depression. Moreover, one-third of patients have significant clinical complications interfering with recovery and prolonging the hospital stay.

Nevertheless, the majority of patients experience significant functional improvement with satisfactory autonomy and quality of life at discharge from rehabilitation. This improvement tends to persist in the mid-term, so most patients continue to live independently. The functional deterioration and hospitalizations observed in some patients were mainly due to noncardiac causes.

Our findings, while confirming the favourable mid-term outcomes after TAVI already shown in several studies, highlight the need for close clinical monitoring in the early

post-procedural phase in order to promptly detect possible clinical complications and to ensure early intervention in patients with advanced degree of fragility.

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