RESEARCH PAPER

Impact of frailty on health-related quality of life 1 year after transcatheter aortic valve implantation

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) brings symptom relief and improvement in health-related quality of life (HRQoL) in the majority of patients treated for symptomatic, severe aortic stenosis. However, there is a substantial group of patients that do not benefit from TAVI. The aim of this study is to investigate the impact of frailty on HRQoL 1 year after TAVI.

Methods: The TAVI Care & Cure Program is an ongoing, prospective, observational study including patients referred for TAVI to our institution. A comprehensive geriatric assessment was performed to evaluate existence of frailty using the Erasmus Frailty Score (EFS). HRQoL was assessed using the EQ-5D-5 L at baseline and 1 year after TAVI.

Results: 239 patients underwent TAVI and completed HRQoL assessment 1 year after TAVI. Seventy (29.3%) patients were classified as frail (EFS ≥ 3). In non-frail patients, the EQ-5D-5 L index did not change (0.71 (± 0.22) to 0.68 (± 0.33) points, P = 0.22); in frail patients, the EQ-5D-5 L index decreased from 0.55 (± 0.26) to 0.44 points (± 0.33) (P = 0.022). Frailty was an independent predictor of deteriorated HRQoL 1 year after TAVI (OR 2.24, 95% CI 1.07–4.70, P = 0.003). In frail patients, the absence of peripheral artery disease (OR 0.17, 95% CI 0.05–0.50, P = 0.001) and renal dysfunction (OR 0.13, 95% CI 0.04–0.41, P < 0.001) at baseline was associated with improved HRQoL 1 year after TAVI.

Conclusion: Frailty is associated with deterioration of HRQoL 1 year after TAVI. Notably, HRQoL did improve in frail patients with no peripheral arterial disease or renal impairment at baseline.

Keywords: Aortic stenosis (AS), Transcatheter aortic valve implantation (TAVI), Mortality, Quality of life, EQ-5D, Frailty, Older people

Key points

• Frailty is an independent predictor of deteriorating quality of life 1 year after TAVI.
• In frail patients, quality of life deteriorated 1 year after TAVI with no change in self-rated health status.
• In frail patients, the absence of peripheral artery disease and renal dysfunction is associated with improvement of quality of life.
• In non-frail patients, quality of life did not deteriorate, and self-rated health status improved.
Introduction

Aortic stenosis (AS) is a common valve disease in older patients, affecting about 3% of the population above 65 years. If not treated, the risk of mortality and deterioration of health-related quality of life (HRQoL) is high [1–3]. HRQoL of patients with severe AS is impaired due to symptoms of impaired exercise tolerance, dyspnea and eventually angina pectoris and/or syncope [4]. TAVI is increasingly used to treat patients with AS and is proven to be safe and effective in a wide variety of patient groups, including older patients [5–7]. Although the indication for TAVI has expanded to low-risk patients, the majority of patients who undergo TAVI are old and frail and have substantial comorbidities. For this specific population, the absolute gain in years may be of less importance than improving their HRQoL.

Previous studies showed an improvement of HRQoL in the majority of patients who underwent TAVI [8–10]. However, some patients do not report improvement in HRQoL [10,11]. Little is known on the factors determining lack of improvement of even deterioration of HRQoL after TAVI. Frailty has proven to be associated with an increased mortality and a higher rate of poor outcomes up to 1 year after TAVI [12,13], but studies on the impact of frailty on HRQoL after TAVI are limited [11]. The aim of this study, therefore, is to investigate the potential impact of frailty on HRQoL after TAVI.

Methods

Study population

The study population consists of 239 patients who underwent TAVI (November 2013–June 2018) within the frame work of the TAVI Care & Cure program [14]. In brief, the TAVI Care & Cure Program is a prospective single-centre multidisciplinary observational cohort study that was initiated in November 2013 and consists of a prospective collection of a comprehensive set of predefined cardiovascular and non-cardiovascular data including a comprehensive geriatric assessment (CGA) and baseline characteristics in addition to procedural and postoperative data of all patients referred for and treated with TAVI. There were no specific exclusion criteria. Treatment decision and strategy were decided during the multidisciplinary heart team meeting (interventional cardiologists, cardiac surgeons, anaesthesiologists, geriatricians and a TAVI-nurse coordinator) [15,16]. The TAVI Care & Cure Program was approved by the Medical Ethics Committee of the Erasmus University Medical Center (MEC-2014-277) and was conducted according to the Helsinki Declaration. All patients provided written informed consent.

Cardiology assessment

Cardiology assessment included determining symptoms using the New York Heart Association (NYHA) classification and the Canadian Cardiovascular Society (CCS) grading of angina pectoris, medical history including cardiovascular and non-cardiovascular comorbidities (Appendix A1 for the complete list of comorbidities), physical examination, laboratory assessment and electrocardiogram. Echocardiography, coronary angiography and multislice computed tomography (MSCT) were examined to evaluate the condition of the aortic valve and to determine access site [17].

Comprehensive geriatric assessment

In the CGA, the following frailty domains and instruments were examined: cognition, measured by the Mini-Mental State Examination (MMSE) [18]; strength, measured by the handgrip strength test [19]; (mal)nutrition, measured by the Malnutrition Universal Screening Tool (MUST) [20]; inactivity in basic activities of daily living, measured by the Katz index (Katz ADL) [21]; inactivity in instrumental activities of daily living, measured by the Lawton and Brody index [22]; and limitation of mobility using the Timed Up and Go Test (TUGT) [23] and 5 Meter Gait Speed Test (5MGST) [24]. A comprehensive explanation of the frailty domains and cutoff points can be found in Appendix A2. Frailty was defined by the Erasmus Frailty Score (EFS) that has been reported to be associated with postoperative delirium and 1-year mortality [12]. The EFS uses five geriatric domains: cognition, strength, (mal)nutrition, inactivity in basic activities of daily living and inactivity in instrumental activities of daily living. Patients were considered frail if the score on three or more domains was below predefined standard cutoff points [12]. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was used to rate existing comorbidities, measuring chronic medical illness burden while taking into account the severity of the chronic disease in 14 items representing individual body systems. The cumulative final score can vary theoretically from 0 to 56. The severity index is calculated dividing the total score through the total number of categories endorsed [25].

Quality of life measurement

HRQoL was assessed using the EuroQol 5 dimensions questionnaire (EQ-5D-5 L) preoperatively and 1 year after TAVI. The EQ-5D-5 L is a generic health utility HRQoL instrument and is qualified for measuring health status within an older population [26]. The EQ-5D-5 L consists of five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which is divided in five levels of functioning: no problems (level 1), some or moderate problems (levels 2 and 3) and severe or extreme problems (levels 4 and 5). Based on the responses to these dimensions, a single index value is estimated using a general population-based algorithm, ranging from −0.446 to 1 (a value of 1 indicating full health, while a value lower than 0 represents a status considered to be worse than death). The EQ-5D index value scores are country specific. Value sets and coefficients for the Dutch population were used for the estimations of the individual EQ-5D index [27]. The second component of the EQ-5D-5 L is the VAS score (visual
analogue scale). This is a standardised instrument to assess self-rated health on a scale with a scoring range from 0 (worst imaginable health state) to 100 (best imaginable health state) [28]. To incorporate data on mortality into the EQ-5D-5 L outcome, we divided our patient group into patients with either improvement or deterioration in HRQoL 1 year after TAVI. Improvement was defined as survival without any worsening in the EQ-5D index 1 year after TAVI compared to baseline. Deterioration was defined as death within 1 year or a decrease in the EQ-5D-5 L index 1 year after TAVI. This approach is comparable to a method previously used for the Kansas City Cardiomyopathy Questionnaire [29].

### TAVI procedure

TAVI was initially performed under general anaesthesia and from September 2015 onwards under local anaesthesia, using the transfemoral approach as default choice. After TAVI, patients were admitted to the intensive care unit for early monitoring for a minimum of 4 h before transferring to the general cardiology ward. From the day of admission up to at least 3 days after procedure, the geriatric consulting team is involved in delirium vigilance and preventing functional decline during admission.

### Statistical analysis

Continuous data are expressed as mean values with standard deviations ± SD. Differences between patients who were frail and non-frail were compared with nonparametric equivalents (Mann–Whitney–Wilcoxon U test). Categorical values were noted as percentages, and differences between patients who were frail and non-frail were compared with the chi-square test or Fisher’s exact test as appropriate. Paired sample t tests were used to analyse the difference between baseline and the EQ-5D-5 L index value at follow-up. The Reliable Change Index (RCI) was calculated measuring the difference between the EQ-5D-5 L index value on baseline and the EQ-5D-5 L index value at follow-up divided by the standard error of the difference between both EQ-5D-5 L index values. For the outcome deterioration of HRQoL 1 year after TAVI, univariate analysis was performed, entering variables with a P-value < 0.10 in the multivariate regression models. For the multivariable model, odds ratios (OR) and corresponding 95% confidence interval (95% CI) were computed, adjusted for age, sex, EQ-5D-5 L index on baseline, current smoking, peripheral artery disease, renal dysfunction, limitation of mobility (5 Meter Gait Speed Test) and frailty (EFS). P-value < 0.05 (two-tailed) was considered statistically significant. Statistical analysis was performed using IBM Statistical Package for Social Science (SPSS) for Windows version 25.

### Results

#### Patients characteristics

A total of 239 patients with severe symptomatic AS who underwent TAVI between November 2013 and May 2019 were assessed with CGA at baseline. About, 197 patients completed HRQoL follow-up after 12 months and 42 patients died within 12 months after TAVI. The mean age of patients was 80.8 ± 6.5 years and 49.8% were men. Seventy (29.3%) patients were frail (Erasmus Frailty Score ≥ 3). Detailed baseline characteristics are shown in Table 1.

#### New York Heart Association functional class

Preoperatively, 62.3% (n = 149) were in NYHA class III or IV (frail patients 81.4%; non-frail patients 54.5%, P < 0.001). One year after the procedure, 51.5% of the frail patients reported an improvement in NYHA functional class compared to 60.6% of non-frail patients (P = 0.224). One year after TAVI, 20.4% of the frail patients were still in NYHA class III or IV vs. 14.3% of the non-frail patients (P = 0.67) (Appendix A3).

#### Quality of life 1 year after TAVI (Eq-5D-5 L)

Improvement of HRQoL was seen in 125 patients (52.3%). Deterioration and/or death within 1 year was found in 110 patients (46.0%). Improvement of HRQOL at 1 year after TAVI was seen more often in non-frail patients as compared to frail patients (58.3 versus 39.7% respectively, P = 0.014). In frail patients, the EQ-5D-5 L index decreased from 0.55 ± 0.33) at baseline to 0.44 points (±0.26) at 1 year.

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### Table 1. Baseline characteristics (n = 239)

| characteristic                      | value       |
|-------------------------------------|-------------|
| Age (years, ±SD)                    | 80.8 ± 6.5  |
| Male gender (%)                     | 119 (49.8%) |
| BMI (kg/m², ±SD)                    | 27.2 ± 4.9  |
| **Cardiovascular risk factors**     |             |
| Hypertension (%)                    | 197 (82.8%) |
| Current smoker (%)                  | 23 (10.2%)  |
| Diabetes mellitus (%)               | 79 (33.1%)  |
| Hypercholesterolemia (%)            | 151 (63.2%) |
| Peripheral artery disease (%)       | 108 (45.2%) |
| **Comorbidities**                   |             |
| CIRS G score (points, ±SD)          | 15.4 ± 4.4  |
| CIRS G index (points, ±SD)          | 1.90 ± 0.3  |
| **Symptoms**                        |             |
| NYHA class 3 or 4 (%)               | 149 (62.3%) |
| Angina CCS classification 3 or 4 (%)| 29 (12.1%)  |
| Vertigo (%)                         | 93 (38.9%)  |
| **Echocardiography**                |             |
| Aortic valve area (cm², ±SD)        | 0.8 ± 0.2   |
| Peak AoV PG (mmHg, ± SD)            | 66.4 ± 21.6 |
| Peak AoV velocity (m/s, ±SD)        | 4.0 ± 0.7   |
| **Frailty indices**                 |             |
| Cognitive impairment probable (%)   | 74 (31%)    |
| Malnutrition probable (%)           | 27 (11.3%)  |
| Limitation of mobility, TUGT (%)    | 35 (14.6%)  |
| Limitation of mobility, 5MGS (%)    | 153 (64%)   |
| Reduced muscle strength, (%)        | 113 (47.3%) |
| Limitation in ADL activity (%)      | 70 (29.3%)  |
| Limitation in iADL activity (%)     | 128 (53.6%) |
| **Erasmus Frailty Score ≥ 3 (%)**   | 70 (29.3%)  |

Abbreviations used: BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; NYHA, New York Heart Association functional class; CCS, Canadian Cardiovascular Society; AoV, aortic valve; PG, pressure gradient; TUGT: Timed Up and Go test; 5MGS, 5 Meter Gait Speed Test; ADL, activities of daily living; iADL, instrumental activities of daily living.
Table 2. Quality of life at baseline and 12 months follow-up in frail and non-frail patients

|                  | Baseline | 12 months | P-value |
|------------------|----------|-----------|---------|
|                  | EQ-5D index | 0.55 (±0.26) | 0.44 (±0.33) | 0.022 |
|                  | EQ-VAS    | 58.4 (±16.8) | 63.4 (±14.6) | 0.095 |
| Frail patients   | EQ-5D index | 0.71 (±0.22) | 0.68 (±0.33) | 0.22 |
|                  | EQ-VAS    | 66.2 (±16.8) | 72.0 (±14.8) | <0.001 |

Values are expressed as means (±). VAS, visual analogue scale.

Table 3. Predictors of deterioration of quality of life 1 year after TAVI

| Variable                  | OR     | 95% CI      | P-value |
|---------------------------|--------|-------------|---------|
| Age                       | 1.01   | 0.96–1.07   | 0.647   |
| Gender                    | 1.13   | 0.56–2.27   | 0.737   |
| EQ-5D-5 L index on baseline | 10.62   | 2.32–48.52 | 0.002   |
| Current smoker            | 3.21   | 1.06–9.77   | 0.040   |
| PAD                       | 1.40   | 0.73–2.66   | 0.312   |
| Renal dysfunction         | 2.12   | 1.11–4.04   | 0.023   |
| Limitation of mobility (5mGST) | 2.29   | 1.35–6.17 | 0.006   |
| Frailty (EFS)             | 2.25   | 1.07–4.70   | 0.003   |

Abbreviations used: PAD, peripheral arterial disease; 5mGST, 5 meter Gait Speed Test; EFS, Erasmus Frailty Score.

Frailty was an independent predictor of deterioration of HRQoL 1 year after TAVI (OR 2.24, 95% CI 1.07–4.70). Current smoking (OR 2.12, 95% CI 1.11–4.04) and limited mobility (5mGST) (OR 2.29, 95% CI 1.35–6.11) were other predictors (Table 3). Postoperative delirium was associated with deterioration of HRQoL 1 year after TAVI in models adjusted for baseline predictors (univariate P-value <0.10) and baseline QoL status (OR 3.45, 95% CI 1.27–9.4). In frail patients, the absence of peripheral artery disease (OR 0.17, 95% CI 0.05–0.50) and renal dysfunction (OR 0.13, 95% CI 0.04–0.41) at baseline was associated with improved HRQoL 1 year after TAVI.

Nineteen (27.1%) frail patients died within 1 year after TAVI versus 22 (13.3%) non-frail patients (P = 0.014).

Discussion

In this study, we found that frailty at baseline is an independent predictor of deterioration of HRQoL 1 year after TAVI. In frail patients HRQoL deteriorated where the self-rated health status did not change. In non-frail patients HRQoL did not deteriorate and the self-rated health status improved. Importantly, in the absence of peripheral arterial disease and renal impairment, frail patients did experience improvement in HRQoL. In both frail and non-frail patients, we found an improvement in New York Heart Association functional class after TAVI.

Previous studies found an improvement in HRQoL after TAVI in the majority of patients [8,10,30]; however, even in large registry studies [10,30], there was a sizable group of patients who did not derive benefits in terms of improving HRQoL. Several factors including comorbidities, high mortality risk and frailty have been associated with poor outcome after TAVI [11–13,31,32]. A previous study found that if frailty was the indication for TAVI, the risk of not improving HRQoL after 1 year was twice as high compared to patients that had more technical indications for TAVI [8]. A substudy of the PARTNER Trial showed that frailty was associated with impaired HRQoL 6 months after TAVI, but this association was not found after 12 months of follow-up, in contrast to our results. In this PARTNER Trial substudy, frailty was estimated by the composite of four items, e.g. gait speed, grip strength, ADL scores and albumin, and almost 50% of the patients was classified as frail [11]. In our study, we use a different frailty score (EFS) where a more comprehensive set of frailty assessment tools are combined and where 30% of our patients were classified as frail, possibly indicating a more strict definition of frailty.

Differences in HRQoL outcomes between the PARTNER Trial substudy and our study could be explained by the difference in frailty definition. There is still a lack of consensus of defining frailty in an optimal frailty assessment [33]. Frail patients are impaired in physical activity, endurance, mobility, strength, etc., because of diminished physiological reserve [34,35]; therefore treating AS alone might not be sufficient to improve overall HRQoL because there still remain factors impairing HRQoL [34,36]. Although we found an
improvement in NYHA class in 50% of frail patients, this did not translate into an improvement in general HRQoL. However, in frail patients, the absence of peripheral artery disease and renal dysfunction at baseline was associated with improvement of HRQoL. Renal dysfunction is one of the most frequent comorbidities in TAVI patients and has been found to significantly worsen the prognosis of patients at short- and long-term follow-up [37]. This study shows that the combination of frailty and certain comorbidities could be associated with a higher chance of not improving HRQoL after TAVI. Although frailty has been associated with higher mortality rates compared to non-frail patients [11–13], survival rates are still higher compared to conservative therapy [38]. The determination of frailty is one of the many variables needed in the process of shared decision-making: concurrent comorbidities, treatment goals, expectations for the future, possible geriatric interventions and technical possibilities; all these aspects are unbearable for optimising treatment for this mostly older, frail and comorbid patient population. The treatment of this group of patients calls for intense collaboration between the geriatrician and cardiologist. This study has several limitations. First, results should be interpreted within the framework of a local population, because of the single-centre aspect of this study. Second, the Erasmus Frailty Score has not been formally validated in a different cohort; therefore, it should not be used in the clinical practice as a risk score to aid decisions. Nonetheless, we do believe that this frailty score is a reflection of the patient’s general condition, since it quantifies deficits in geriatric domains essential for optimal functioning in patients. It can be helpful in identifying those patients with frailty and therefore a higher chance of negative outcomes after TAVI.

In addition, the study population is relatively small; however, previously described studies included a similar number of patients. In this study we used the Eq-5D to measure general health-related quality of life. Because of its generality, the Eq-5D might fail to capture and incorporate factors in valuing QoL, such as socio-economic status, home support or incorporating events like falls or rehospitalisation.

Further research in a larger cohort focused on postoperative HRQoL and QoL in the broader sense is necessary to evaluate our current findings.

In conclusion, we found that frailty at baseline was associated with deterioration of HRQoL 1 year after TAVI and with no change of self-estimated health status. However, HRQoL did improve in frail patients with no peripheral arterial disease or renal impairment. Finally, patients who suffered from postoperative delirium had a poorer outcome, necessitating more diligence in delirium prevention strategy.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

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