European Journal of Cardio-Thoracic Surgery 53 (2018) 129–135
doi:10.1093/ejcts/ezx228 Advance Access publication 18 July 2017

ORIGINAL ARTICLE

Cite this article as: Auensen A, Hussain AI, Garratt AM, Gullestad LL, Pettersen KI. Patient-reported outcomes after referral for possible valve replacement in patients with severe aortic stenosis. Eur J Cardiothorac Surg 2018;53:129–35.

Patient-reported outcomes after referral for possible valve replacement in patients with severe aortic stenosis

Andreas Auensen[a,b,*], Amjad I. Hussain[a,c], Andrew M. Garratt[d], Lars L. Gullestad[a,b] and Kjell I. Pettersen[a,b]

[a] Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[b] Faculty of Medicine, University of Oslo, Oslo, Norway
[c] Faculty of Medicine, Centre for Heart Failure Research, University of Oslo, Oslo, Norway
[d] Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway

* Corresponding author. Department of Cardiology, Faculty of Medicine, OUS Rikshospitalet, Oslo University Hospital, PO Box 4950 Nydalen, 0424 Oslo, Norway. Tel: +47-2-95970176; fax: +47-2-23073917; e-mail: andreas.auensen@medisin.uio.no (A. Auensen).

Received 8 March 2017; received in revised form 15 May 2017; accepted 31 May 2017

Abstract

OBJECTIVES: Health-related quality of life (HRQoL) is an important outcome after surgical aortic valve replacement (SAVR). To improve interpretation of HRQoL, mean score change and change in terms of minimal important difference (MID) were assessed using validated instruments for measuring patient-reported outcomes in patients with severe aortic stenosis referred for possible SAVR.

METHODS: Of the 442 included patients with severe aortic stenosis evaluated for possible SAVR, 351 were referred to SAVR (operated) and 91 to medical treatment (unoperated). At presurgical evaluation and 1 year postoperatively, HRQoL was assessed using SF-36v2 and EQ-5D. Results were compared with outcomes reported in unoperated patients. We explored the association of clinical factors and improvements corresponding to MID.

RESULTS: Among the operated patients, statistically significant change was found for EQ-5D scores and SF-36 scale scores for physical functioning, role-physical, bodily pain, general health, vitality and physical summary score. The largest proportion of operated patients achieving change corresponding to at least MID was 61.5% for physical summary score. Change in unoperated patients also related largely to physical scales of the SF-36. However, smaller proportions of unoperated patients reported improvements, and larger proportions reported decline reaching MID. Baseline scores, but no clinical covariates, were consistently associated with improved HRQoL reaching MID across instruments for those referred to SAVR.

CONCLUSIONS: This study found improvement in HRQoL 1 year after SAVR for patients with severe aortic stenosis. Results in unoperated patients suggest that HRQoL deteriorates 1 year after evaluation of possible SAVR.

CLINICAL TRIAL REGISTRATION: www.clinicaltrials.gov (NCT01794832).

Keywords: Severe aortic valve stenosis • Surgical aortic valve replacement • Patient-reported outcomes • Quality of life

INTRODUCTION

Aortic stenosis (AS) is present in approximately 2% of individuals aged 70–80 years [1], and AS is the valvular heart disease that most commonly requires surgical treatment [2]. Left unoperated, patients with severe, symptomatic AS face a dismal prognosis with increased mortality and decreased health-related quality of life (HRQoL) [3]. For patients with low-to-moderate surgical risk, current guidelines recommend surgical aortic valve replacement (SAVR) [4]. After coronary artery bypass grafting, SAVR is the second most common cardiac operation [2].

Improved HRQoL is a main outcome after SAVR alongside symptom relief and lower mortality [4]. However, relatively few studies report HRQoL as a main outcome [5, 6], and methodological differences make interpretation difficult [7]. Moreover, few studies report change in HRQoL using validated instruments with results from before and after SAVR [8, 9]. More well-designed studies addressing HRQoL benefits in patients are required [7].

One aim of this study was to report the change in HRQoL from presurgical evaluation to 1-year follow-up after SAVR or continued medical treatment using widely tested and applied instruments; the SF-36v2 [10] and EuroQol 5 Dimensions (EQ-5D) [11]. Both these instruments have been assessed for the minimal important difference (MID), which is designed to help the interpretation of score changes. Another aim was to identify and report the proportion of patients that have health outcomes considered clinically important or 'meaningful', as opposed to statistically significant changes [12]. Previous studies have found improvements in HRQoL for patients undergoing SAVR [13]; however, few studies have investigated potentially modifiable

factors related to improvements in HRQoL after SAVR. Lastly, our aim was to assess associations between clinical factors and improvement corresponding to MID.

MATERIALS AND METHODS

Study design and patient population

This observational cohort included patients with AS referred to a tertiary centre (Oslo University Hospital Rikshospitalet, Norway) between May 2010 and March 2013 for evaluation of possible aortic valve replacement (AVR). Additional inclusion criteria were age >18 years and the ability to read and write in Norwegian. Patients without severe AS, who were unwilling to participate or had undergone previous AVR were excluded. Subjects scheduled for transcatheter aortic valve implantation (TAVI) were also excluded due to the limited number of such interventions performed during this period.

Severe AS was defined in accordance with current guidelines [4]. All patients underwent a standard workup during the evaluation (baseline). In cases of a low-flow, low-gradient state, with either a preserved or a reduced left ventricular ejection fraction, patients were further evaluated using low-dose dobutamine stress and/or transoesophageal echocardiography. The heart team was blinded to study data.

All participants gave a written informed consent. The study protocol was approved by the regional committee for ethics in medicine, complied with the Declaration of Helsinki, and was registered at www.clinicaltrials.gov (NCT01794832) (18 June 2017, date last accessed)

Health-related quality of life instruments

Patients were sent a postal questionnaire (QNR) that included the SF-36v2 [10] and EQ-5D [11] before attending the presurgical evaluation and before the outpatient visit at 1-year follow-up.

The SF-36v2 is a 36-item general HRQoL instrument that has 36 questions that contribute to 8 domains or scale scores of physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning, role-emotional (RE) and mental health (MH) [10]. The 8 scales also contribute to 2 summary scores: the physical component summary (PCS) and mental summary score (MCS) scales, which were standardized for comparison with a 1998 general US population (mean 50, SD 10) [10].

The EQ-5D includes 5 questions covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The questions have a 3-point scale of no problems, some or moderate problems and extreme problems. The scoring algorithm that is based on preferences for the EQ-5D health states gives the EQ-5D index score that ranges from −0.54 to 1, where higher scores represents higher HRQoL [14].

Determining the minimal important difference

The methodologies for determination of MID for the SF-36v2 and EQ-5D differed. There are 2 main approaches to deriving the MID: the anchor- and distribution-based methods [15, 16].

For SF-36v2, the suggested MID standard in the User's Manual for the SF-36v2® Health Survey (second edition) was used [10], which defines a significant change at the individual patient level (responder criteria) for each scale with an anchor-based approach. For EQ-5D, the MID was determined by integrating anchor- and distribution-based methods [12] using data from the Canadian population included in the 2011 Commonwealth Fund Survey of Sicker Adults. According to the aforementioned literature [10, 17], the exact thresholds for MID in this article were as follows: PF ±3.5 points; RP ±3.2 points; BP ±4.5 points; GH ±5.7 points; VT ±5.5 points; social functioning ±5.0 points; RE ±3.8 points; MH ±5.5 points; PCS ±3.1 points; MCS ±3.8 points; EQ-5D ±0.099 points.

Statistical methods

Descriptive statistics included frequencies and proportions for categorical variables, mean and standard deviation or as median and interquartile range as appropriate for continuous variables. Means and proportions were compared using χ^2 tests for categorical variables or *t*-tests or the Mann–Whitney test for continuous variables. Grouping of patients into operated and unoperated was based on the intention-to-treat principle. Association between baseline variables and patients experiencing an MID for SF-36v2 and EQ-5D were assessed by univariate logistic regression analysis performed by including independent variables based on existing literature and clinical experience [18, 19]. Before entering the regression models, covariates were $\log_{10}$ transformed or standardized (mean 0 and SD 1), as appropriate. Multivariable logistic regression analyses were performed by forced inclusion of baseline scores (for each instrument), age, gender and inclusion of covariates, which in univariate analysis were significantly associated with attaining MID at a level of <0.2. For all models, the criteria of variance inflation factor <8 and tolerance >0.2 were met. A comprehensive exploratory analysis of correlations with baseline variables and PCS, MCS and EQ-5D was performed using Pearson's product–moment correlation coefficient or Spearman's rank correlation coefficient, as appropriate. Data analyses were performed using STATA version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. StataCorp LP, College Station, TX, USA).

RESULTS

Patients and clinical characteristics

Figure 1 shows the study flow. Of the 573 consecutively registered eligible patients with AS, 68 refused participation, 20 had moderate AS, 5 were subsequently diagnosed with other diseases and 38 were referred to TAVI. Among the 442 included patients, 91 patients were referred to continued medical treatment (unoperated) and 351 patients were assigned to undergo SAVR. Three patients did not complete the baseline QNR, and hence, 348 of those referred to SAVR were subsequently included in the final analysis focusing on HRQoL. Mostly patients with planned procedures were included in the analyses of HRQoL. Only 3 of the 348 operated patients were urgently operated. Supplementary Material, Table S1 displays the operative details of patients. There were 103 of 348 (29.6%) patients receiving concomitant bypass surgery. Three patients died while awaiting SAVR, 15 patients died before follow-up and 55 patients did not complete follow-up QNRs, leaving 275 of 351 (78.3%) patients with complete QNRs (complete answer on at least 1 item of SF-36v2 or EQ-5D) at baseline and follow-up to allow analysis of change from

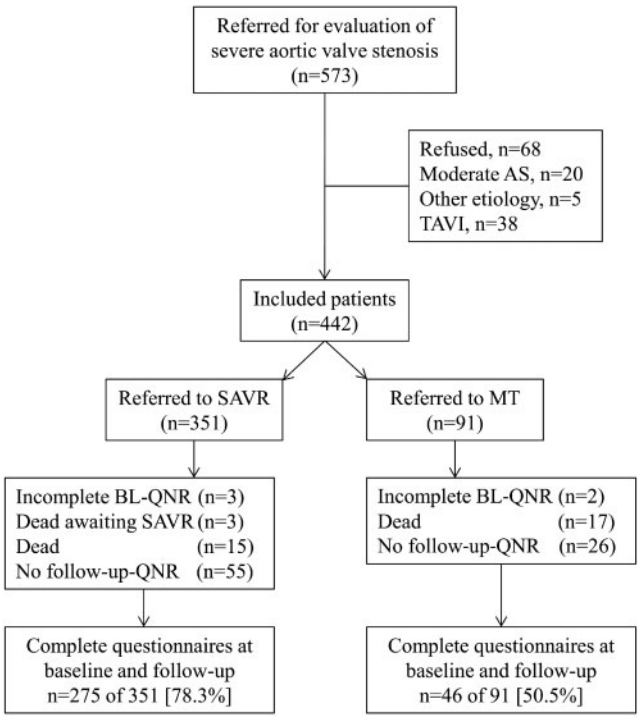

Figure 1: Study flow. TAVI: transcatheter aortic valve implantation; SAVR: surgical aortic valve stenosis; MT: medical treatment; BL: baseline; QNR: questionnaire.

'pairable QNRs'. Among the unoperated patients, 2 did not complete the baseline QNR, 17 died before follow-up and 26 did not complete the follow-up QNR, leaving 46 of 91 (50.5%) patients in the analyses of change.

Table 1 presents the baseline characteristics for the operated and unoperated cohort of patients.

Among the operated patients, those completing both QNRs had a lower prevalence of diabetes mellitus [17 of 76 patients (18.4%) vs 17 of 275 patients (6.2%), $P = 0.002$], worse scores for the Charlson comorbidity index ($P = 0.001$) and statistically significant lower baseline SF-36v2 scores across all scales than those who dropped out of the study (data not shown).

Among the unoperated patients, those having pairable QNRs had less coronary artery disease [8 of 46 patients (17.4%) vs 17 of 45 patients (37.8%), $P = 0.03$] and atrial fibrillation [10 of 46 patients (21.7%) vs 19 of 45 (42.2%), $P = 0.04$], better Charlson comorbidity index scores ($P = 0.02$) and a higher SF-36v2 physical function scores (37.4 ± 13.1 vs 30.9 ± 11.9, $P = 0.02$). Furthermore, better New York Heart Association class ($P = 0.05$), N-terminal pro-brain natriuretic peptide (NT-proBNP) [median 119 (interquartile range, IQR 48–337) vs median 284 (IQR 126–578), $P = 0.01$] and high-sensitive troponin T [median 15 (IQR 10–29) vs median 25.5 (IQR 16.0–42.5), $P = 0.01$] was observed in those with pairable QNRs compared with those answering at both time points (data not shown).

Change in health-related quality of life from baseline to follow-up

Table 2 presents the mean scores at baseline and follow-up for SF-36v2 and EQ-5D for operated and unoperated patients. For operated patients, statistically significant improvements were observed for SF-36 PF, RP, BP, GH, MH and VT. The SF-36 PCS and EQ-5D scores also showed significant improvements, whereas MCS scores were unchanged among those referred to SAVR. Among the unoperated patients, there was a statistically significant decline in SF-36v2 PF and RP, whereas no statistically significant changes were found for the other scales and EQ-5D.

The magnitude of change and experiencing minimal important differences

For SF-36 scales, the proportion of operated patients experiencing improvement corresponding to at least MID ranged from 56.3% (PF) to 36.9% (RE) (Fig. 2). The amount of operated patients experiencing improvement equivalent to MID for PCS, MCS and EQ-5D was 61.5%, 31.2% and 47.6%, respectively. The largest proportions of patients with improvements corresponding to at least MID 1 year after SAVR were for SF-36 scales that relate mostly to physical health. The majority of operated patients also had similar levels of improvement for VT. Except for MH and EQ-5D, where no patients reported a deterioration corresponding to MID, the proportions of patients who experienced a score deterioration corresponding to MID or worse 1 year after SAVR ranged from 30.6% for RE to 10.6% for GH. There were 157 individuals (57.1% of operated patients with pairable QNRs) who reported a deterioration corresponding to at least MID for any of the scales of SF-36 or EQ-5D. We did not find an association between such a deterioration and perioperative variables (postoperative wound-healing problems, receiving >4 units of red packed cells during surgery, spending >2 days in the intensive care unit), number of days from initial referral to operation or length of hospital stay in days (data not shown).

Among unoperated patients, the proportions reporting MID improvement were generally smaller across both instruments (range 11.3–33.3%) (Fig. 3). Furthermore, the proportion of patients reporting MID deterioration was generally larger for both instruments. There were no unoperated patients with deteriorations reaching MID for SF-36 MH or EQ-5D.

Associations with experiencing positive change after surgical aortic valve replacement

Supplementary Material, Table S2 shows the associations of selected covariates having attained a score improvement that was at least equivalent to the MID for the PCS. In the multivariable model, lower baseline PCS [odds ratio (OR) 0.94; beta coefficient (β) −4.00, 95% confidence interval (CI) 0.91–0–97, $P < 0.001$] and lower age at baseline (OR 0.96; β −2.59, 95% CI 0.93–0.99, $P = 0.010$) were significantly associated with attaining MID for PCS 1 year following SAVR. Supplementary Material, Table S3 shows that for MCS, lower baseline MCS (OR 0.90; β −6.00, 95% CI 0.87–0.93, $P < 0.001$) was the only covariate associated with attaining MID at 1-year follow-up after surgery. For EQ-5D, multivariable analysis shows that lower baseline EQ-5D score (OR 0.33; β −5.62, 95% CI 0.22–0.48, $P < 0.001$), male gender (OR 2.11; β 2.38, 95% CI 1.14–3.89, $P = 0.02$) and lower baseline [$\log_{10}$] NT-proBNP (OR 0.50; β −2.36, 95% CI 0.28–0.89, $P = 0.02$) were significantly associated with attaining MID at follow-up for operated patients (Supplementary Material, Table S4).

DISCUSSION

Although operated patients in our cohort had statistically significant improvements in mean scores for all SF-36v2 scales

Table 1: Baseline characteristics for operated and unoperated patients among those completing questionnaires at baseline and follow-up (pairable)

Variables	Pairable questionnaires in operated patients (*N* = 275)	Pairable questionnaires in unoperated patients (*N* = 46)	*P*-value
Demography			
Mean age, years	72.7 ± 10.4	81.8 ± 8.3	<0.001
Male gender, *n* (%)	162 (58.9)	21 (45.7)	0.09
Medical history, *n* (%)			
Hypertension	131 (47.6)	20 (43.5)	0.60
Coronary artery disease	82 (29.8)	8 (17.4)	0.08
Heart failure	14 (5.1)	3 (6.5)	0.69
Atrial fibrillation, all types	48 (17.5)	10 (21.7)	0.49
Diabetes mellitus (I or II)	17 (6.2)	5 (10.9)	0.24
Charlson comorbidity index, *n* (%)			0.20
0	131 (47.6)	19 (41.3)	
1–2	82 (29.8)	21 (45.7)	
≥3	14 (5.1)	6 (13.0)	
EuroSCORE II, median ± IQR	2.2 (3.4–1.2)	4.3 (1.9–6.4)	<0.001
NYHA classification, *n* (%)			<0.001
Class I	17 (6.2)	17 (37.0)	
Class II	142 (51.6)	17 (37.0)	
Class III/IV	116 (42.2)	12 (26.1)	
CCS (grade), *n* (%)			0.001
Score 0	146 (53.1)	0 (0.0)	
Scores 1–2	113 (41.1)	42 (91.3)	
Scores 3–4	16 (5.8)	4 (8.7)	
Echocardiographic measures			
Biplane LVEF, %	56.6 ± 8.3	57.2 ± 10.7	0.70
Aortic peak velocity, m/s	4.71 ± 0.74	4.5 ± 0.7	0.08
Aortic mean gradient, mmHg	55.5 ± 17.6	49.9 ± 16.4	0.04
Aortic valve area, cm^2	0.69 ± 0.21	0.70 ± 0.2	0.73
Biochemical values			
Haemoglobin, g/dl	13.8 ± 1.4	13.3 ± 1.6	0.03
eGFR, ml/min/1.73 m^2	79.0 ± 32.8	59.6 ± 27.5	<0.001
NT-proBNP, pmol/l [median (IQR)]	70 (29–178)	119 (48–337)	0.02
hs-TnT, ng/ml [median (IQR)]	12 (10–22)	15 (10–29)	0.30
Health-related QoL, mean score			
Physical functioning	41.0 ± 10.1	37.3 ± 13.0	0.03
Role-physical	38.3 ± 12.3	36.2 ± 13.4	0.30
Bodily pain	47.5 ± 10.8	45.0 ± 13.7	0.18
General health	44.0 ± 9.8	42.3 ± 9.9	0.29
Vitality	45.0 ± 12.2	43.7 ± 13.5	0.53
Social functioning	47.0 ± 11.3	44.8 ± 13.1	0.22
Role-emotional	46.1 ± 11.9	42.5 ± 16.6	0.10
Mental health	51.7 ± 9.9	49.1 ± 11.5	0.12
PCS	40.5 ± 10.4	37.0 ± 13.1	0.08
MCS	51.1 ± 10.9	49.4 ± 13.2	0.42
EQ-5D	0.74 ± 0.20	0.69 ± 0.27	0.08

Values are expressed as means ± SD. Pairable questionnaire indicates at least 1 scale of SF-36v2 or complete EQ-5D.

EuroSCORE II: European System for Cardiac Operative Risk Evaluation; IQR: interquartile range; NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate (Cockcroft–Gault formula); NT-proBNP: N-terminal pro-brain natriuretic peptide; hs-TnT: high-sensitive troponin T; QoL: quality of life; EQ-5D: EuroQol 5 Dimensions.

assessing physical health, as well as for VT and EQ-5D scores, the proportion who experienced change in HRQoL equivalent to MID across the different instruments ranged from approximately one- to two-thirds of patients. Among operated patients, most improvements reaching an MID were found for SF-36 scales assessing physical health, and the highest proportions were found for the PCS, where 61.5% of patients achieved such a score change. With the exception of MH and EQ-5D, some of those who underwent SAVR experienced a deterioration corresponding to the MID with proportions of patients ranging from 10.6% to 30.6%. There were few statistically significant associations between baseline variables and achieving MID improvement; dependent on the instrument, baseline instrument score, age, gender and NT-proBNP were statistically significant covariates in multivariable analysis for operated patients. Compared with operated patients, the proportions of unoperated patients experiencing MID improvement were smaller, and larger proportions reported change corresponding to MID deterioration.

Integrating patient-reported outcomes in clinical trials has recently been encouraged by the research community [20]. However, there are challenges regarding methodology, interpretation and implications for such outcomes [5, 7]. There are relatively few prospectively designed cohorts reporting HRQoL as a main outcome [21], and the results are often limited to

Table 2: Mean scores at baseline, follow-up and change in mean scores for scales of SF-36v2, summary scores of SF-36v2 and EQ-5D for operated and unoperated patients with pairable questionnaires

	Operated patients					Unoperated patients				
Instrument	*n*	Baseline	Follow-up	Δ	*P*-value	*n*	Baseline	Follow-up	Δ	*P*-value
PF	268	41.0 ± 10.1	45.8 ± 10.1	4.8	<0.001	44	37.3 ± 13.0	34.0 ± 13.7	-3.3	0.01
RP	258	38.3 ± 12.3	42.5 ± 11.9	4.1	<0.001	41	36.2 ± 13.4	32.7 ± 13.8	-3.5	0.04
BP	264	47.5 ± 10.8	51.6 ± 11.3	4.1	<0.001	40	45.0 ± 13.7	44.0 ± 13.1	-0.9	0.62
GH	264	44.0 ± 9.8	50.4 ± 10.5	6.4	<0.001	43	42.3 ± 9.9	40.6 ± 12.0	-1.8	0.21
VT	264	45.0 ± 12.2	49.4 ± 12.2	4.4	<0.001	42	43.7 ± 13.5	42.2 ± 15.1	-1.5	0.37
SF	274	47.0 ± 11.3	48.4 ± 11.1	1.4	0.07	46	44.8 ± 13.1	41.2 ± 14.9	-3.6	0.10
RE	252	46.1 ± 11.9	46.9 ± 12.0	0.9	0.29	40	42.5 ± 16.6	37.8 ± 18.0	-4.7	0.11
MH	263	51.7 ± 9.9	52.9 ± 10.8	1.2	0.04	42	49.1 ± 11.5	49.3 ± 10.5	0.2	0.92
PCS	231	40.5 ± 10.4	46.6 ± 10.7	6.1	<0.001	33	37.0 ± 13.1	34.5 ± 12.3	-2.5	0.06
MCS	231	51.1 ± 10.9	51.1 ± 11.6	0.0	0.96	33	49.4 ± 13.2	46.2 ± 13.7	-3.2	0.21
EQ-5D	260	0.74 ± 0.20	0.79 ± 0.21	0.04	0.002	45	0.69 ± 0.27	0.62 ± 0.34	-0.07	0.13

Values are expressed as means ± SD.

Δ: delta (follow-up score minus baseline score); PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary; EQ-5D: EuroQol 5 Dimensions.

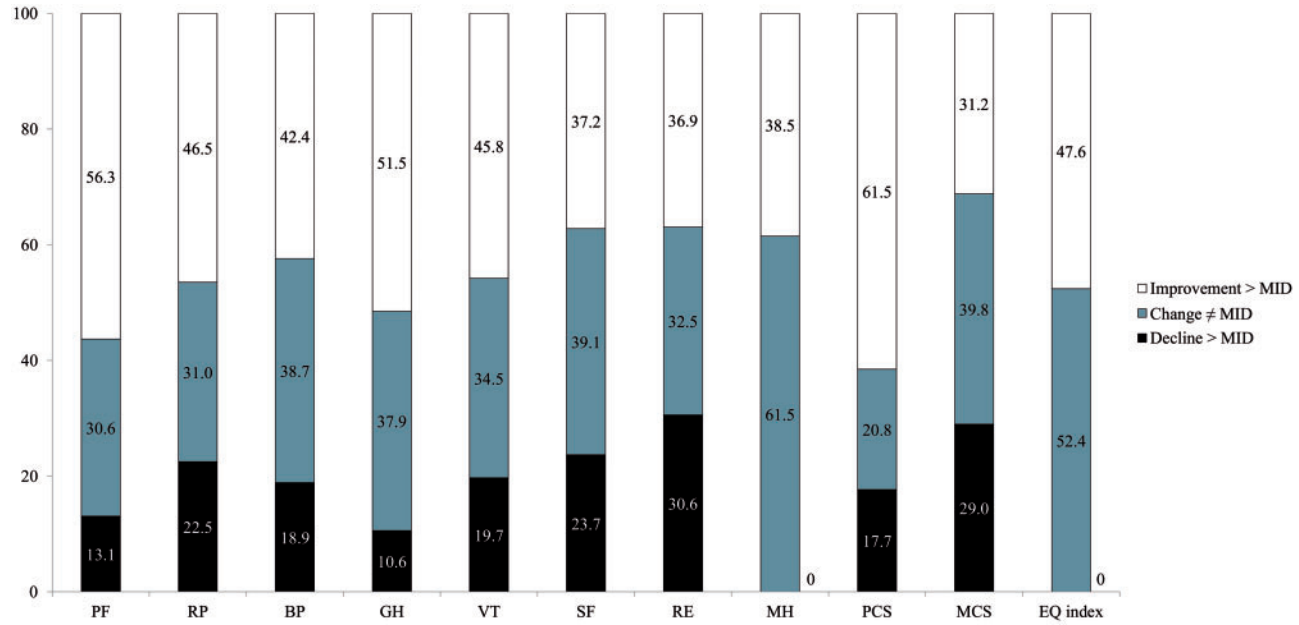

Figure 2: Proportion (%) of operated patients reporting change from presurgical evaluation (baseline) to 1-year follow-up after surgical aortic valve replacement based on MID for scales of SF-36v2 and EQ-5D. MID: minimal important difference; PF: physical functioning; BP: bodily pain; RP: role-physical; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component summary; MCS: mental summary score; EQ-5D: EuroQol 5 Dimensions.

elderly patients with high surgical risk [9]. Furthermore, some studies focusing on HRQoL report measurements using a single-validated instrument at a single time point postoperatively. This methodology precludes the important consideration of intra-individual change in HRQoL as a health outcome and that differences in health status at baseline may influence the magnitude of reported change between the 2 time points. This was observed in the current study where baseline instrument scores were prognostic factors for the levels of improvement including the MID. Single postoperative measurements also preclude the MID, which is important for the interpretation of changes in HRQoL. Furthermore, the present study was designed so that the potential influence of physicians on baseline measurements was minimized. The QNRs were administered before the decision of whether or not to operate was made. This might be important when measuring HRQoL since preparation for surgery may influence patients' perception of health.

Our results are similar to a smaller Dutch study that reports changes in SF-36 scores from before operation to 12 months after SAVR in patients with symptomatic AS [22]. The results in that study also report a similar pattern of deterioration largely related to the physical health status in unoperated patients. Regarding EQ-5D, one study reported a similar trend of mean score improvement 1 year after SAVR in 70 patients >75 years [23], but MID was not reported in that study.

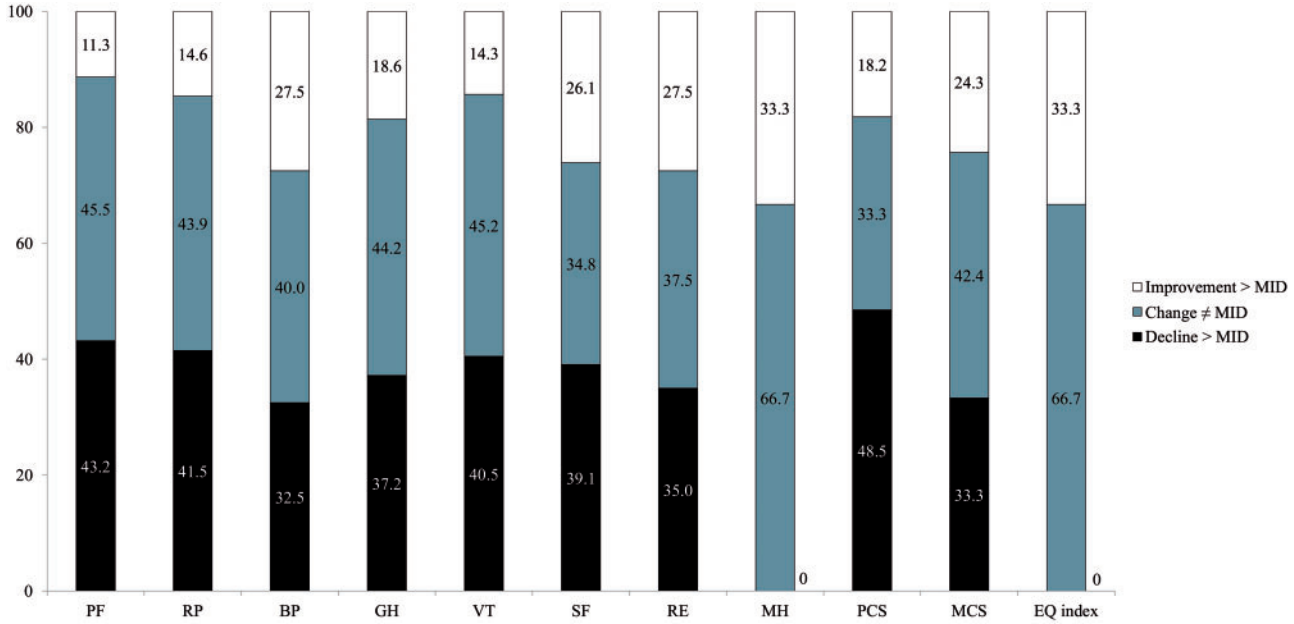

Figure 3: Proportion (%) of patients reporting change from presurgical evaluation (baseline) to 1-year follow-up after referral to continued medical treatment (unoperated) based on MID for scales of SF-36v2 and EQ-5D. MID: minimal important difference; PF: physical functioning; BP: bodily pain; RP: role-physical; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component summary; MCS: mental summary score; EQ-5D: EuroQol 5 Dimensions.

Attaining minimal important difference and associated factors in operated patients

The proportions of patients experiencing MID differed across scales and instruments. For operated patients, the largest proportion reporting change corresponding to MID was for SF-36 PCS (61.5%). Interestingly, the smallest proportion of positive MID was reported for RE (36.9%). Furthermore, PF was the scale with the highest proportion of positive MID combined with the second least negative MID, suggesting that improvement after SAVR is mostly related to physical health. Although this tendency is not different from the findings when analysing change in the mean scores, the introduction of MID gives important advantages for further exploration and interpretation of change.

As demonstrated in multivariable analyses, the baseline score was the only covariate consistently associated with attaining improved MID across the different instruments. Patient age, gender and NT-proBNP were also significantly associated, suggesting that younger patients are more likely to attain an MID for PCS, males are more likely to attain MID for the EQ-5D and increased levels of NT-proBNP (heart failure) is associated with lower chance of MID for the EQ-5D. The latter association suggests that patients should undergo AVR before myocardial function declines.

Clinical application and future perspectives

In terms of survival, preoperative New York Heart Association status and other patient characteristics, the present cohort is similar to other series following patients with severe AS after SAVR [24].

Moreover, results in the present cohort show the magnitude of change in HRQoL that can be expected in terms of 'meaningful' improvements following SAVR. Some may argue that it is discouraging if only one- to two-thirds of patients report a 'meaningful' improvement, and a non-negligible proportion of patients report a deterioration in HRQoL corresponding to MID 1 year after SAVR. However, when comparing these findings with change reported among the unoperated patients, results suggest that quality of life is indeed better for those referred to SAVR. Importantly, a comparison between operated and unoperated patients is not straightforward considering the different baseline characteristics, but the instruments seem to measure HRQoL changes appropriately, both in terms of mean changes and by means of MID. Considering the issue of timing of surgery and that eligible patients may sometimes be declined SAVR after inaccurately being labelled 'asymptomatic', future studies should investigate whether HRQoL assessments might be useful in cases where symptom status is unclear.

There are many uncertainties and unanswered questions with regard to the MID [10]. Wyrwich *et al.* [25, 26] presented MID for the SF-36v2 as determined by experts, patients and general practitioners. Interestingly, these articles present thresholds for MID that differ largely between the 3 perspectives, underlining the difficulty of determining the MID.

This study, combining clinical research and recommended interpretations of HRQoL outcomes by presenting results in terms of MID, may serve as a reference for future research. In an era where it is likely that more patients will be offered interventional procedures (such as TAVI), and patient-centred medicine is emerging, knowledge on HRQoL outcomes and proper interpretation of results is warranted.

A comparison of operated and unoperated patients was undertaken because randomization is ethically unfeasible. This ethical consideration will inherently limit the study designs in research on outcomes in patients with severe AS. As one of the aims of our study was to increase the understanding of HRQoL data and hopefully raise awareness of such outcomes among clinicians, we believe that results in unoperated patients would be of interest to readers by providing the best possible context for comparison. Despite originating from a group with higher age, more comorbidities and a higher dropout rate, we believe that the results from unoperated patients serve the purpose of forming a quantitative base for comparison of change with operated patients. However, the distribution of factors that may influence HRQoL

measurements is far from evenly balanced across the 2 groups and certainly represents a limitation. The purpose of reporting results in unoperated patients was not to provide a basis for a head-to-head comparison with operated patients but rather to inform about the methodology and understanding of results.

Limitations

The single-centre design limits the generalizability of our findings. Excluded patients were more comorbid with lower scores for all HRQoL instruments at baseline, thus limiting the results based on data from 'healthy survivors'. Because of a low number of patients ($n = 38$) and limited experience with the TAVI procedure at our centre during the time of the study, we chose to exclude patients referred for TAVI.

The study was limited to the 2 most widely tested and applied instruments, the EQ-5D and SF-36. To the best of our knowledge, there are currently no alternative recommendations for the MID, which are more up to date, suitable for our study or superior in terms of disease specificity or methodology.

In addition to the smaller number of medically treated patients in this cohort, this group was heterogeneous, as there were different reasons for not undergoing surgery. Three-year all-cause mortality among the groups of unoperated patients differed ['asymptomatic' 10 of 34 patients (29.4%) vs 'patient refusal' 9 of 20 patients (45.0%) vs 'high-risk' 25 of 37 patients (67.6%), log-rank test, $P = 0.04$]. Caution should be exercised in interpretation of change in this group and comparison with operated patients. We were not able to compare the results with the age- and sex-matched normal population [3, 9, 13, 22], because such data are not available for the Norwegian population.

CONCLUSION

Using widely tested and applied instruments, this study confirms that HRQoL is improved after SAVR for most patients with severe AS. Except for baseline scores, there were few strong associations between clinical covariates at baseline and achieving MID in operated patients. In unoperated patients, HRQoL deteriorated 1 year after evaluation for possible AVR. By presenting change in terms of MID, this study may improve interpretation of patient-reported outcomes among clinicians.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Funding

This work was supported by Oslo University Hospital.

Conflict of interest: none declared.

REFERENCES

[1] Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. Circulation 2005; 111:3316–26.

[2] Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation 2005;111:920–5.

[3] van Geldorp MWA, Heuvelman HJ, Kappetein AP, Busschbach JJV, Cohen DJ, Takkenberg JJM *et al.* Quality of life among patients with severe aortic stenosis. Neth Heart J 2013;21:21–7.

[4] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H *et al.* Guidelines on the management of valvular heart disease (version 2012). Eur J Cardiothorac Surg 2012;42:S1–44.

[5] Nugteren LB, Sandau KE. Critical review of health-related quality of life studies of patients with aortic stenosis. J Cardiovasc Nurs 2010;25:25–39.

[6] Barreiro CJ, Patel ND, Fitton TP, Williams JA, Bonde PN, Chan V *et al.* Aortic valve replacement and concomitant mitral valve regurgitation in the elderly impact on survival and functional outcome. Circulation 2005; 122(9 Suppl):I443–7.

[7] Shan L, Saxena A, McMahon R, Wilson A, Newcomb A. A systematic review on the quality of life benefits after aortic valve replacement in the elderly. J Thorac Cardiovasc Surg 2013;145:1173–89.

[8] Goldsmith IR, Lip GY, Patel RL. A prospective study of changes in patients' quality of life after aortic valve replacement. J Heart Valve Dis 2001;10:346–53.

[9] Lam BK, Hendry PJ. Patients over 80 years: quality of life after aortic valve replacement. Age Ageing 2004;33:307–9.

[10] Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the SF-36v2® Health Survey, 2nd edn. Lincoln, RI: Qual. Inc., 2007.

[11] Rabin R, de Charro F. EQ-SD: a measure of health status from the EuroQol Group. Ann Med 2001;33:337–43.

[12] Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003;56:395–407.

[13] Sundt TM, Bailey MS, Moon MR, Mendeloff EN, Huddleston CB, Pasque MK *et al.* quality of life after aortic valve replacement at the age of > 80 - years. Circulation 2000;102:70–4.

[14] Mark DB. Assessing quality-of-life outcomes in cardiovascular clinical research. Nat Rev Cardiol 2016;13:286–308.

[15] Lydick AE, Epstein RS, Lydick E, Epstein RS. Interpretation of quality of life changes. Qual Life Res 1993;2:221–6.

[16] Bjorner JB, Wallenstein GV, Martin MC, Lin P, Blaisdell-Gross B, Piech CT *et al.* Interpreting score differences in the SF-36 Vitality scale: using clinical conditions and functional outcomes to define the minimally important difference. Curr Med Res Opin 2007;23:731–9.

[17] Tsiplova K, Pullenayegum E, Cooke T, Xie F. EQ-5D-derived health utilities and minimally important differences for chronic health conditions: 2011 Commonwealth Fund Survey of Sicker Adults in Canada. Qual Life Res 2016;25:3009–16.

[18] Sedrakyan A, Hebert P, Vaccarino V, Paltiel AD, Elefteriades JA, Mattera J *et al.* Quality of life after aortic valve replacement with tissue and mechanical implants. J Thorac Cardiovasc Surg 2004;28:266–72.

[19] Baberg HT, Dirlich M, Laczkovics A, Grewe P, Bojara W, de Zeeuw J *et al.* Determinants of health-related quality of life after aortic valve replacement in six-month survivors of intervention. J Heart Valve Dis 2004;13:914–20.

[20] Anker SD, Agewall S, Borggrefe M, Calvert M, Jaime Caro J, Cowie MR *et al.* The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. Eur Heart J 2014;35:2001–9.

[21] Heijmeriks JA, Pourrier S, Dassen P, Prenger K, Wellens HJ. Comparison of quality of life after coronary and/or valvular cardiac surgery in patients >75 years of age with younger patients. Am J Cardiol 1999;83:1129–32.

[22] van Geldorp MWA, Heuvelman HJ, Kappetein AP, Busschbach JJV, Takkenberg JJM, Bogers AJJC. The effect of aortic valve replacement on quality of life in symptomatic patients with severe aortic stenosis. Neth Heart J 2013;21:28–35.

[23] van Laar C, Kievit PC, Noyez L. Surgical aortic valve replacement in patients older than 75 years: is there really a quality of life benefit? Neth Heart J 2015;23:174–9.

[24] Mohr FW, Holzhey D, Möllmann H, Beckmann A, Veit C, Figulla HR *et al.* The German Aortic Valve Registry: 1-year results from 13 680 patients with aortic valve disease. Eur J Cardiothorac Surg 2014;46:808–16.

[25] Wyrwich KW, Spertus JA, Kroenke K, Tierney WM, Babu AN, Wolinsky FD. Clinically important differences in health status for patients with heart disease: an expert consensus panel report. Am Heart J 2004;147:615–22.

[26] Wyrwich KW, Metz SM, Kroenke K, William M, Babu AN, Wolinsky FD. Triangulating patient and clinician perspectives on clinically important differences in health-related quality of life among patients with heart disease. Health Serv Res 2007;42:2257–74.