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Self-reported health status, treatment decision and survival in asymptomatic and symptomatic patients with aortic stenosis under conservative treatment – a cross-sectional study with 18 months follow-up

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ABSTRACT

Objectives To investigate symptoms and self-reported health of patients conservatively treated for aortic stenosis (AS) and to identify factors associated with treatment decision and patient outcomes.

Design A cross-sectional survey with an 18-month follow-up.

Setting One tertiary university hospital in Western Norway.

Participants In all, 1436 patients were diagnosed with AS between 2000-2012, and those 245 still under conservative treatment in 2013 were included in this study.

Primary and secondary outcome measures Primary outcome measures were symptoms and self-reported health status. Secondary outcomes were treatment decision and patient survival after 18 months.

Results A total of 136 patients with mean (SD) age 79 (12) years, 52% men responded. Among conservatively treated patients 77% were symptomatic. The symptom most frequently experienced was dyspnoea. Symptomatic patients reported worse physical and mental health compared to asymptomatic patients (effect size 1.24 and 0.74 respectively). In addition, symptomatic patients reported significantly higher levels of anxiety and depression compared to asymptomatic patients. However, symptom status did not correlate with haemodynamic severity of AS. After 18 months, 117 (86%) were still alive, 20% had undergone AVR and 7% transcatheter aortic valve implantation (TAVI). When adjusting for age, gender, symptomatic status, severity of AS, and EuroSCORE, patients with severe AS had more than six fold chance of being scheduled for AVR or TAVI compared to those with moderate AS (HR: 6.3, 95% CI: 1.9, 21.2, $p = 0.003$). Patients with EuroSCORE ≥ 11 had less chance for undergoing AVR or TAVI compared to those with EuroSCORE ≤ 5 (HR: 0.06, 95% CI: 0.01, 0.46, $p = 0.007$).

Conclusions Symptoms affected both physical and mental health in conservatively treated AS patients. Many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. The referral practice for AVR is a path for further investigation.

Key words: aortic stenosis; symptoms; health status; treatment decision; aortic valve replacement

Strengths and limitations of the study

- The study is targeting an understudied group of patients as very few studies have investigated self-reported health in AS patients under conservative treatment.
- The study employs standardized and validated questionnaires.
- Patient-reported outcomes are important to inform health professionals as well as policymakers in order to improve the quality of care to patients with AS.
- Patients were diagnosed with AS 1-11 years before the survey.
- The study is limited by the moderate response rate, and that it was carried out as a single-centre study.

INTRODUCTION

Aortic stenosis (AS) is the most common heart valve disease in the western world causing significant morbidity and mortality. As a result of an aging population, the prevalence of AS is increasing. [1] AS is most commonly caused by a degenerative calcification process leading to leaflet immobility, which in turn causes impaired blood flow through the heart and symptoms of pressure overload. [2] The three cardinal symptoms of AS, indicating the need for clinical intervention are; breathlessness, chest pain and light-headedness. [1] An unknown proportion of patients remain asymptomatic for several years despite the presence of haemodynamically severe disease. [3] Symptomatic AS has been associated with a sharp increase in death risk with an estimated 50% death rate at 2 years unless aortic valve replacement (AVR) is performed. [3] While much is known about the pathophysiology of AS, little is known about the disease burden placed on patients' daily life, whether symptomatic or asymptomatic. [4]

Current European guidelines recommend AVR for patients with a Class I assessment. These are patients who are symptomatic with severe AS, asymptomatic patients with severe systolic dysfunction or patients offered AVR as a concomitant procedure during another primary open cardiac surgery indication. [5] Despite these recommendations, studies have documented poor adherence to evidence-based guidelines, as 33-60% of the patients with severe symptomatic AS are inappropriately excluded from AVR. [6] Hence, there seems to be a gap between what is recommended and the real clinical practice. For various reasons, there are a large percentage of suitable candidates that are currently not referred for AVR. [5 7] Further, transcatheter aortic valve implantation (TAVI) has become widely accepted as an alternative to AVR and medical therapy for patients at high surgical risk. [5]

There are some reports on patient-reported outcomes in individuals with AS before and after AVR or TAVI. [8] However, few studies have focused on the quality of life or self-reported health status of symptomatic or asymptomatic AS patients who receive conservative treatment (i.e. medical therapy) and in whom surgical intervention is postponed or declined by the heart team or by the patient. [4 9]

The aims of this study were to investigate symptoms and self-reported health of patients conservatively treated for AS and to identify factors associated with treatment decision and patient outcomes.

METHODS

Study design and participants

A cross-sectional design was used to investigate factors related to patient-reported health status and the impact of valve disease on the patients' daily life. Patients were followed up for 18 months after the survey. Study endpoints were having undergone TAVI or AVR, or all-cause death.

In April 2013, a postal questionnaire was sent along with a pre-stamped return envelope to 1436 patients ≥ 18 years of age, able to write and understand Norwegian and diagnosed with AS. Results from the patients that had undergone AVR (N = 1191) are reported elsewhere [10]. Two-hundred and forty-five patients diagnosed with AS between 2000-2012 and still under conservative treatment were included in this study. To be included, candidate participants had to have echocardiographically verified AS in the native aortic valve, with at least a maximum transvalvular gradient of ≥40 mm Hg. Severe AS was defined according to current guidelines.[5] Patients had to fulfil at least one of the following haemodynamic criteria: an aortic valve area (AVA) < 1 cm^2; a mean pressure gradient > 40 mmHg or a peak aortic jet

velocity > 4 m/s, as demonstrated by Doppler echocardiography. Moderate AS was defined as having an AVA of 1.5-1.0 cm^2, a mean pressure gradient of 25-40 mm Hg or a peak aortic jet velocity of 3.0-4.0 m/s. [5]

Data collection

Hospital information system registries and patient medical records were used to identify patients eligible for the study and to exclude patients with a maximum aortic gradient of less than 40 mm Hg, or patients who were cognitively impaired or deceased. Socio-demographic variables, smoking status, symptoms, co-morbidities; and physical and mental health status were obtained by means of patient self-reports. Clinical variables such as date of AS diagnosis, reasons for declining an AVR or TAVI, results from Doppler echocardiography examination, treatment modalities, and survival were retrieved from patient medical records. Expected operative risk was calculated using numeric and logistic EuroSCORE I classification (Euroscore.org).

Self-reported health status and symptoms

Measurement of self-reported health status was obtained using the Short Form 12 (SF-12) health questionnaire. [11] SF-12 has been used to assess health status in AS patients undergoing AVR or TAVI. [12] The SF-12 (standard v. 1.0) questionnaire consists of 12 items. The first question asks the patient to rate his/her health as excellent, very good, good, fair, or poor. In the survival analysis for the present study, the response categories 'excellent' and 'very good', and 'fair' and 'poor' were merged. SF-12 has two summary measures: a physical component summary (PCS) and a mental component summary (MCS). [11] Each component summary results in a score ranging from 0 to 100. Summary scores are then standardised to a mean of

50 and a standard deviation of 10. Higher scores represent better-perceived health status. Internal reliability (Cronbach's α) was 0.89 and 0.88 for PSC and MSC, respectively.

To evaluate the burden of symptoms related to dyspnoea or heart failure, the Minnesota Living with Heart Failure Questionnaire (MLHFQ*)* was used. MLHFQ is a widely used disease-specific tool with well-documented validity, reliability, and sensitivity for symptoms related to heart failure. [13 14] All of the symptoms listed on the MLHFQ are also symptoms that may occur in individuals with AS. [15] Health impairment is evaluated using a 6-point scale, ranging from 0 (no impact) to 5 (severe impact). The instrument produces a total score (21 items; range: 0 to 105); a physical dimension sub-score (PDS) (8 items; range: 0 to 40); and an emotional dimension sub-score (EDS) (5 items; range 0 to 25). Lower scores indicate better health. For MLHFQ, Cronbach's α was 0.94 for PDS and 0.88 for EDS.

Self-reported symptoms of angina were obtained using a single question: 'Have you had chest pain (yes/no)?' One question from the MLHFQ was used to determine the proportion of patients with dyspnoea: 'Did your heart failure prevent you from living as you wanted during the last month by making you short of breath?' Possible answers ranged from 0 (no impact) to 5 (severe impact). Response values of ≥ 2 were categorised as symptomatic. Light-headedness was assessed by the question: 'How much has light-headedness influenced your daily activities the last four weeks?' Possible responses were: 1(not at all), 2 (a little), 3 (some), 4 (much), and 5 (very much). Response values of 3-5 were categorised as symptomatic. Cut-off points were set to avoid including patients who experienced very little discomfort as symptomatic.

The Hospital Anxiety and Depression Scale (HADS) was used to assess possible symptoms of anxiety or depression. [16] HADS consists of a seven-item sub-scale for anxiety (HADS-A) and a seven-item sub-scale for depression (HADS-D). For all items, responses are scored on a four-category scale, with 0 representing no symptoms and 3 representing maximum symptoms. The scores on each sub-scale range from 0 to 21. For identifying possible cases of anxiety and depressive disorders, the HADS has an optimal cut-off score of at least 8 for both sub-scales. [16] The Cronbach's α value were 0.86 for HADS-A and 0.75 for HADS-D.

The New York Heart Association (NYHA) Functional Classification was used to describe the impact of the disease on daily activities. [17] NYHA classifies patients into four categories (I-IV), with higher classes indicating more severe symptoms and limitations in physical activity. The self-assessed NYHA classification tool asks patients to assign themselves to a NYHA class by ticking one of four boxes indicating categories that best describe their ability to perform physical activity. This tool is a well-documented and valid method of assessing symptoms of heart failure. [17]

Ethics

The present study was conducted in accordance with the ethical guidelines contained in the World Medical Association's Declaration of Helsinki (2004) and was approved by the Regional Medical Ethics Committee of Western Norway (No. 2010/01954). Information about the study, the possibility of withdrawing at any time, and confidentiality issues were included in the letter that accompanied the questionnaire. Informed consent was taken as a patient returning the completed questionnaire. In accordance with the regional ethical committee, patients who failed to respond by mail were contacted once by telephone in order to encourage them to complete the questionnaire.

Statistical analysis

Descriptive statistics for continuous variables are presented as means and standard deviations (SDs). For comparisons between groups, the unpaired t-test was used. Descriptive statistics for categorical variables are presented as counts and proportions, and comparisons done using the exact chi-square test. Correlation between continuous variables was estimated by Pearson's correlation (r). Kaplan-Meier analysis was used to assess patient survival and cumulative incidence of AVR/TAVI after 18 months. Cox regression analysis was used to evaluate time-related events and their associations with baseline characteristics. Results are reported as hazard ratios (HRs) and 95% confidence interval (CIs). The statistical analyses were performed using SPSS for Windows 22 (IBM, Corp., Release 2013, Armonk, NY, USA), STATA/SE 14.0 for Windows, 02, 2015), Matlab 9.0 (The MathWorks Inc., Natick, MA, 2016) and Venn Diagram Plotter: (http://omics.pnl.gov/software/venn-diagram-plotter). A two-sided p-value ≤ 0.05 was considered statistically significant.

To evaluate the clinical importance of differences in self-reported physical and mental health of symptomatic and asymptomatic patients, we computed effect sizes (ES statistics) by dividing the mean differences in scores by the SD of the norm data. [18] To interpret the effect size, we followed the suggestion of Cohen, and regarded effect sizes of 0.2- 0.5 as small, 0.5-0.8 as moderate, and 0.8 and above as large. [18]

RESULTS

Patients' characteristics, symptoms and health status

Of the 245 patients treated conservatively and not having undergone AVR or TAVI by April 2013, 137 patients (56%) returned the questionnaire. One patient was excluded from further analysis due to a congenital subvalvular AS (Figure 1). No statistical significant differences

were found between responders and non-responders with respect to age (p = 0.157) or gender (p = 0.062).

The mean (SD) age was 79 (12) years and 52% were men. One-hundred and five (77%) patients were symptomatic. The most frequently self-reported symptom was dyspnoea, 57 (71%); followed by chest pain 49 (61%) and light-headedness 26 (33%). Overlapping symptoms are shown in Figure 2. Patients with symptomatic AS were older, had attained a lower educational level, were more often living alone, were placed in a higher NYHA class, had a higher EuroSCORE I, and were more often on medication such as beta-blockers and statins, as compared to asymptomatic patients (Table 1)

Of the 136 patients, 22 (16%) were not accepted for AVR by the heart team, whilst 12 (9%) patients declined AVR by themselves. The remaining 102 (75%) were considered as potential surgical candidates and remained under medical observation (Figure 3). The distribution of AS severity, symptomatic status and treatment decision at baseline are shown in Figure 1. No gender differences were found for severity of AS, chest pain, dyspnoea, light-headedness or numbers of symptoms reported. Risk stratification of all 136 patients revealed that 29 patients (21%) had a numeric EuroSCORE ≤ 5, 81 (60%) had a EuroSCORE between 6-10, and 26 (19%) had a EuroSCORE of 11-15.

Patients with asymptomatic AS reported better physical and mental health status compared to symptomatic patients. The estimated effect size for the differences in SF-12 measures between symptomatic and asymptomatic patients was 1.24 for the PCS and 0.74 for the MCS. The assessment of the impact of AS on the patients' daily life (MLHFQ), showed that it had a

significantly larger impact in symptomatic patients. In addition, asymptomatic patients had significantly lower HADS scores compared to symptomatic patients (Table 2).

Eighteen months follow-up

Eighteen months after the survey, 117 (86%) patients were still alive. Twenty-two (16%) had undergone AVR, 5 (4%) had undergone AVR in combination with coronary artery bypass grafting (CABG) and 10 (7%) had undergone TAVI. Nineteen patients (14%) had died; 1 died 6 days after AVR. The flow chart of patient outcomes (survival and AVR/TAVI) within the 18 months follow-up is shown in Figure 1.

Among the 102 individuals with medical observation at the time of the survey, 22 (21%) had undergone AVR, 7 (7%) had TAVI and 9 (9%) had died. Additionally, 2 patients were scheduled for AVR and 2 for TAVI during follow-up. Among the 22 patients previously not accepted for AVR by the heart team, 3 (14%) had undergone TAVI and 5 (23%) had died. Four of the 12 patients who decided to receive conservative treatment had died; and none had undergone AVR or TAVI.

Of the 20 patients with asymptomatic severe AS, only 3 (15%) had undergone an exercise test. One of them had a rise in blood pressure and a decrease of 2 mm in the ST-segment on EKG, but no symptoms of angina. He was finally accepted for surgery, but died before the operation. In the other two cases, the patients experienced a slight rise in pulse, but in both cases the test ended prematurely due to limb fatigue.

Of the 31 patients with symptomatic severe AS at baseline without surgical treatment after 18 months, five died prior to the end of the study. Of the latter, one had been accepted for AVR

and one for TAVI. The remaining 24 patients were still treated conservatively after 18 months, either due to symptoms unrelated to AS (n = 3), patients' decision (n = 1), horizontal aortic root not eligible for TAVI (n = 1), Alzheimer disease (n = 1), or vague symptoms (n = 3). The remaining 15 patients had, for unknown reasons, not been referred for cardiac surgery. Six of the patients with asymptomatic severe AS at baseline were treated with AVR (n = 4) or TAVI (n = 2) within 18 months. All of them developed symptoms, mainly dyspnoea before the intervention.

Multiple Cox regression analysis for selection of AVR or TAVI was performed and included age, gender, symptomatic status, severity of AS, and EuroSCORE as variables (Figure 4). Patients with severe AS had more than six fold chance of being scheduled for AVR or TAVI compared to those with moderate AS (HR: 6.3, 95% CI: 1.9, 21.2, p = 0.003). EuroSCORE ≥ 11decreased the chance for undergoing AVR or TAVI compared to having EuroSCORE ≤ 5 (HR: 0.06, 95% CI: 0.01 to 0.458, p = 0.007).

Self-rated general health at baseline tended to predict event-free survival (Figure 5a), and EuroSCORE tended to predict overall survival (Figure 5b) by the 18–months-follow-up, but the results were not statistically significant.

DISCUSSION

In the present study, the relationship between patient-reported outcomes and the severity of AS were investigated by employing well-established health status instruments. The results revealed that symptoms had a larger influence on the conservatively treated patients' physical and mental health than the severity of AS. AS severity alone, as measured by Doppler echocardiography examinations, did not differ between symptomatic and asymptomatic patients.

Previous studies have shown that important outcomes such as symptoms, function, and well-being are weakly associated with objective measures of disease severity. [19] It is known that the degree of AS at the onset of symptoms differs among patients. [3] The symptom most frequently experienced by patients in this study was dyspnoea. Dyspnoea was also the most frequent symptom observed in patients selected for AVR or TAVI. Since the presence of dyspnoea predicts worse survival for patients with AS, [20] our treatment algorithm is well supported by clinical outcome studies [20] and guidelines. [5] In the present study, mild symptoms of shortness of breath were classified as asymptomatic AS. Surprisingly, nearly 60% of the asymptomatic patients classified themselves within NYHA class II, indicating they experienced shortness of breath or tiredness, or palpitations when performing strenuous activities. Rather than attributing these two symptoms solely to exercise induced AS another plausible explanation is the presence of other co-morbidities, advanced age or their generally poor physical condition.

Symptomatic and asymptomatic patients also differed in physical and mental health status, with the latter having better scores. As the effect size showed, this difference is also clinically relevant. [18] Although neither the Doppler echocardiogram measurements (i.e. AS severity) nor number of co-morbidities differed between the two groups, the analyses showed that patient-reported outcomes did differ. This is in line with the reports of van Geldorp et al, who concluded that even minor AS symptoms may have a major impact on patients' physical and mental well-being, as well as quality of life. [4] They also concluded that there was no relationship between stenosis severity and patients' physical or mental health, but symptoms severity according to NYHA classification corresponded well with the SF-36 scores.

The health status in our population of conservatively treated AS patients was worse than previously reported in patients who had undergone AVR. [10] This was the case both for physical and mental health measures in SF-12 and MLHFQ, indicating that both give valid measures of health status in a conservatively treated AS population. These results also confirm the benefit of improved health status after treatment for AS with AVR or TAVI, as demonstrated in recent prospective studies. [12 21-23] Patients who graded their general health as fair or poor tended to have a lower 18-month event-free survival, as compared to those grading their health as good or better, but the difference was not statistically significant. Self-rated health has been shown to predict mortality one year after TAVI [24] and in other cardiac populations, such as women experiencing myocardial infarction, [25] patients with heart failure, [26] Veterans Affairs' heart patients with a variety of diseases, [27] and patients experiencing adverse clinical events one year after percutaneous coronary intervention. [28]

In the present study, symptomatic patients reported significantly higher levels of both anxiety and depression compared to asymptomatic patients, indicating that AS symptoms have a great impact on mental health. Compared to the cohort of patients having undergone AVR responding to the same questionnaire, [10] the conservatively treated symptomatic patients in the present study reported a higher level of anxiety and depression. However, the conservatively treated asymptomatic patients reported a lower level of anxiety and depression than patients that had undergone AVR. This again bolsters the findings that AS symptoms have a negative impact on patients' mental health and thereby that valve surgery can reduce this mental burden.

In symptomatic patients with severe AS, aortic valve surgery is generally recommended both by European and American guidelines. [5 29] Fifty-five per cent of the patients who fulfilled the

criteria for receiving AVR, either were not on the waiting list for AVR or had been treated with AVR or TAVI within 18 months after the survey. The low proportion of asymptomatic AS patients who underwent exercise testing may suggest that the indication for surgery was underestimated. Symptomatic status can be difficult to determine, especially in elderly patients, as they tend to minimise or deny symptoms, or reduce their physical activity level to avoid symptoms. [30] One-third of the patients who report to be asymptomatic develop symptoms during exercise testing; thus this type of testing is recommended to unmask symptoms in patients with severe AS. [31] With appropriate supervision and monitoring, symptom-limited stress testing is safe in severe AS and can add important prognostic value especially in older people that might have problems performing a treadmill exercise test due to coexisting morbidities. [31]

One possible explanation for the observation that many patients are not referred for surgery despite having severe symptomatic AS, is that patients are discharged from the university hospital without providing a clear treatment algorithm given to local hospitals, cardiologists in private practice, or general practitioners. Multidisciplinary heart teams, together with the patients and their family, should base their decision of open-surgery, TAVI or conservative treatment according to current guidelines, co-morbidities, and operative risks. Although the majority of the patients being denied surgery at baseline had a EuroSCORE of > 10, an elevated EuroSCORE did not fully explain why some patients still were not referred for surgery. As EuroSCORE is known to overestimate the risk of death, especially in low-risk patients scheduled for isolated AVR, the postoperative mortality risk may have been overestimated in some of the patients. [32]

There is robust evidence that AVR prolongs life in patients with symptomatic and severe AS. This is regardless of severity of symptoms or the response to medical treatment. [3] It is also of

utmost importance that health professionals inform patients with AS to contact their physician as soon as symptoms occur. The optimal time for intervention is still open to debate. Some argue that early elective surgery in asymptomatic patients with severe AS might be worthwhile, since rapid deterioration is associated with the disease. [33] AS severity, not symptomatic status, predicted selection for surgical treatment in this cohort. The gap between the existing guidelines and their actual application has been demonstrated in previous studies. [5 7] Close follow-up of the asymptomatic patients is important also, as severe symptoms or cardiac death may occur suddenly. [33]

Study strengths and limitations

Very few studies have investigated self-reported health in AS patients under conservative treatment. Patient-reported outcomes are important to inform health professionals as well as policymakers in order to improve the quality of care to patients with AS. Thus, the present study has some methodological limitations. It was carried out as a single-centre study, which may decrease the generalisability of the results. The sample, however, represents patients from both densely populated and rural areas. Another limitation is the retrospective design of the study and that we gathered only limited data prospectively. Further, a potential limitation is the moderate response rate of 56%. A possible reason for this response rate can be that some of the patients were still asymptomatic, and perhaps not motivated to take the time to answer the questionnaire. Alternatively, patients with severe disease burden were incapable of completing the questionnaire.

CONCLUSIONS

Patients receiving conservative treatment for AS, are an understudied group of cardiac patients. The present study demonstrated that AS symptoms have great impact on patients'

physical and mental health status. However, this impact does not reflect the severity of AS. Still, many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. Our results indicate that the referral practice for aortic valve surgery ought to be carefully scrutinised. Further well-designed prospective studies are needed to fully understand the disease burden of AS and to optimise the timing of surgical intervention. Self-reported health status may be a valuable supplement to physical examination during the clinical evaluation of high-risk AS patients.

Footnotes

Contribution KO, RH, JEN and TMN are responsible for study concept and design. KO and TMN are responsible for data collection. GEE, KO and TMN are responsible for data analysis. KO, RH, JEN and TMN are responsible for initial draft of manuscript. KO, RH, JEN, GEE and TMN are responsible for interpretation of data. All authors revised the paper critically for important intellectual content and approved the final manuscript. KO, GEE and TMN had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest The authors declare that there is no conflict of interest.

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Table 1. Baseline characteristics of 136 patients aged 35 to 95 years diagnosed with severe to moderate aortic stenosis in the period 2000 to 2012 who replied to a postal questionnaire in 2013.

Variable	All (N= 136)	Symptomatic (n = 105)	Asymptomatic (n = 31)	p-value*
Basic characteristics				
Age in years; *mean (SD) range*	79 (11) 35-95	80 (10)	75 (12)	**0.025**
Gender, men, *n (%)*	70 (52)	55 (52)	15 (48)	0.696
Living alone, *n (%)*	51 (38)	44 (42)	7 (23)	0.052
Education, *n (%)*				**0.037**
Elementary school	73 (54)	62 (60)	11 (36)	
High School	33 (24)	23 (22)	10 (32)	
University/College	29 (22)	19 (18)	10 (32)	
Smoking, *n (%)*				0.121
Current smoker	11 (8)	9 (9)	2 (7)	
Previous smoker	58 (43)	49 (47)	9 (30)	
Never smoked	66 (49)	47 (45)	19 (63)	
Sa-NYHA, *mean (SD)*	2.18 (0.87)	2.34 (0.88)	1.66 (0.55)	**<0.001**
NYHA I, *n (%)*	25 (19)	14 (14)	11 (40)	
NYHA II, *n (%)*	70 (53)	53 (52)	17 (57)	
NYHA III, *n (%)*	22 (17)	21 (21)	1 (3)	
NYHA IV, *n (%)*	14 (11)	14 (14)	0 (0)	
Doppler echocardiography examination				
Ejection fraction *(%), mean (SD)*	59 (9)	58 (10)	60 (7)	0.304
V-max (m/s), *mean (SD)*	4.0 (0.7)	4.0 (0.7)	3.9 (0.4)	0.418
AVA (cm^2 /BSI), *mean (SD)*	0.54 (0.2)	0.53 (0.2)	0.57 (0.2)	0.257
Mean aortic gradient, *mean (SD)*	41 (15)	42 (15)	38 (12)	0.115
Severity of AS				0.159
Severe AS, *n (%)*	101 (74)	81 (80)	20 (20)	
Moderate AS, *n (%)*	35 (26)	24 (65)	11 (35)	
Aortic regurgitation, *n (%)*				0.067
Mild (1/4)	55 (40)	43 (41)	19 (18)	
Moderate (2/4)	27 (20)	19 (18)	8 (25)	
Moderate-to-severe (3/4)	2 (1.5))	0 (0)	2 (6)	
EuroSCORE-log, *mean (SD)*	12.8 (11.6)	13.9 (11.8)	9.0 (10.3)	**0.027**
EuroSCORE-numeric, *mean (SD)*	8.0 (3.1)	8.3 (3.1)	6.9 (2.8)	**0.022**
Years since diagnosis, *mean (SD)*	5.7 (3.2)	5.5 (3.1)	6.3 (3.5)	0.207
Medical history, *n (%)*				
Diuretics	34 (25)	30 (29)	4 (13)	0.078
Beta-blockers	87 (64)	71 (68)	16 (52)	0.104
Statins	80 (59)	67 (64)	13 (42)	**0.030**
Myocardial infarction	24 (18)	18 (20)	6 (18)	0.753
Stroke	19 (14)	16 (16)	3 (10)	0.394
AF intermittent	33 (28)	28 (32)	5 (17)	0.140
AF permanent	8 (7)	7 (7)	1 (3)	0.454
COPD	8 (6)	8 (8)	0 (0)	0.109
Arthritis	25 (19)	22 (22)	3 (10)	0.139

Osteoporosis	18 (14)	15 (15)	3 (0)	0.454
Cancer	26 (20)	21 (21)	5 (16)	0.539
PCI	18 (13)	14 (13)	4 (13)	
Previous CABG	6 (4)	6 (6)	0 (0)	0.336
Pacemaker	10 (8)	7 (7)	3 (10)	0.555

SD: standard deviation; Sa-NYHA: Self-assessed New York Heart Association functional classification; AVA: aortic valve area; V-max: maximum jet velocity; CABG: coronary artery bypass grafting; AF: atrial fibrillation; COPD: chronical obstructive pulmonary disease. * Tests comparing symptomatic versus asymptomatic (bolded p-values significance at $p \leq 0.05$).

Table 2. Baseline self-reported health status of 136 patients aged 35 to 95 years diagnosed with aortic stenosis in the period 2000 to 2012 responding to the questionnaire in 2013, data differentiated by symptomatic status.

Variable	All (N= 136)	Symptomatic (n = 105)	Asymptomatic (n = 31)	p-value
SF-12, PCS, *mean (SD)*	36.8 (11.7)	33.8 (11)	46.2 (9)	**<0.001**
SF-12, MCS, *mean (SD)*	52.3 (10.4)	50.6 (11)	58.0 (4)	**<0.001**
MLHFQ Physical *mean (SD)*	11.8 (11.3)	14.9 (11)	3.3 (5)	**<0.001**
MLHFQ Emotional *mean (SD)*	3.1 (5.1)	3.9 (6)	0.6 (2)	**<0.001**
HADS-A, *mean (SD)*	3.9 (3.4)	4.2 (4)	2.9 (2)	**0.036**
HADS-D, *mean (SD)*	4.5 (3.4)	5.0 (4)	2.7 (2)	**<0.001**
HADS-A $\geq$ 8, *n (%)*	18 (14)	17 (17)	1 (3)	0.071
HADS-D $\geq$ 8, *n (%)*	24 (18)	22 (22)	2 (7)	0.056

SD: standard deviation; PCS: physical component summary of SF-12; MCS: mental component summary of SF-12; MLHFQ: Minnesota Living with Heart Failure Questionnaire; HADS-A: Hospital Anxiety and Depression Scale, anxiety component; HADS-D: Hospital Anxiety and Depression Scale, depression component

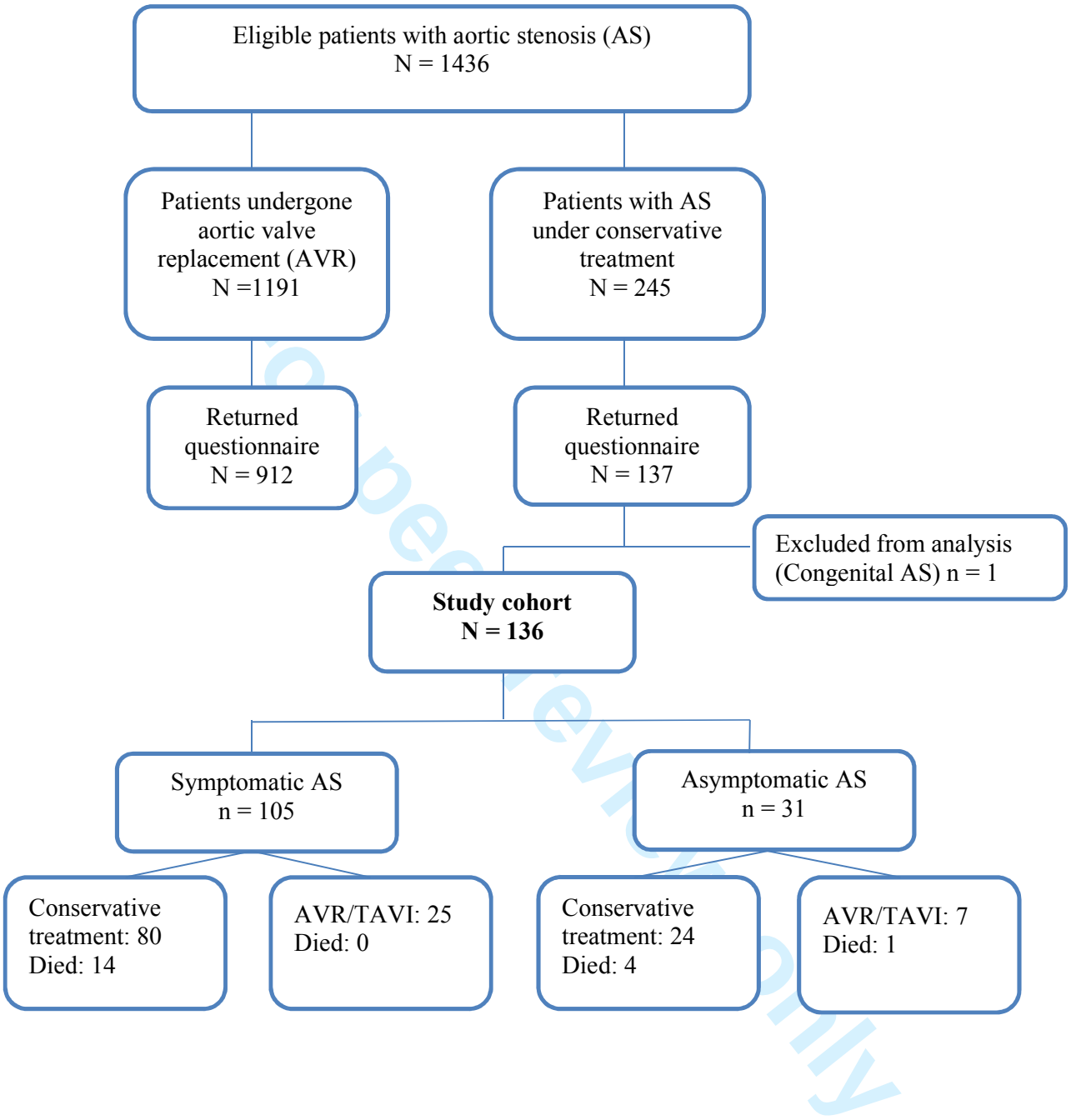


Figure 1. Flowchart showing patient with and without aortic valve replacement participating in the study, and outcomes after 18-months follow-up for136 patients aged 35 to 95 years under conservative treatment at the time of survey. Patients were diagnosed between the years 2000 to 2012 and were invited to complete the questionnaire in year 2013.

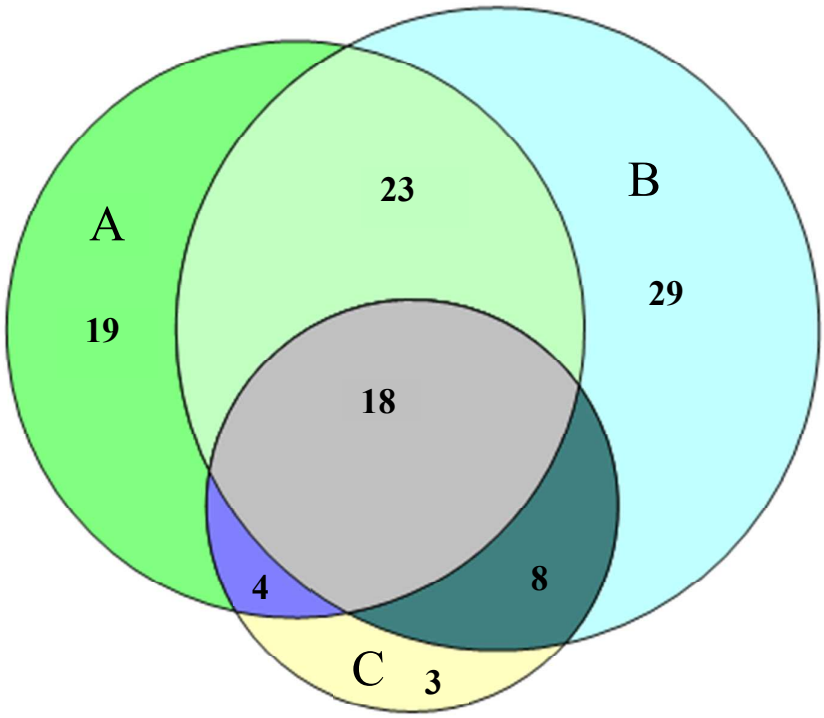
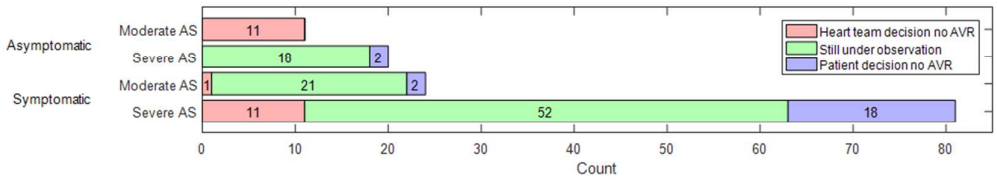


Figure 2. Number of symptomatic AS patients with overlapping symptoms (N = 105)
A: Chest pain. B: Dyspnoea. C: Light-headedness.



Figur 3. Reasons for not having undergone AVR at baseline in 136 patients with symptomatic and asymptomatic severe-to-moderate aortic stenosis.

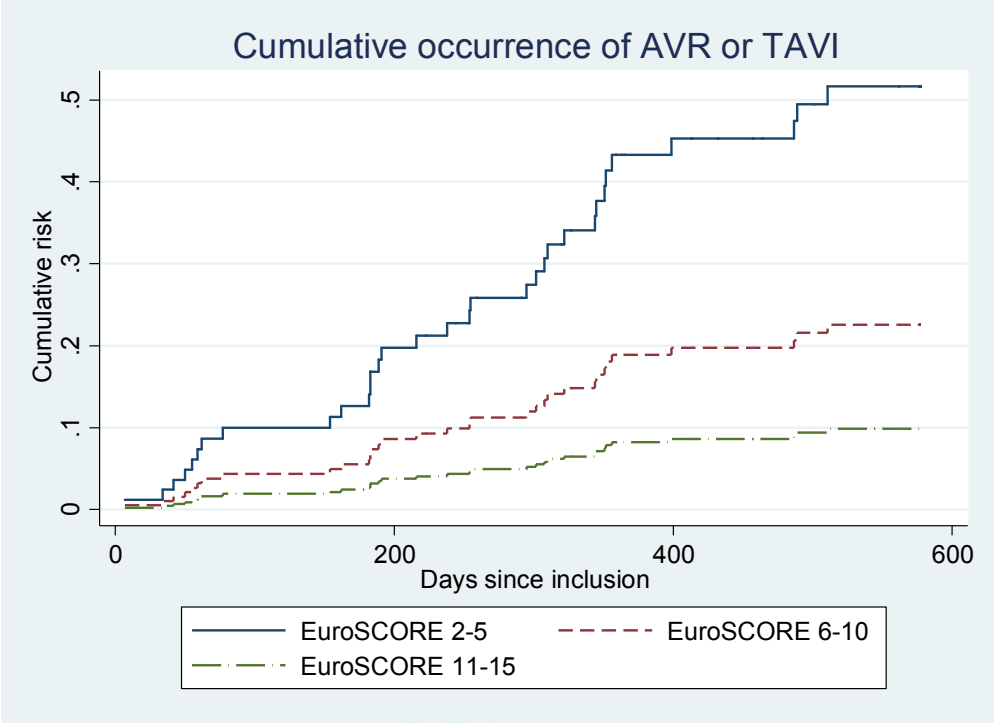


Figure 4. Cumulative occurrence of AVR or TAVI from Cox model, according to EuroSCORE range (likelihood ratio p-value (LR-p) = 0.011) in patients with aortic stenosis within 18 months adjusted for gender (LR-p = 0.336); age (LR-p =0.223); symptomatic status (LR-p = 0.437); and severity of aortic stenosis (LR-p = 0.002).

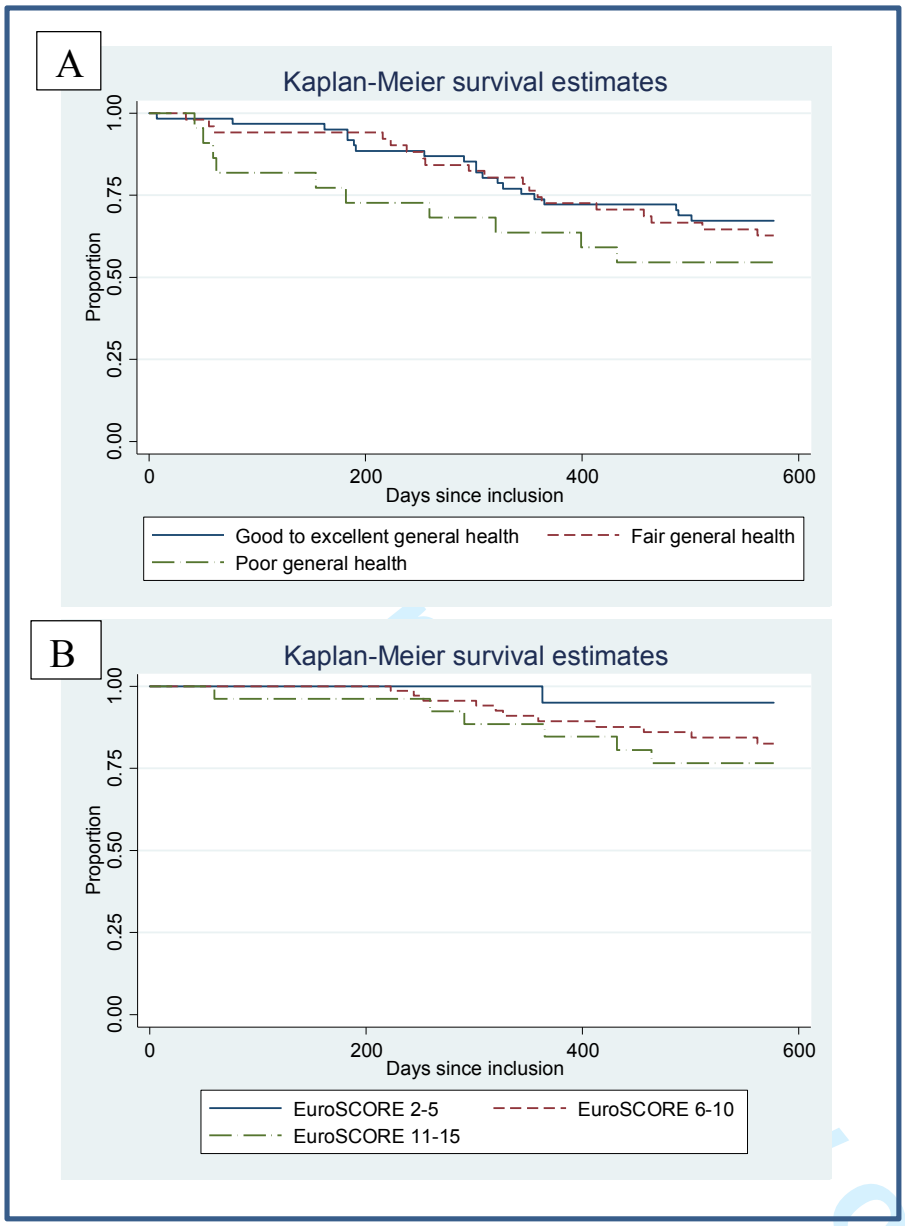


Figure 5. Kaplan-Meier curves showing: A, event-free survival in patients with aortic stenosis according to self-rated general health category at baseline (log rank test: p = 0.418). B, overall survival in patients with aortic stenosis (AVR or TAVI censored) according to numeric EuroSCORE I range (log rank test: p = 0.209).

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Self-reported health status, treatment decision and survival in asymptomatic and symptomatic patients with aortic stenosis in a Western Norway population undergoing conservative treatment – a cross-sectional study with 18 months follow-up

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ABSTRACT

Objectives To investigate symptoms and self-reported health of patients conservatively treated for aortic stenosis (AS) and to identify factors associated with treatment decision and patient outcomes.

Design A cross-sectional survey with an 18-month follow-up.

Setting One tertiary university hospital in Western Norway.

Participants In all, 1436 patients were diagnosed with AS between 2000-2012, and those 245 still under conservative treatment in 2013 were included in this study.

Primary and secondary outcome measures Primary outcome measures were symptoms and self-reported health status. Secondary outcomes were treatment decision and patient survival after 18 months.

Results A total of 136 patients, mean (SD) age 79 (12) years, 52% men responded. Among conservatively treated patients 77% were symptomatic. The symptom most frequently experienced was dyspnoea. Symptomatic patients reported worse physical and mental health compared to asymptomatic patients (effect size 1.24 and 0.74 respectively). In addition, symptomatic patients reported significantly higher levels of anxiety and depression compared to asymptomatic patients. However, symptom status did not correlate with haemodynamic severity of AS. After 18 months, 117 (86%) were still alive, 20% had undergone surgical aortic valve replacement (AVR) and 7% transcatheter aortic valve implantation (TAVI). When adjusting for age, gender, symptomatic status, severity of AS, and EuroSCORE, patients with severe AS had more than six fold chance of being scheduled for AVR or TAVI compared to those with moderate AS (HR: 6.3, 95% CI: 1.9, 21.2, p =0.003). Patients with EuroSCORE $\geq$11 had less chance for undergoing AVR or TAVI compared to those with EuroSCORE $\leq$ 5 (HR: 0.06, 95% CI: 0.01, 0.46, p =0.007).

Conclusions Symptoms affected both physical and mental health in conservatively treated AS patients. Many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. The referral practice for AVR is a path for further investigation.

Key words: aortic stenosis; symptoms; health status; treatment decision; aortic valve replacement

Strengths and limitations of the study

- The study is targeting an understudied group of patients as very few studies have investigated self-reported health in AS patients under conservative treatment.
- The study employs standardized and validated questionnaires.
- Patient-reported outcomes are important to inform health professionals as well as policymakers in order to improve the quality of care to patients with AS.
- Patients were diagnosed with AS 1-11 years before the survey.
- The study is limited by the moderate response rate, and that it was carried out as a single-centre study.

INTRODUCTION

Aortic stenosis (AS) is the most common heart valve disease in the western world causing significant morbidity and mortality. As a result of an aging population, the prevalence of AS is increasing. [1] AS is most commonly caused by a degenerative calcification process leading to leaflet immobility, which in turn causes impaired blood flow through the heart and symptoms of pressure overload. [2] The three cardinal symptoms of AS, indicating the need for clinical intervention are; breathlessness, chest pain and dizziness or syncope. [1] An unknown proportion of patients remain asymptomatic for several years despite the presence of haemodynamically severe disease. [3] Symptomatic AS has been associated with a sharp increase in death risk with an estimated 50% death rate at 2 years unless aortic valve replacement (AVR) is performed. [3] While much is known about the pathophysiology of AS, little is known about the disease burden placed on patients' daily life, whether symptomatic or asymptomatic. [4]

Current European guidelines recommend AVR for patients with a Class I assessment. These are patients who are symptomatic with severe AS, asymptomatic patients with severe systolic dysfunction or patients offered AVR as a concomitant procedure during another primary open cardiac surgery indication. [5] Despite these recommendations, studies have documented poor adherence to evidence-based guidelines, as 33-60% of the patients with severe symptomatic AS are inappropriately excluded from AVR. [6] Hence, there seems to be a gap between what is recommended and the real clinical practice. For various reasons, there are a large percentage of suitable candidates that are currently not referred for AVR. [5 7] Further, transcatheter aortic valve implantation (TAVI) has become widely accepted as an alternative to AVR and medical therapy for patients at high surgical risk. [5]

There are some reports on patient-reported outcomes in individuals with AS before and after AVR or TAVI. [8] However, few studies have focused on the quality of life or self-reported health status of symptomatic or asymptomatic AS patients who receive conservative treatment (i.e. medical therapy) and in whom surgical intervention is postponed or declined either by the heart team or by the patient. [4 9]

The aims of this study were to investigate symptoms and self-reported health of patients conservatively treated for AS and to identify factors associated with treatment decision and patient outcomes.

METHODS

Study design and participants

A cross-sectional design was used to investigate factors related to patient-reported health status and the impact of valve disease on the patients' daily life. Patients were followed up for 18 months after the survey. Study endpoints were having undergone TAVI or AVR, or all-cause death.

In April 2013, a postal questionnaire was sent along with a pre-stamped return envelope to 1436 patients ≥ 18 years of age, able to write and understand Norwegian and diagnosed with AS in a tertiary university hospital in Western Norway. Results from the patients that had undergone AVR (N = 1191) are reported elsewhere [10]. Two-hundred and forty-five patients diagnosed with AS between 2000-2012 and still under conservative treatment were included in this study. To be included, candidate participants had to have echocardiographically verified AS in the native aortic valve, with at least a maximum transvalvular gradient of ≥40 mm Hg. Severe AS was defined according to current guidelines.[5] Patients had to fulfil at least one of the following haemodynamic criteria: an aortic valve area (AVA) < 1 cm^2; mean

pressure gradient > 40 mmHg or peak aortic jet velocity > 4 m/s, as demonstrated by Doppler echocardiography. Moderate AS was defined as having an AVA of 1.5-1.0 cm^2, a mean pressure gradient of 25-40 mm Hg or a peak aortic jet velocity of 3.0-4.0 m/s. [5]

Data collection

Hospital information system registries and patient medical records were used to identify patients eligible for the study and to exclude patients with a maximum aortic gradient of less than 40 mm Hg, or patients who were cognitively impaired or deceased. Socio-demographic variables, smoking status, symptoms, co-morbidities; and physical and mental health status were obtained by means of patient self-reports. Clinical variables such as date of AS diagnosis, reasons for declining an AVR or TAVI, results from Doppler echocardiography examination regarding severity of AS and aortic regurgitation (AR), treatment modalities, and survival were retrieved from patient medical records. Expected operative risk was calculated using numeric and logistic EuroSCORE I classification (www.euroscore.org).

Self-reported health status and symptoms

Measurement of self-reported health status was obtained using the Short Form 12 (SF-12) health questionnaire. [11] SF-12 has been used to assess health status in AS patients undergoing AVR or TAVI. [12] The SF-12 (standard v. 1.0) questionnaire consists of 12 items. The first question asks the patient to rate his/her health as excellent, very good, good, fair, or poor. In the survival analysis for the present study, the response categories 'excellent' and 'very good', and 'fair' and 'poor' were merged. SF-12 has two summary measures: a physical component summary (PCS) and a mental component summary (MCS). [11] Each component summary results in a score ranging from 0 to 100. Summary scores are then standardised to a mean of

50 and a standard deviation of 10. Higher scores represent better-perceived health status. Internal reliability (Cronbach's α) was 0.89 and 0.88 for PSC and MSC, respectively.

To evaluate the burden of symptoms related to dyspnoea or heart failure, the Minnesota Living with Heart Failure Questionnaire (MLHFQ*)* was used. MLHFQ is a widely used disease-specific tool with well-documented validity, reliability, and sensitivity for symptoms related to heart failure. [13 14] All of the symptoms listed on the MLHFQ are also symptoms that may occur in individuals with AS. [15] Health impairment is evaluated using a 6-point scale, ranging from 0 (no impact) to 5 (severe impact). The instrument produces a total score (21 items; range: 0 to 105); a physical dimension sub-score (PDS) (8 items; range: 0 to 40); and an emotional dimension sub-score (EDS) (5 items; range 0 to 25). Lower scores indicate better health. For MLHFQ, Cronbach's α was 0.94 for PDS and 0.88 for EDS.

The categories of symptomatic or asymptomatic AS was determined by patients' self-report in the survey. Symptoms of angina were obtained using a single question: 'Have you had chest pain (yes/no)?' One question from the MLHFQ was used to determine the proportion of patients with dyspnoea: 'Did your heart failure prevent you from living as you wanted during the last month by making you short of breath?' Possible answers ranged from 0 (no impact) to 5 (severe impact). Response values of ≥ 2 were categorised as symptomatic. Dizziness/syncope was assessed by the question: 'How much has dizziness/syncope influenced your daily activities the last four weeks?' Possible responses were: 1(not at all), 2 (a little), 3 (some), 4 (much), and 5 (very much). Response values of 3-5 were categorised as symptomatic. Cut-off points were set to avoid including patients who experienced very little discomfort as symptomatic.

The Hospital Anxiety and Depression Scale (HADS) was used to assess possible symptoms of anxiety or depression. [16] HADS consists of a seven-item sub-scale for anxiety (HADS-A) and a seven-item sub-scale for depression (HADS-D). For all items, responses are scored on a four-category scale, with 0 representing no symptoms and 3 representing maximum symptoms. The scores on each sub-scale range from 0 to 21. For identifying possible cases of anxiety and depressive disorders, the HADS has an optimal cut-off score of at least 8 for both sub-scales. [16] The Cronbach's α value were 0.86 for HADS-A and 0.75 for HADS-D.

The New York Heart Association (NYHA) Functional Classification was used to describe the impact of the disease on daily activities. [17] NYHA classifies patients into four categories (I-IV), with higher classes indicating more severe symptoms and limitations in physical activity. The self-assessed NYHA classification tool asks patients to assign themselves to a NYHA class by ticking one of four boxes indicating categories that best describe their ability to perform physical activity. This tool is a well-documented and valid method of assessing symptoms of heart failure. [17]

Ethics

The present study was conducted in accordance with the ethical guidelines contained in the World Medical Association's Declaration of Helsinki (2004) and was approved by the Regional Medical Ethics Committee of Western Norway (No. 2010/01954). Information about the study, the possibility of withdrawing at any time, and confidentiality issues were included in the letter that accompanied the questionnaire. Informed consent was taken as a patient returning the completed questionnaire. In accordance with the regional ethical committee, patients who failed to respond by mail were contacted once by telephone in order to encourage them to complete the questionnaire.

Statistical analysis

Descriptive statistics for continuous variables are presented as means and standard deviations (SDs). For comparisons between groups, the unpaired t-test was used. Descriptive statistics for categorical variables are presented as counts and proportions, and comparisons done using the exact chi-square test. Correlation between continuous variables was estimated by Pearson's correlation (r). Kaplan-Meier analysis was used to assess patient survival and cumulative incidence of AVR/TAVI after 18 months. Cox regression analysis was used to evaluate time-related events and their associations with baseline characteristics, such as age, gender, symptomatic status, severity of AS and EuroSCORE based on clinical experience and previous research[6] Results are reported as hazard ratios (HRs) and 95% confidence interval (CIs). No imputing of missing data was performed.

The statistical analyses were performed using SPSS for Windows 22 (IBM, Corp., Release 2013, Armonk, NY, USA), STATA/SE 14.0 for Windows, 02, 2015), Matlab 9.0 (The MathWorks Inc., Natick, MA, 2016) and Venn Diagram Plotter: (http://omics.pnl.gov/software/venn-diagram-plotter). A two-sided p-value ≤ 0.05 was considered statistically significant. To evaluate the clinical importance of differences in self-reported physical and mental health of symptomatic and asymptomatic patients, we computed effect sizes (ES statistics) by dividing the mean differences in scores by the SD of the norm data. [18] To interpret the effect size, we followed the suggestion of Cohen, and regarded effect sizes of 0.2- 0.5 as small, 0.5-0.8 as moderate, and 0.8 and above as large. [18]

RESULTS

Patients' characteristics, symptoms and health status

Of the 245 patients treated conservatively and not having undergone AVR or TAVI by April 2013, 137 patients (56%) returned the questionnaire. One patient was excluded from further

analysis due to a congenital subvalvular AS (Figure 1). No statistical significant differences were found between responders and non-responders with respect to age (p = 0.157) or gender (p = 0.062).

The mean (SD) age was 79 (12) years and 52% were men. One-hundred and five (77%) patients were symptomatic. The most frequently self-reported symptom was dyspnoea, 57 (71%); followed by chest pain 49 (61%) and dizziness/syncope 26 (33%). Overlapping symptoms are shown in Figure 2. Patients with symptomatic AS were older, had attained a lower educational level, were more often living alone, were placed in a higher NYHA class, had a higher EuroSCORE I, and were more often on medication such as beta-blockers and statins, as compared to asymptomatic patients (Table 1)

Of the 136 patients, 22 (16%) were not accepted for AVR by the heart team, whilst 12 (9%) patients declined AVR by themselves. The remaining 102 (75%) were considered as potential surgical candidates and remained under medical observation. The distribution of AS severity, symptomatic status and treatment decision at baseline are shown in Figure 1. No gender differences were found for severity of AS, chest pain, dyspnoea, dizziness/syncope or numbers of symptoms reported. Risk stratification of all 136 patients revealed that 29 patients (21%) had a numeric EuroSCORE ≤ 5, 81 (60%) had a EuroSCORE between 6-10, and 26 (19%) had a EuroSCORE of 11-15.

Patients with asymptomatic AS reported better physical and mental health status compared to symptomatic patients. The estimated effect size for the differences in SF-12 measures between symptomatic and asymptomatic patients was 1.24 for the PCS and 0.74 for the MCS. The assessment of the impact of AS on the patients' daily life (MLHFQ), showed that it had a

significantly larger impact in symptomatic patients. In addition, asymptomatic patients had significantly lower HADS scores compared to symptomatic patients (Table 2).

Eighteen months follow-up

Eighteen months after the survey, of the 136 patients, 117 (86%) were still alive, Of whom 23 (16%) had undergone isolated AVR, including 5 with AVR in combination with coronary artery bypass grafting (CABG) and 10 (7%) had undergone TAVI. Nineteen patients (14%) had died; whereas1 died 6 days after AVR. The flow chart of patient outcomes (survival and AVR/TAVI) within the 18 months follow-up is shown in Figure 1.

Among the 102 individuals with medical observation at the time of the survey (Figure 3), 22 (21%) had undergone AVR, 7 (7%) had TAVI and 9 (9%) had died. Additionally, 2 patients were scheduled for AVR and 2 for TAVI during follow-up. Among the 22 patients previously declined from AVR by the heart team, 3 (14%) had undergone TAVI and 5 (23%) had died. Four of the 12 patients who decided to receive conservative treatment had died; and none had undergone AVR or TAVI.

Of the 20 patients with asymptomatic severe AS (Table 1), only 3 (15%) had undergone an exercise test. One of them had a rise in blood pressure and a decrease of 2 mm in the ST-segment on EKG, but no symptoms of angina. He was finally accepted for surgery, but died before the operation. In the other two cases, the patients experienced a slight rise in pulse, but in both cases the test ended prematurely due to limb fatigue.

After 18 months, of the 81 patients with symptomatic severe AS at baseline, 31had still not undergone surgical treatment, and five had died prior to the end of the study. Of the latter, one

had been accepted for AVR and one for TAVI. The remaining 26 patients were still treated conservatively after 18 months, either due to symptoms unrelated to AS (n = 3), patients' decision (n = 1), horizontal aortic root not eligible for TAVI (n = 1), Alzheimer disease (n = 1), or vague symptoms (n = 3). The remaining 17 patients had, for unknown reasons, not been referred for cardiac surgery. Seven of the 20 patients with asymptomatic severe AS at baseline were treated with AVR (n = 5) or TAVI (n = 2) within 18 months. All of them developed symptoms, mainly dyspnoea before the intervention.

Multiple Cox regression analysis for selection of AVR or TAVI was performed and included age, gender, symptomatic status, severity of AS, and EuroSCORE as variables (Figure 4). Patients with severe AS had more than six fold chance of being scheduled for AVR or TAVI compared to those with moderate AS (HR: 6.3, 95% CI: 1.9, 21.2, p = 0.003). EuroSCORE ≥ 11decreased the chance for undergoing AVR or TAVI compared to having EuroSCORE ≤ 5 (HR: 0.06, 95% CI: 0.01 to 0.458, p = 0.007).

Self-rated general health at baseline tended to predict event-free survival (Figure 5a), and EuroSCORE tended to predict overall survival (Figure 5b) by the 18–months-follow-up, but the results were not statistically significant.

DISCUSSION

In the present study, the relationship between patient-reported outcomes and the severity of AS were investigated by employing well-established health status instruments. The results revealed that symptoms had a larger influence on the conservatively treated patients' physical and mental health than the severity of AS. AS severity alone, as measured by Doppler echocardiography examinations, did not differ between symptomatic and asymptomatic patients.

Previous studies have shown that important outcomes such as symptoms, function, and well-being are weakly associated with objective measures of disease severity. [19] It is known that the degree of AS at the onset of symptoms differs among patients. [3] The symptom most frequently experienced by patients in this study was dyspnoea. Dyspnoea was also the most frequent symptom observed in patients selected for AVR or TAVI. Since the presence of dyspnoea predicts worse survival for patients with AS, [20] our treatment algorithm is well supported by clinical outcome studies [20] and guidelines. [5] In the present study, mild symptoms of shortness of breath were classified as asymptomatic AS. Surprisingly, nearly 60% of the asymptomatic patients classified themselves within NYHA class II, indicating they experienced shortness of breath or tiredness, or palpitations when performing strenuous activities. Rather than attributing these two symptoms solely to exercise induced AS another plausible explanation is the presence of other co-morbidities, advanced age or their generally poor physical condition.

Symptomatic and asymptomatic patients also differed in physical and mental health status, with the latter having better scores. As the effect size showed, this difference is also clinically relevant. [18] Although neither the Doppler echocardiogram measurements (i.e. AS severity) nor number of co-morbidities differed between the two groups, the analyses showed that patient-reported outcomes did differ. This is in line with the reports of van Geldorp et al, who concluded that even minor AS symptoms may have a major impact on patients' physical and mental well-being, as well as quality of life. [4] They also concluded that there was no relationship between stenosis severity and patients' physical or mental health, but symptoms severity according to NYHA classification corresponded well with the SF-36 scores.

Patients who graded their general health as fair or poor tended to have a lower 18-month event-free survival, as compared to those grading their health as good or better, but the difference was not statistically significant. Self-rated health has been shown to predict mortality one year after TAVI. [21]

In the present study, symptomatic patients reported significantly higher levels of both anxiety and depression compared to asymptomatic patients, indicating that AS symptoms have a great impact on mental health. Compared to the cohort of patients having undergone AVR responding to the same questionnaire, [10] conservatively treated symptomatic patients in the present study reported a higher level of anxiety and depression. This supports the findings that AS symptoms have a negative impact on patients' mental health, suggesting that valve surgery can reduce this mental burden.

In symptomatic patients with severe AS, aortic valve surgery is generally recommended both by European and American guidelines. [5 22] Fifty-five per cent of the patients who fulfilled the criteria for receiving AVR, either were not on the waiting list for AVR or had been treated with AVR or TAVI within 18 months after the survey. The low proportion of asymptomatic AS patients who underwent exercise testing may suggest that the indication for surgery was underestimated. Symptomatic status can be difficult to determine, especially in elderly patients, as they tend to minimise or deny symptoms, or effectively reduce their physical activity level to avoid symptoms. [23] One-third of the patients who report to be asymptomatic develop symptoms during exercise testing; thus this type of testing is recommended to unmask symptoms in patients with severe AS. [24] With appropriate supervision and monitoring, symptom-limited stress testing is safe in severe AS and can add important

prognostic value especially in older people that might have problems performing a treadmill exercise test due to coexisting morbidities. [24]

A possible explanation why many patients are not referred for surgery despite severe symptomatic AS, is that the patients are discharged from the university hospital without being implemented into a treatment algorithm provided for the local hospitals, cardiologists in private practice or general practitioners. Multidisciplinary heart teams, together with the patients and their family, should conclude with either conservative treatment, AVR or TAVI according to current guidelines, shared decision making, co-morbidities and operative risks. Although the majority of the patients declined for surgery at baseline had a EuroSCORE of > 10, a high EuroSCORE did not fully explain why some patients still were not referred for surgery. As EuroSCORE is known to overestimate the risk of postoperative mortality, especially in low-risk patients scheduled for isolated AVR, the postoperative mortality risk may have been overestimated in some of the patients. [25]

AS severity, and not symptomatic status, predicted selection for surgical treatment in this cohort. The gap between the existing guidelines and their actual application has been demonstrated in previous studies. [5 7] Close follow-up of the asymptomatic patients is also important, as severe symptoms or cardiac death may occur suddenly. [26] There is robust evidence that AVR prolongs life in patients with symptomatic and severe AS. This is regardless of severity of symptoms or the response to medical treatment. [3] It is also of utmost importance that health professionals inform patients with AS to contact their physician as soon as symptoms occur. The optimal time for intervention is still open to debate. Some argue that early elective surgery in asymptomatic patients with severe AS might be worthwhile, since rapid deterioration is associated with the disease. [26] Early surgery in patients with severe

asymptomatic AS has also shown to improve long-term survival by decreasing cardiac mortality [27] as well as lower 5-year incidences of all cause death and heart failure hospitalisation compared to conservative treated patients. [28] In addition, an ongoing prospective multicentre randomised controlled trial (the AVATAR trail) is testing the hypothesis that elective AVR is superior to medical treatment until symptom onset in asymptomatic patients with isolated severe AVR and normal LVEF. [29]

Study strengths and limitations

Very few studies have investigated self-reported health in AS patients under conservative treatment. Patient-reported outcomes are important to inform health professionals as well as policymakers in order to improve the quality of care to patients with AS. Thus, the present study has some methodological limitations. It was carried out as a single-centre study, which may decrease the generalisability of the results. The sample, however, represents patients from both densely populated and rural areas. Another limitation is the retrospective design of the study and that we gathered only limited data prospectively. Further, a potential limitation is the moderate response rate of 56%. A possible reason for this response rate can be that some of the patients were still asymptomatic, and perhaps not motivated to take the time to answer the questionnaire. Alternatively, patients with severe disease burden were incapable of completing the questionnaire.

CONCLUSIONS

Patients receiving conservative treatment for AS are an understudied group of cardiac patients. The present study demonstrated that AS symptoms have great impact on patients' physical and mental health status. However, this impact does not reflect the severity of AS. Still, many patients with symptomatic severe AS are not scheduled for surgery, despite the

recommendations in current guidelines. Our results indicate that the referral practice for aortic valve surgery ought to be carefully scrutinised. Further well-designed prospective studies are needed to fully understand the disease burden of AS and to optimise the timing of surgical intervention. Self-reported health status may be a valuable supplement to physical examination during the clinical evaluation of high-risk AS patients.

Footnotes

Contribution KO, RH, JEN and TMN are responsible for study concept and design. KO and TMN are responsible for data collection. GEE, KO and TMN are responsible for data analysis. KO, RH, JEN and TMN are responsible for initial draft of manuscript. KO, RH, JEN, GEE and TMN are responsible for interpretation of data. All authors revised the paper critically for important intellectual content and approved the final manuscript. KO, GEE and TMN had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval was obtained by the Regional Medical Ethics Committee of Western Norway (No. 2010/01954).

Data sharing statement No additional data are available.

Provenance and peer review Not commissioned; externally peer reviewed

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Table 1. Baseline characteristics of 136 patients aged 35 to 95 years diagnosed with severe to moderate aortic stenosis in the period 2000 to 2012 who replied to a postal questionnaire in 2013.

Variable	All (N= 136)	Symptomatic (n = 105)	Asymptomatic (n = 31)	p-value*
Basic characteristics				
Age in years; *mean (SD) range*	79 (11) 35-95	80 (10)	75 (12)	**0.025**
Gender, men, *n (%)*	70 (52)	55 (52)	15 (48)	0.696
Living alone, *n (%)*	51 (38)	44 (42)	7 (23)	0.052
Education, *n (%)*				**0.037**
Elementary school	73 (54)	62 (60)	11 (36)	
High School	33 (24)	23 (22)	10 (32)	
University/College	29 (22)	19 (18)	10 (32)	
Smoking, *n (%)*				0.121
Current smoker	11 (8)	9 (9)	2 (7)	
Previous smoker	58 (43)	49 (47)	9 (30)	
Never smoked	66 (49)	47 (45)	19 (63)	
Sa-NYHA, *mean (SD)*	2.18 (0.87)	2.34 (0.88)	1.66 (0.55)	**<0.001**
NYHA I, *n (%)*	25 (19)	14 (14)	11 (40)	
NYHA II, *n (%)*	70 (53)	53 (52)	17 (57)	
NYHA III, *n (%)*	22 (17)	21 (21)	1 (3)	
NYHA IV, *n (%)*	14 (11)	14 (14)	0 (0)	
Doppler echocardiography examination				
Ejection fraction *(%), mean (SD)*	59 (9)	58 (10)	60 (7)	0.304
V-max (m/s), *mean (SD)*	4.0 (0.7)	4.0 (0.7)	3.9 (0.4)	0.418
AVA (cm^2 /BSI), *mean (SD)*	0.54 (0.2)	0.53 (0.2)	0.57 (0.2)	0.257
Mean aortic gradient, *mean (SD)*	41 (15)	42 (15)	38 (11)	0.115
Severity of AS				0.159
Severe AS, *n (%)*	101 (74)	81 (80)	20 (20)	
Moderate AS, *n (%)*	35 (26)	24 (65)	11 (35)	
Aortic regurgitation, *n (%)*				0.067
Mild (1/4)	55 (40)	43 (41)	19 (18)	
Moderate (2/4)	27 (20)	19 (18)	8 (25)	
Moderate-to-severe (3/4)	2 (1.5))	0 (0)	2 (6)	
EuroSCORE-log, *mean (SD)*	12.8 (11.6)	13.9 (11.8)	9.0 (10.3)	**0.027**
EuroSCORE-numeric, *mean (SD)*	8.0 (3.1)	8.3 (3.1)	6.9 (2.8)	**0.022**
Years since diagnosis, *mean (SD)*	5.7 (3.2)	5.5 (3.1)	6.3 (3.5)	0.207
Medical history, *n (%)*				
Diuretics	34 (25)	30 (29)	4 (13)	0.078
Beta-blockers	87 (64)	71 (68)	16 (52)	0.104
Statins	80 (59)	67 (64)	13 (42)	**0.030**
Myocardial infarction	24 (18)	18 (20)	6 (18)	0.753
Stroke	19 (14)	16 (16)	3 (10)	0.394
AF intermittent	33 (28)	28 (32)	5 (17)	0.140
AF permanent	8 (7)	7 (7)	1 (3)	0.454
COPD	8 (6)	8 (8)	0 (0)	0.109
Arthritis	25 (19)	22 (22)	3 (10)	0.139

Osteoporosis	18 (14)	15 (15)	3 (0)	0.454
Cancer	26 (20)	21 (21)	5 (16)	0.539
PCI	18 (13)	14 (13)	4 (13)	
Previous CABG	6 (4)	6 (6)	0 (0)	0.336
Pacemaker	10 (8)	7 (7)	3 (10)	0.555

SD: standard deviation; Sa-NYHA: Self-assessed New York Heart Association functional classification; AVA: aortic valve area; V-max: maximum jet velocity; CABG: coronary artery bypass grafting; AF: atrial fibrillation; COPD: chronical obstructive pulmonary disease. * Tests comparing symptomatic versus asymptomatic (bolded p-values significance at $p \leq 0.05$).

Table 2. Baseline self-reported health status of 136 patients aged 35 to 95 years diagnosed with aortic stenosis in the period 2000 to 2012 responding to the questionnaire in 2013, data differentiated by symptomatic status.

Variable	All (N= 136)	Symptomatic (n = 105)	Asymptomatic (n = 31)	p-value
SF-12, PCS, *mean (SD)*	36.8 (11.7)	33.8 (11)	46.2 (9)	**<0.001**
SF-12, MCS, *mean (SD)*	52.3 (10.4)	50.6 (11)	58.0 (4)	**<0.001**
MLHFQ Physical *mean (SD)*	11.8 (11.3)	14.9 (11)	3.3 (5)	**<0.001**
MLHFQ Emotional *mean (SD)*	3.1 (5.1)	3.9 (6)	0.6 (2)	**<0.001**
HADS-A, *mean (SD)*	3.9 (3.4)	4.2 (4)	2.9 (2)	**0.036**
HADS-D, *mean (SD)*	4.5 (3.4)	5.0 (4)	2.7 (2)	**<0.001**
HADS-A $\geq$ 8, *n (%)*	18 (14)	17 (17)	1 (3)	0.071
HADS-D $\geq$ 8, *n (%)*	24 (18)	22 (22)	2 (7)	0.056

SD: standard deviation; PCS: physical component summary of SF-12; MCS: mental component summary of SF-12; MLHFQ: Minnesota Living with Heart Failure Questionnaire; HADS-A: Hospital Anxiety and Depression Scale, anxiety component; HADS-D: Hospital Anxiety and Depression Scale, depression component

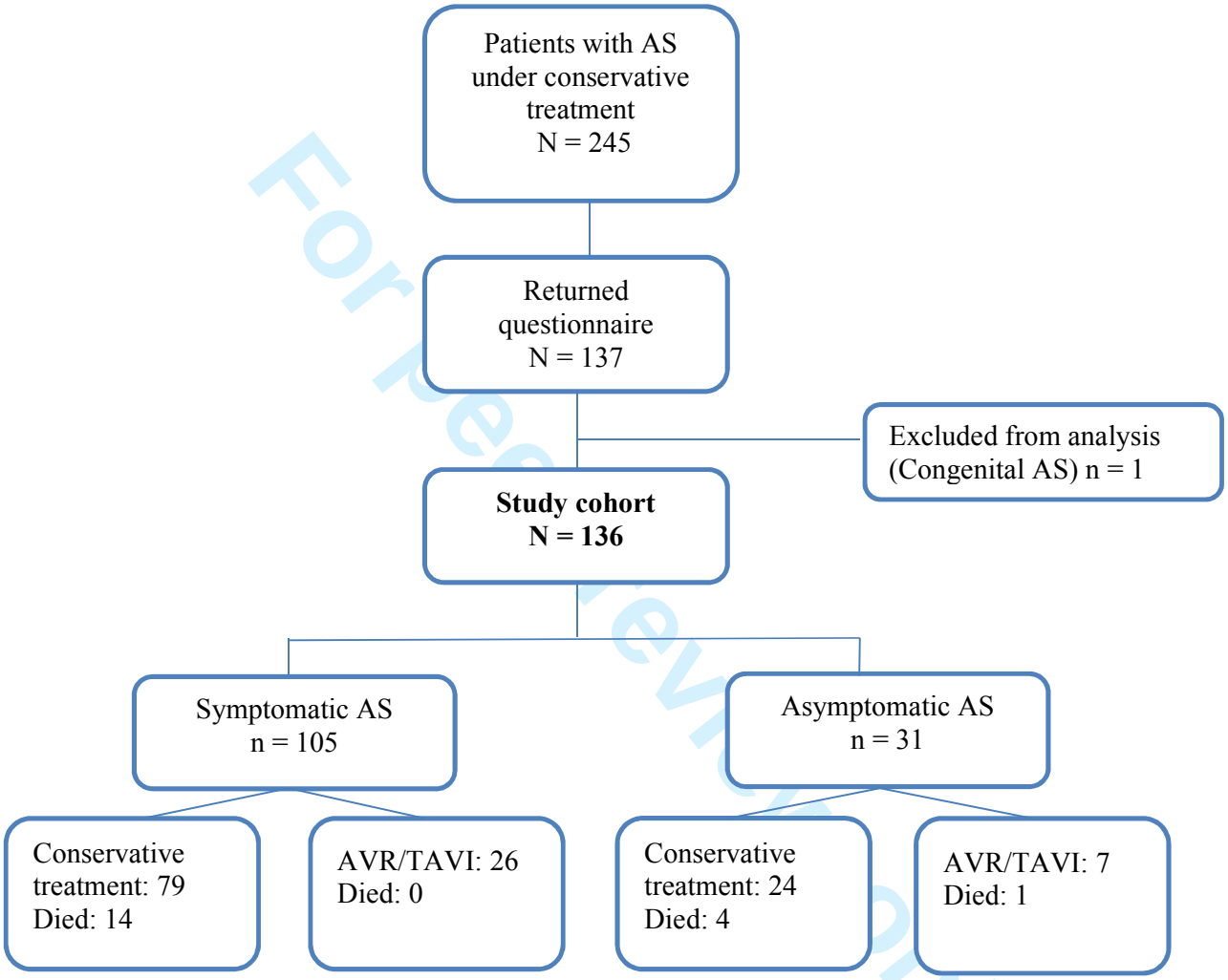


Figure 1. Flowchart showing patient with and without aortic valve replacement participating in the study, and outcomes after 18-months follow-up for136 patients aged 35 to 95 years under conservative treatment at the time of survey. Patients were diagnosed between the years 2000 to 2012 and were invited to complete the questionnaire in year 2013.

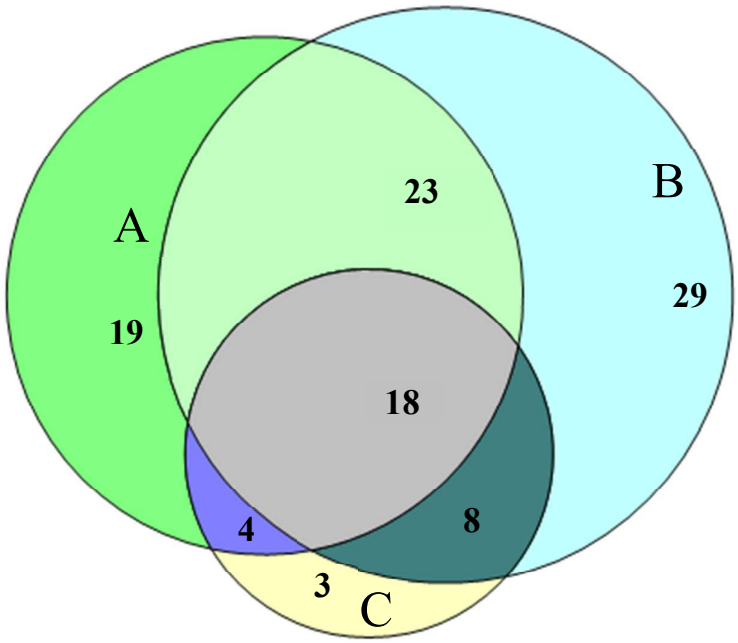
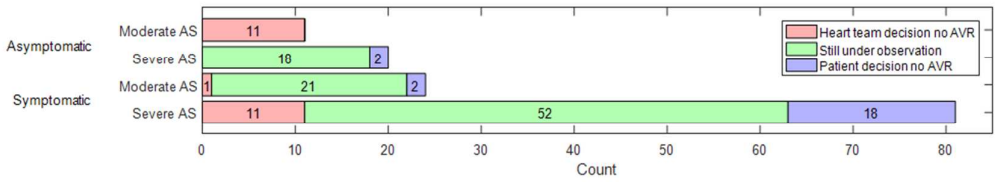


Figure 2. Number of symptomatic AS patients with overlapping symptoms (N = 105)
A: Chest pain. B: Dyspnoea. C: Dizziness/syncope



Figur 3. Reasons for not having undergone AVR at baseline in 136 patients with symptomatic and asymptomatic severe-to-moderate aortic stenosis.

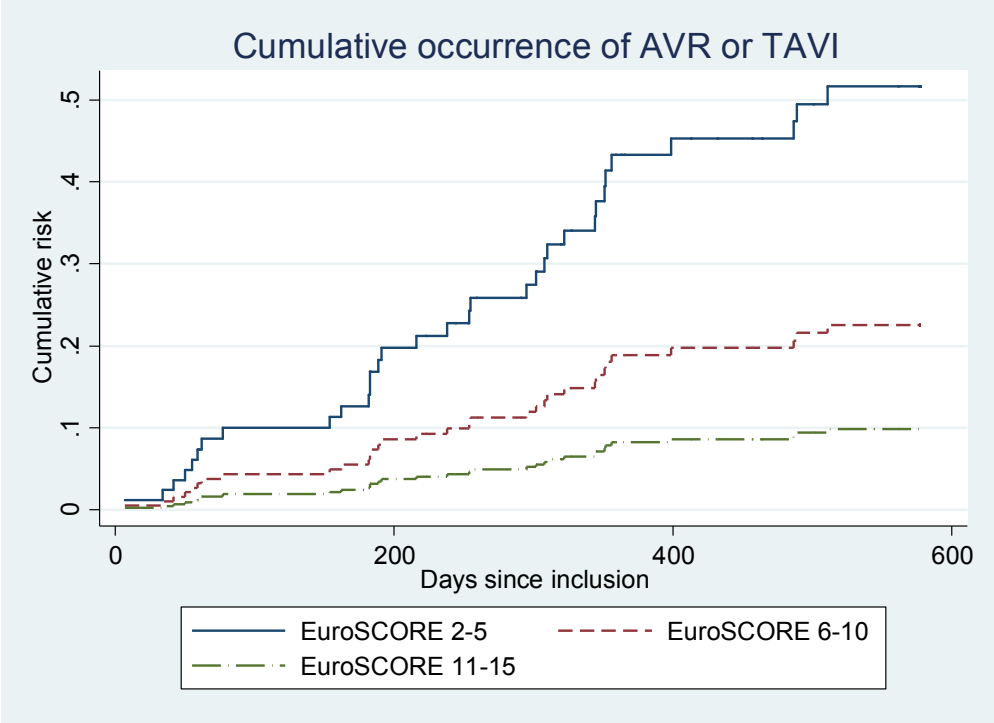


Figure 4. Cumulative occurrence of AVR or TAVI from Cox model, according to EuroSCORE range (likelihood ratio p-value (LR-p) = 0.011) in patients with aortic stenosis within 18 months adjusted for gender (LR-p = 0.336); age (LR-p =0.223); symptomatic status (LR-p = 0.437); and severity of aortic stenosis (LR-p = 0.002).

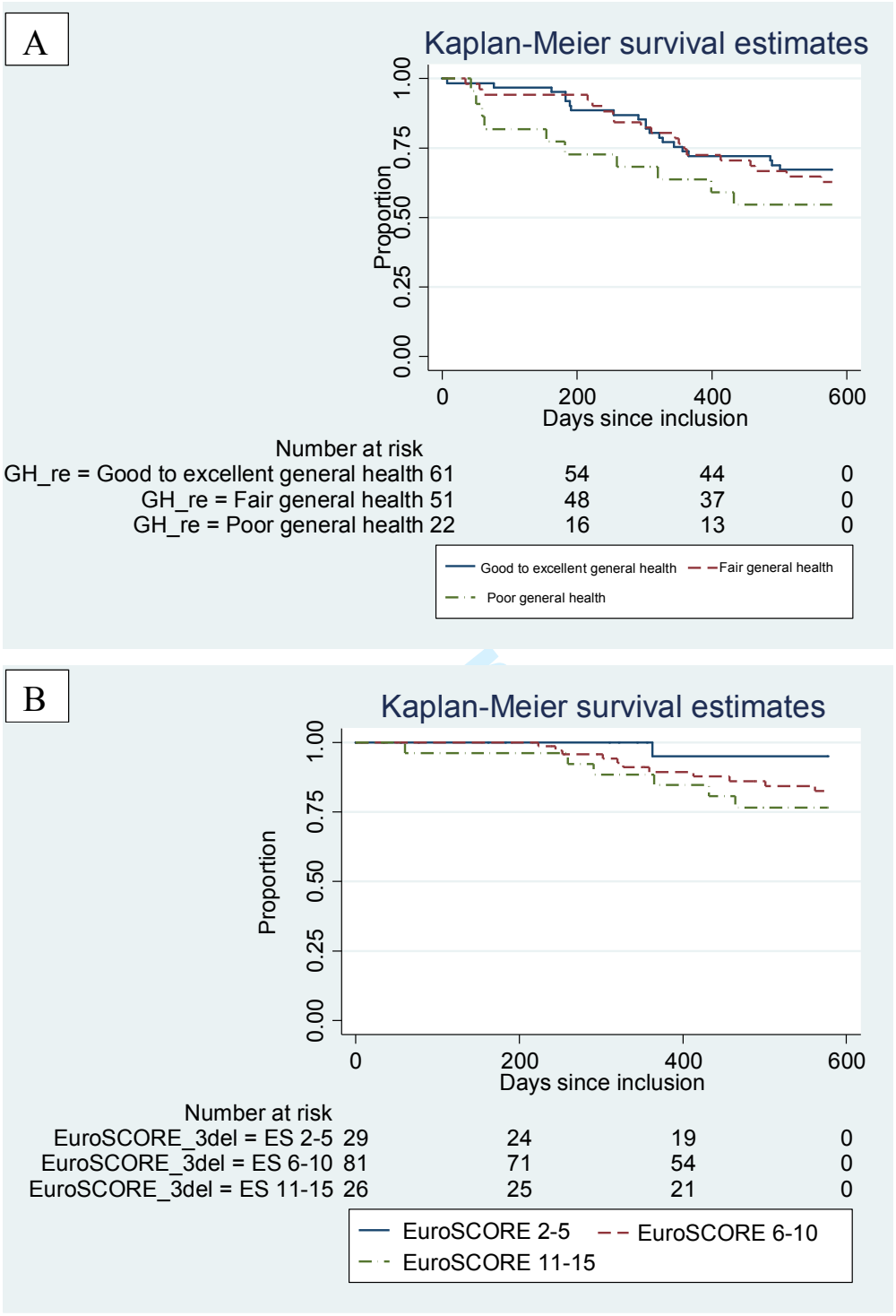


Figure 5. Kaplan-Meier curves showing: A, event-free survival in patients with aortic stenosis according to self-rated general health category at baseline (log rank test: p = 0.418). B, overall survival in patients with aortic stenosis (AVR or TAVI censored) according to numeric EuroSCORE I range (log rank test: p = 0.209).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract The study's design can be found in the title (p1) and in the abstract (p2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. This is shown in page 2.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Very few studies have investigated the disease burden of aortic stenosis placed on patients' daily life, whether symptomatic or asymptomatic. Current European guidelines recommend AVR for patients with severe symptomatic AS. Despite this many patients fulfilling these guidelines are not referred for surgery (p4).
Objectives	3	State specific objectives, including any prespecified hypotheses The objectives were to investigate symptoms and self-reported health of patients conservatively treated for aortic stenosis (AS) and to identify factors associated with treatment decision and patient outcomes. (p5)
Methods		
Study design	4	Present key elements of study design early in the paper A cross-sectional design (survey) with an 18 month follow-up regarding treatment decision and survival (p5).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Patients diagnosed with AS at a tertiary university hospital in western Norway and fulfilling inclusion criteria (p5-6) were invited to a postal survey in April 2013. 18 months after the survey, information on selection of treatment and survival were retrieved from patients' medical records (p6)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants To be included in the survey participants had to have echocardiographically verified AS in the native aortic valve, with at least a maximum transvalvular gradient of ≥40 mm Hg (p5). This information was retrieved from patients' medical records.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Primary outcome measures were symptoms and self-reported health status. Secondary outcomes were treatment decision and patient survival after 18 months (p1). Severe AS was defined according to current guidelines. Patients had to fulfil at least one of the following haemodynamic criteria: an aortic valve area (AVA) < 1 cm^2; a mean pressure gradient > 40 mmHg or a peak aortic jet velocity > 4 m/s, as demonstrated by Doppler echocardiography. Moderate AS was defined as having an AVA of 1.5-1.0 cm^2, a mean pressure gradient of 25-40 mm Hg or a peak aortic jet velocity of 3.0-4.0 m/s (p5-6). Definition of symptomatic status is described on p7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

		Socio-demographic variables, smoking status, symptoms, co-morbidities; and physical and mental health status were obtained by means of patient self-reports. Clinical variables such as date of AS diagnosis, reasons for declining an AVR or TAVI, results from Doppler echocardiography examination regarding severity of AS and AR, treatment modalities, and survival were retrieved from patient medical records. Expected operative risk was calculated using numeric and logistic EuroSCORE I classification (www.euroscore.org) (p6).
Bias	9	Describe any efforts to address potential sources of bias Analyses were performed to investigate possible differences between responders and non-responders. No statistical significant differences were found between responders and non-responders with respect to age (p = 0.157) or gender (p = 0.062) (p10).
Study size	10	Explain how the study size was arrived at All eligible patients were invited to participate in the survey.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. Descriptive statistics for continuous variables are presented as means and standard deviations (SDs). For comparisons between groups, the unpaired t-test was used. Descriptive statistics for categorical variables are presented as counts and proportions, and comparisons done using the exact chi-square test. Correlation between continuous variables was estimated by Pearson's correlation (p9).We decided to compare symptomatic and asymptomatic patients with respect to symptoms, self-reported health as well as AS severity to investigate how the variables correlated.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding This has been done in the Statistical methods section (p9). Control for confounding in the analysis of survival was done by using Cox regression.
		(*b*) Describe any methods used to examine subgroups and interactions Descriptive statistics were used for examining the subgroups with symptomatic and asymptomatic AS (Table 1 and 2). For survival analysis we used Kaplan-Meier in subgroups defined by symptomatic status, severity of AS and EUROscore.
		(*c*) Explain how missing data were addressed No imputing of missing data was performed, this is stated on p9.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy Not applicable
		(*e*) Describe any sensitivity analyses This was not applicable.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed As shown in Figure 1 (p22) 245 eligible patients were invited to participate in the survey, 137 responded, 1 was excluded due to congenital AS. Thus 136 were included in further analysis.
		(b) Give reasons for non-participation at each stage Non participants were those who did not return the questionnaire. They

		did not differ from participants with respect to age or gender.
		(c) Consider use of a flow diagram A flow diagram is used in Figure 1 to show treatment selection in patients with symptomatic and asymptomatic AS (p22).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders This is shown in Table1 (p20-21)
		(b) Indicate number of participants with missing data for each variable of interest Number of missing data on self-reported heath appears in Table 2. Non-responders are given in Figure 1. There were no missing data on treatment selection or survival data. We were able to calculate EuroSCORE in all patients. EF: 8 (5.9%) missing, mean gradient 6 (4.4%) missing, AVA 20 (14.7%) missing, V max 40 (29.4%) missing.
Outcome data	15*	Report numbers of outcome events or summary measures This is given in the Results chapter (p 9-12)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Not applicable.
		(*b*) Report category boundaries when continuous variables were categorized No continuous variables were categorized.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses All relevant results are reported.
Discussion		
Key results	18	Summarise key results with reference to study objectives One-hundred and five (77%) patients were symptomatic. The most frequently self-reported symptom was dyspnoea, 57 (71%); followed by chest pain 49 (61%) and light-headedness 26 (33%). Patients with asymptomatic AS reported better physical and mental health status compared to symptomatic patients. No associations were found between AS severity and symptoms. Eighteen months after the survey 117 (86%) were still alive. Twenty-tree (16%) had undergone AVR and 10 (7%) had undergone TAVI. Nineteen patients (14%) had died (p11). Many patients with symptomatic severe AS are not scheduled for surgery after 18 months, despite the recommendations in current guidelines. (p9-12)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Some limitations are that this was a single centre study with a moderate response rate and that some data were retrospective collected. Using EuroSCORE in AS patients might have overestimated the postoperative mortality risk. Because the data from patients' records was retrieved retrospective some missing data might have made the results less precise. See also p16

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence The present study demonstrated that AS symptoms have great impact on patients' physical and mental health status. However, this impact does not reflect the severity of AS. This is in line with previous studies. Still, many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. Our results indicate that the referral practice for aortic valve surgery ought to be carefully scrutinised. Further well-designed prospective studies are needed to fully understand the disease burden of AS and to optimise the timing of surgical intervention. Recent studies indicate also patients with asymptomatic severe AS will benefit from surgical treatment, and that watch-full waiting not always is the best solution.
Generalisability	21	Discuss the generalisability (external validity) of the study results The results might be of limited value due to that the data was only collected at a single centre, but we believe that this centre is a typical representative for the population of patients in Norway.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. The study was funded by a research grant from the Western Norway Health Authority that supported the PhD education for the first author. The study also received funding from The Norwegian Nursing Association to finance expenses of carrying out the survey.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Self-reported health status, treatment decision and survival in asymptomatic and symptomatic patients with aortic stenosis in a Western Norway population undergoing conservative treatment – a cross-sectional study with 18 months follow-up

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Self-reported health status, treatment decision and survival in asymptomatic and symptomatic patients with aortic stenosis in a Western Norway population undergoing conservative treatment – a cross-sectional study with 18 months follow-up

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ABSTRACT

Objectives To investigate symptoms and self-reported health of patients conservatively treated for aortic stenosis (AS) and to identify factors associated with treatment decision and patient outcomes.

Design A cross-sectional survey with an 18-month follow-up.

Setting One tertiary university hospital in Western Norway.

Participants In all, 1436 patients were diagnosed with AS between 2000-2012, and those 245 still under conservative treatment in 2013 were included in this study.

Primary and secondary outcome measures Primary outcome measures were symptoms and self-reported health status. Secondary outcomes were treatment decision and patient survival after 18 months.

Results A total of 136 patients with mean (SD) age 79 (12) years, 52% men responded. Among conservatively treated patients 77% were symptomatic. The symptom most frequently experienced was dyspnoea. Symptomatic patients reported worse physical and mental health compared to asymptomatic patients (effect size 1.24 and 0.74 respectively). In addition, symptomatic patients reported significantly higher levels of anxiety and depression compared to asymptomatic patients. However, symptom status did not correlate with haemodynamic severity of AS. After 18 months, 117 (86%) were still alive, 20% had undergone surgical aortic valve replacement (AVR) and 7% transcatheter aortic valve implantation (TAVI). When adjusting for age, gender, symptomatic status, severity of AS, and EuroSCORE, patients with severe AS had more than six fold chance of being scheduled for AVR or TAVI compared to those with moderate AS (HR: 6.3, 95% CI: 1.9, 21.2, $p = 0.003$). Patients with EuroSCORE ≥ 11 had less chance for undergoing AVR or TAVI compared to those with EuroSCORE ≤ 5 (HR: 0.06, 95% CI: 0.01, 0.46, $p = 0.007$).

Conclusions Symptoms affected both physical and mental health in conservatively treated AS patients. Many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. The referral practice for AVR is a path for further investigation.

Key words: aortic stenosis; symptoms; health status; treatment decision; aortic valve replacement

Strengths and limitations of the study

- The study is targeting an understudied group of patients as very few studies have investigated self-reported health in AS patients under conservative treatment.
- The study employs standardized and validated questionnaires.
- Patient-reported outcomes are important to inform health professionals as well as policymakers in order to improve the quality of care to patients with AS.
- Patients were diagnosed with AS 1-11 years before the survey.
- The study is limited by the moderate response rate, and that it was carried out as a single-centre study.

INTRODUCTION

Aortic stenosis (AS) is the most common heart valve disease in the western world causing significant morbidity and mortality. As a result of an aging population, the prevalence of AS is increasing. [1] AS is most commonly caused by a degenerative calcification process leading to leaflet immobility, which in turn causes impaired blood flow through the heart and symptoms of pressure overload. [2] The three cardinal symptoms of AS, indicating the need for clinical intervention are; breathlessness, chest pain and dizziness or syncope. [1] An unknown proportion of patients remain asymptomatic for several years despite the presence of haemodynamically severe disease. [3] Symptomatic AS has been associated with a sharp increase in death risk with an estimated 50% death rate at 2 years unless aortic valve replacement (AVR) is performed. [3] While much is known about the pathophysiology of AS, little is known about the disease burden placed on patients' daily life, whether symptomatic or asymptomatic. [4]

Current European guidelines recommend AVR for patients with a Class I assessment. These are patients who are symptomatic with severe AS, asymptomatic patients with severe systolic dysfunction or patients offered AVR as a concomitant procedure during another primary open cardiac surgery indication. [5] Despite these recommendations, studies have documented poor adherence to evidence-based guidelines, as 33-60% of the patients with severe symptomatic AS are inappropriately excluded from AVR. [6] Hence, there seems to be a gap between what is recommended and the real clinical practice. For various reasons, there are a large percentage of suitable candidates that are currently not referred for AVR. [5 7] Further, transcatheter aortic valve implantation (TAVI) has become widely accepted as an alternative to AVR and medical therapy for patients at high surgical risk. [5]

There are some reports on patient-reported outcomes in individuals with AS before and after AVR or TAVI. [8] However, few studies have focused on the quality of life or self-reported health status of symptomatic or asymptomatic AS patients who receive conservative treatment (i.e. medical therapy) and in whom surgical intervention is postponed or declined either by the heart team or by the patient. [4 9]

The aims of this study were to investigate symptoms and self-reported health of patients conservatively treated for AS and to identify factors associated with treatment decision and patient outcomes.

METHODS

Study design and participants

A cross-sectional design was used to investigate factors related to patient-reported health status and the impact of valve disease on the patients' daily life. Patients were followed up for 18 months after the survey. Study endpoints were having undergone TAVI or AVR, or all-cause death.

In April 2013, a postal questionnaire was sent along with a pre-stamped return envelope to 1436 patients ≥ 18 years of age, able to write and understand Norwegian and diagnosed with AS in a tertiary university hospital in Western Norway. Results from the patients that had undergone AVR (N = 1191) are reported elsewhere [10]. Two-hundred and forty-five patients diagnosed with AS between 2000-2012 and still under conservative treatment were included in this study. To be included, candidate participants had to have echocardiographically verified AS in the native aortic valve, with at least a maximum transvalvular gradient of ≥40 mm Hg. Severe AS was defined according to current guidelines.[5] Patients had to fulfil at least one of the following haemodynamic criteria: an aortic valve area (AVA) < 1 cm^2; mean

pressure gradient > 40 mmHg or peak aortic jet velocity > 4 m/s, as demonstrated by Doppler echocardiography. Moderate AS was defined as having an AVA of 1.5-1.0 cm^2, a mean pressure gradient of 25-40 mm Hg or a peak aortic jet velocity of 3.0-4.0 m/s. [5]

Data collection

Hospital information system registries and patient medical records were used to identify patients eligible for the study and to exclude patients with a maximum aortic gradient of less than 40 mm Hg, or patients who were cognitively impaired or deceased. Socio-demographic variables, smoking status, symptoms, co-morbidities; and physical and mental health status were obtained by means of patient self-reports. Clinical variables such as date of AS diagnosis, reasons for declining an AVR or TAVI, results from Doppler echocardiography examination regarding severity of AS and aortic regurgitation (AR), treatment modalities, and survival were retrieved from patient medical records. Expected operative risk was calculated using numeric and logistic EuroSCORE I classification (www.euroscore.org).

Self-reported health status and symptoms

Measurement of self-reported health status was obtained using the Short Form 12 (SF-12) health questionnaire. [11] SF-12 has been used to assess health status in AS patients undergoing AVR or TAVI. [12] The SF-12 (standard v. 1.0) questionnaire consists of 12 items. The first question asks the patient to rate his/her health as excellent, very good, good, fair, or poor. In the survival analysis for the present study, the response categories 'excellent' and 'very good', and 'fair' and 'poor' were merged. SF-12 has two summary measures: a physical component summary (PCS) and a mental component summary (MCS). [11] Each component summary results in a score ranging from 0 to 100. Summary scores are then standardised to a mean of

50 and a standard deviation of 10. Higher scores represent better-perceived health status. Internal reliability (Cronbach's α) was 0.89 and 0.88 for PSC and MSC, respectively.

To evaluate the burden of symptoms related to dyspnoea or heart failure, the Minnesota Living with Heart Failure Questionnaire (MLHFQ*)* was used. MLHFQ is a widely used disease-specific tool with well-documented validity, reliability, and sensitivity for symptoms related to heart failure. [13 14] All of the symptoms listed on the MLHFQ are also symptoms that may occur in individuals with AS. [15] Health impairment is evaluated using a 6-point scale, ranging from 0 (no impact) to 5 (severe impact). The instrument produces a total score (21 items; range: 0 to 105); a physical dimension sub-score (PDS) (8 items; range: 0 to 40); and an emotional dimension sub-score (EDS) (5 items; range 0 to 25). Lower scores indicate better health. For MLHFQ, Cronbach's α was 0.94 for PDS and 0.88 for EDS.

The categories of symptomatic or asymptomatic AS was determined by patients' self-report in the survey. Symptoms of angina were obtained using a single question: 'Have you had chest pain (yes/no)?' One question from the MLHFQ was used to determine the proportion of patients with dyspnoea: 'Did your heart failure prevent you from living as you wanted during the last month by making you short of breath?' Possible answers ranged from 0 (no impact) to 5 (severe impact). Response values of ≥ 2 were categorised as symptomatic. Dizziness/syncope was assessed by the question: 'How much has dizziness/syncope influenced your daily activities the last four weeks?' Possible responses were: 1(not at all), 2 (a little), 3 (some), 4 (much), and 5 (very much). Response values of 3-5 were categorised as symptomatic. Cut-off points were set to avoid including patients who experienced very little discomfort as symptomatic. Timing of symptoms for valve replacement was not a goal in this

cross-sectional study of symptomatic and asymptomatic patients with aortic stenosis and their subsequent prognosis. Hence, patients were not assessed repeatedly for study purposes.

The Hospital Anxiety and Depression Scale (HADS) was used to assess possible symptoms of anxiety or depression. [16] HADS consists of a seven-item sub-scale for anxiety (HADS-A) and a seven-item sub-scale for depression (HADS-D). For all items, responses are scored on a four-category scale, with 0 representing no symptoms and 3 representing maximum symptoms. The scores on each sub-scale range from 0 to 21. For identifying possible cases of anxiety and depressive disorders, the HADS has an optimal cut-off score of at least 8 for both sub-scales. [16] The Cronbach's α value were 0.86 for HADS-A and 0.75 for HADS-D.

The New York Heart Association (NYHA) Functional Classification was used to describe the impact of the disease on daily activities. [17] NYHA classifies patients into four categories (I-IV), with higher classes indicating more severe symptoms and limitations in physical activity. The self-assessed NYHA classification tool asks patients to assign themselves to a NYHA class by ticking one of four boxes indicating categories that best describe their ability to perform physical activity. This tool is a well-documented and valid method of assessing symptoms of heart failure. [17]

Ethics

The present study was conducted in accordance with the ethical guidelines contained in the World Medical Association's Declaration of Helsinki (2004) and was approved by the Regional Medical Ethics Committee of Western Norway (No. 2010/01954). Information about the study, the possibility of withdrawing at any time, and confidentiality issues were included in the letter that accompanied the questionnaire. Informed consent was taken as a

patient returning the completed questionnaire. In accordance with the regional ethical committee, patients who failed to respond by mail were contacted once by telephone in order to encourage them to complete the questionnaire.

Statistical analysis

Descriptive statistics for continuous variables are presented as means and standard deviations (SDs). For comparisons between groups, the unpaired t-test was used. Descriptive statistics for categorical variables are presented as counts and proportions, and comparisons done using the exact chi-square test. Correlation between continuous variables was estimated by Pearson's correlation (r). Kaplan-Meier analysis was used to assess patient survival and cumulative incidence of AVR/TAVI after 18 months. Cox regression analysis was used to evaluate time-related events and their associations with baseline characteristics, such as age, gender, symptomatic status, severity of AS and EuroSCORE based on clinical experience and previous research[6] Results are reported as hazard ratios (HRs) and 95% confidence interval (CIs). No imputing of missing data was performed.

The statistical analyses were performed using SPSS for Windows 22 (IBM, Corp., Release 2013, Armonk, NY, USA), STATA/SE 14.0 for Windows, 02, 2015), Matlab 9.0 (The MathWorks Inc., Natick, MA, 2016) and Venn Diagram Plotter: (http://omics.pnl.gov/software/venn-diagram-plotter). A two-sided p-value ≤ 0.05 was considered statistically significant. To evaluate the clinical importance of differences in self-reported physical and mental health of symptomatic and asymptomatic patients, we computed effect sizes (ES statistics) by dividing the mean differences in scores by the SD of the norm data. [18] To interpret the effect size, we followed the suggestion of Cohen, and regarded effect sizes of 0.2- 0.5 as small, 0.5-0.8 as moderate, and 0.8 and above as large. [18]

RESULTS

Patients' characteristics, symptoms and health status

Of the 245 patients treated conservatively and not having undergone AVR or TAVI by April 2013, 137 patients (56%) returned the questionnaire. One patient was excluded from further analysis due to a congenital subvalvular AS (Figure 1). No statistical significant differences were found between responders and non-responders with respect to age ($p = 0.157$) or gender ($p = 0.062$).

The mean (SD) age was 79 (12) years and 52% were men. One-hundred and five (77%) patients were symptomatic. The most frequently self-reported symptom was dyspnoea, 57 (71%); followed by chest pain 49 (61%) and dizzines/suncope 26 (33%). Overlapping symptoms are shown in Figure 2. Patients with symptomatic AS were older, had attained a lower educational level, were more often living alone, were placed in a higher NYHA class, had a higher EuroSCORE I, and were more often on medication such as beta-blockers and statins, as compared to asymptomatic patients (Table 1)

Of the 136 patients, 22 (16%) were not accepted for AVR by the heart team, whilst 12 (9%) patients declined AVR by themselves. The remaining 102 (75%) were considered as potential surgical candidates and remained under medical observation. The distribution of AS severity, symptomatic status and treatment decision at baseline are shown in Figure 1. No gender differences were found for severity of AS, chest pain, dyspnoea, dizziness/syncope or numbers of symptoms reported. Risk stratification of all 136 patients revealed that 29 patients (21%) had a numeric EuroSCORE ≤ 5, 81 (60%) had a EuroSCORE between 6-10, and 26 (19%) had a EuroSCORE of 11-15.

Patients with asymptomatic AS reported better physical and mental health status compared to symptomatic patients. The estimated effect size for the differences in SF-12 measures between symptomatic and asymptomatic patients was 1.24 for the PCS and 0.74 for the MCS. The assessment of the impact of AS on the patients' daily life (MLHFQ), showed that it had a significantly larger impact in symptomatic patients. In addition, asymptomatic patients had significantly lower HADS scores compared to symptomatic patients (Table 2).

Eighteen months follow-up

Eighteen months after the survey, of the 136 patients, 117 (86%) were still alive, Of whom 22 (16%) had undergone isolated AVR, including 5 with AVR in combination with coronary artery bypass grafting (CABG) and 10 (7%) had undergone TAVI. Nineteen patients (14%) had died; whereas1 died 6 days after AVR. The flow chart of patient outcomes (survival and AVR/TAVI) within the 18 months follow-up is shown in Figure 1.

Among the 102 individuals with medical observation at the time of the survey (Figure 3), 22 (21%) had undergone AVR, 7 (7%) had TAVI and 9 (9%) had died. Additionally, 2 patients were scheduled for AVR and 2 for TAVI during follow-up. Among the 22 patients previously declined from AVR by the heart team, 3 (14%) had undergone TAVI and 5 (23%) had died. Four of the 12 patients who decided to receive conservative treatment had died; and none had undergone AVR or TAVI.

Of the 20 patients with asymptomatic severe AS (Table 1), only 3 (15%) had undergone an exercise test. One of them had a rise in blood pressure and a decrease of 2 mm in the ST-segment on EKG, but no symptoms of angina. He was finally accepted for surgery, but died

before the operation. In the other two cases, the patients experienced a slight rise in pulse, but in both cases the test ended prematurely due to limb fatigue.

After 18 months, of the 81 patients with symptomatic severe AS at baseline, 31had still not undergone surgical treatment, and five had died prior to the end of the study. Of the latter, one had been accepted for AVR and one for TAVI. The remaining 26 patients were still treated conservatively after 18 months, either due to symptoms unrelated to AS (n = 3), patients' decision (n = 1), horizontal aortic root not eligible for TAVI (n = 1), Alzheimer disease (n = 1), or vague symptoms (n = 3). The remaining 17 patients had, for unknown reasons, not been referred for cardiac surgery. Seven of the 20 patients with asymptomatic severe AS at baseline were treated with AVR (n = 5) or TAVI (n = 2) within 18 months. All of them developed symptoms, mainly dyspnoea before the intervention.

Multiple Cox regression analysis for selection of AVR or TAVI was performed and included age, gender, symptomatic status, severity of AS, and EuroSCORE as variables (Figure 4). Patients with severe AS had more than six fold chance of being scheduled for AVR or TAVI compared to those with moderate AS (HR: 6.3, 95% CI: 1.9, 21.2, p = 0.003). EuroSCORE ≥ 11decreased the chance for undergoing AVR or TAVI compared to having EuroSCORE ≤ 5 (HR: 0.06, 95% CI: 0.01 to 0.458, p = 0.007).

Self-rated general health at baseline tended to predict event-free survival (Figure 5a), and EuroSCORE tended to predict overall survival (Figure 5b) by the 18–months-follow-up, but the results were not statistically significant.

DISCUSSION

In the present study, the relationship between patient-reported outcomes and the severity of AS were investigated by employing well-established health status instruments. The results revealed that symptoms had a larger influence on the conservatively treated patients' physical and mental health than the severity of AS. AS severity alone, as measured by Doppler echocardiography examinations, did not differ between symptomatic and asymptomatic patients.

Previous studies have shown that important outcomes such as symptoms, function, and well-being are weakly associated with objective measures of disease severity. [19] It is known that the degree of AS at the onset of symptoms differs among patients. [3] The symptom most frequently experienced by patients in this study was dyspnoea. Dyspnoea was also the most frequent symptom observed in patients selected for AVR or TAVI. Since the presence of dyspnoea predicts worse survival for patients with AS, [20] our treatment algorithm is well supported by clinical outcome studies [20] and guidelines. [5] In the present study, mild symptoms of shortness of breath were classified as asymptomatic AS. Surprisingly, nearly 60% of the asymptomatic patients classified themselves within NYHA class II, indicating they experienced shortness of breath or tiredness, or palpitations when performing strenuous activities. Rather than attributing these two symptoms solely to exercise induced AS another plausible explanation is the presence of other co-morbidities, advanced age or their generally poor physical condition.

Symptomatic and asymptomatic patients also differed in physical and mental health status, with the latter having better scores. As the effect size showed, this difference is also clinically relevant. [18] Although neither the Doppler echocardiogram measurements (i.e. AS severity) nor number of co-morbidities differed between the two groups, the analyses showed that patient-

reported outcomes did differ. This is in line with the reports of van Geldorp et al, who concluded that even minor AS symptoms may have a major impact on patients' physical and mental well-being, as well as quality of life. [4] They also concluded that there was no relationship between stenosis severity and patients' physical or mental health, but symptoms severity according to NYHA classification corresponded well with the SF-36 scores.

Patients who graded their general health as fair or poor tended to have a lower 18-month event-free survival, as compared to those grading their health as good or better, but the difference was not statistically significant. Self-rated health has been shown to predict mortality one year after TAVI. [21]

In the present study, symptomatic patients reported significantly higher levels of both anxiety and depression compared to asymptomatic patients, indicating that AS symptoms have a great impact on mental health. Compared to the cohort of patients having undergone AVR responding to the same questionnaire, [10] conservatively treated symptomatic patients in the present study reported a higher level of anxiety and depression. This supports the findings that AS symptoms have a negative impact on patients' mental health, suggesting that valve surgery can reduce this mental burden.

In symptomatic patients with severe AS, aortic valve surgery is generally recommended both by European and American guidelines. [5 22] Fifty-five per cent of the patients who fulfilled the criteria for receiving AVR, either were not on the waiting list for AVR or had been treated with AVR or TAVI within 18 months after the survey. The low proportion of asymptomatic AS patients who underwent exercise testing may suggest that the indication for surgery was underestimated. Symptomatic status can be difficult to determine, especially in elderly

patients, as they tend to minimise or deny symptoms, or effectively reduce their physical activity level to avoid symptoms. [23] One-third of the patients who report to be asymptomatic develop symptoms during exercise testing; thus this type of testing is recommended to unmask symptoms in patients with severe AS. [24] With appropriate supervision and monitoring, symptom-limited stress testing is safe in severe AS and can add important prognostic value especially in older people that might have problems performing a treadmill exercise test due to coexisting morbidities. [24]

A possible explanation why many patients are not referred for surgery despite severe symptomatic AS, is that the patients are discharged from the university hospital without being implemented into a treatment algorithm provided for the local hospitals, cardiologists in private practice or general practitioners. Multidisciplinary heart teams, together with the patients and their family, should conclude with either conservative treatment, AVR or TAVI according to current guidelines, shared decision making, co-morbidities and operative risks. Although the majority of the patients declined for surgery at baseline had a EuroSCORE of > 10, a high EuroSCORE did not fully explain why some patients still were not referred for surgery. As EuroSCORE is known to overestimate the risk of postoperative mortality, especially in low-risk patients scheduled for isolated AVR, the postoperative mortality risk may have been overestimated in some of the patients. [25]

AS severity, and not symptomatic status, predicted selection for surgical treatment in this cohort. The gap between the existing guidelines and their actual application has been demonstrated in previous studies. [5 7] Close follow-up of the asymptomatic patients is also important, as severe symptoms or cardiac death may occur suddenly. [26] There is robust evidence that AVR prolongs life in patients with symptomatic and severe AS. This is

regardless of severity of symptoms or the response to medical treatment. [3] It is also of utmost importance that health professionals inform patients with AS to contact their physician as soon as symptoms occur and close follow-up of asymptomatic patients is recommended. [27] The optimal time for intervention is still open to debate. [27] Some argue that early elective surgery in asymptomatic patients with severe AS might be worthwhile, since rapid deterioration is associated with the disease. [26] Early surgery in patients with severe asymptomatic AS has also shown to improve long-term survival by decreasing cardiac mortality [28] as well as lower 5-year incidences of all cause death and heart failure hospitalisation compared to conservative treated patients. [29] In addition, an ongoing prospective multicentre randomised controlled trial (the AVATAR trail) is testing the hypothesis that elective AVR is superior to medical treatment until symptom onset in asymptomatic patients with isolated severe AVR and normal LVEF. [30]

Study strengths and limitations

Very few studies have investigated self-reported health in AS patients under conservative treatment. Patient-reported outcomes are important to inform health professionals as well as policymakers in order to improve the quality of care to patients with AS. Thus, the present study has some methodological limitations. It was carried out as a single-centre study, which may decrease the generalisability of the results. The sample, however, represents patients from both densely populated and rural areas. Another limitation is the retrospective design of the study and that we gathered only limited data prospectively. Further, a potential limitation is the moderate response rate of 56%. A possible reason for this response rate can be that some of the patients were still asymptomatic, and perhaps not motivated to take the time to answer the questionnaire. Alternatively, patients with severe disease burden were incapable of completing the questionnaire.

CONCLUSIONS

Patients receiving conservative treatment for AS are an understudied group of cardiac patients. The present study demonstrated that AS symptoms have great impact on patients' physical and mental health status. However, this impact does not reflect the severity of AS. Still, many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. Our results indicate that the referral practice for aortic valve surgery ought to be carefully scrutinised. Further well-designed prospective studies are needed to fully understand the disease burden of AS and to optimise the timing of surgical intervention. Self-reported health status may be a valuable supplement to physical examination during the clinical evaluation of high-risk AS patients.

Footnotes

Contribution KO, RH, JEN and TMN are responsible for study concept and design. KO and TMN are responsible for data collection. GEE, KO and TMN are responsible for data analysis. KO, RH, JEN and TMN are responsible for initial draft of manuscript. KO, RH, JEN, GEE and TMN are responsible for interpretation of data. All authors revised the paper critically for important intellectual content and approved the final manuscript. KO, GEE and TMN had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest The authors declare that there is no conflict of interest.

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Data sharing statement No additional data are available.

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Table 1. Baseline characteristics of 136 patients aged 35 to 95 years diagnosed with severe to moderate aortic stenosis in the period 2000 to 2012 who replied to a postal questionnaire in 2013.

Variable	All (N= 136)	Symptomatic (n = 105)	Asymptomatic (n = 31)	p-value*
Basic characteristics				
Age in years; *mean (SD) range*	79 (11) 35-95	80 (10)	75 (12)	**0.025**
Gender, men, *n (%)*	70 (52)	55 (52)	15 (48)	0.696
Living alone, *n (%)*	51 (38)	44 (42)	7 (23)	0.052
Education, *n (%)*				**0.037**
Elementary school	73 (54)	62 (60)	11 (36)	
High School	33 (24)	23 (22)	10 (32)	
University/College	29 (22)	19 (18)	10 (32)	
Smoking, *n (%)*				0.121
Current smoker	11 (8)	9 (9)	2 (7)	
Previous smoker	58 (43)	49 (47)	9 (30)	
Never smoked	66 (49)	47 (45)	19 (63)	
Sa-NYHA, *mean (SD)*	2.18 (0.87)	2.34 (0.88)	1.66 (0.55)	**<0.001**
NYHA I, *n (%)*	25 (19)	14 (14)	11 (40)	
NYHA II, *n (%)*	70 (53)	53 (52)	17 (57)	
NYHA III, *n (%)*	22 (17)	21 (21)	1 (3)	
NYHA IV, *n (%)*	14 (11)	14 (14)	0 (0)	
Doppler echocardiography examination[a]				
Ejection fraction *(%), mean (SD)*	59 (9)	58 (10)	60 (7)	0.304
V-max (m/s), *mean (SD)*	4.0 (0.7)	4.0 (0.7)	3.9 (0.4)	0.418
AVA (cm^2 /BSI), *mean (SD)*	0.54 (0.2)	0.53 (0.2)	0.57 (0.2)	0.257
Mean aortic gradient, *mean (SD)*	41 (15)	42 (15)	38 (11)	0.115
Severity of AS				0.159
Severe AS, *n (%)*	101 (74)	81 (80)[b]	20 (20)[b]	
Moderate AS, *n (%)*	35 (26)	24 (65)[b]	11 (35)[b]	
Aortic regurgitation, *n (%)*				0.067
Mild (1/4)	55 (40)	43 (41)	19 (18)	
Moderate (2/4)	27 (20)	19 (18)	8 (25)	
Moderate-to-severe (3/4)	2 (1.5))	0 (0)	2 (6)	
EuroSCORE-log, *mean (SD)*	12.8 (11.6)	13.9 (11.8)	9.0 (10.3)	**0.027**
EuroSCORE-numeric, *mean (SD)*	8.0 (3.1)	8.3 (3.1)	6.9 (2.8)	**0.022**
Years since diagnosis, *mean (SD)*	5.7 (3.2)	5.5 (3.1)	6.3 (3.5)	0.207
Medical history, *n (%)*				
Diuretics	34 (25)	30 (29)	4 (13)	0.078
Beta-blockers	87 (64)	71 (68)	16 (52)	0.104
Statins	80 (59)	67 (64)	13 (42)	**0.030**
Myocardial infarction	24 (18)	18 (20)	6 (18)	0.753
Stroke	19 (14)	16 (16)	3 (10)	0.394
AF intermittent	33 (28)	28 (32)	5 (17)	0.140
AF permanent	8 (7)	7 (7)	1 (3)	0.454
COPD	8 (6)	8 (8)	0 (0)	0.109
Arthritis	25 (19)	22 (22)	3 (10)	0.139

Osteoporosis	18 (14)	15 (15)	3 (0)	0.454
Cancer	26 (20)	21 (21)	5 (16)	0.539
PCI	18 (13)	14 (13)	4 (13)	
Previous CABG	6 (4)	6 (6)	0 (0)	0.336
Pacemaker	10 (8)	7 (7)	3 (10)	0.555

SD: standard deviation; Sa-NYHA: Self-assessed New York Heart Association functional classification; AVA: aortic valve area; V-max: maximum jet velocity; CABG: coronary artery bypass grafting; AF: atrial fibrillation; COPD: chronical obstructive pulmonary disease. * Tests comparing symptomatic versus asymptomatic (bolded p-values significance at $p \leq 0.05$). [a] Figures are mean values for moderate and severe stenosis. [b] Symptomatic or asymptomatic patients are % of all patients with severe or moderate AS.

Table 2. Baseline self-reported health status of 136 patients aged 35 to 95 years diagnosed with aortic stenosis in the period 2000 to 2012 responding to the questionnaire in 2013, data differentiated by symptomatic status.

Variable	All (N= 136)	Symptomatic (n = 105)	Asymptomatic (n = 31)	p-value
SF-12, PCS, *mean (SD)*	36.8 (11.7)	33.8 (11)	46.2 (9)	**<0.001**
SF-12, MCS, *mean (SD)*	52.3 (10.4)	50.6 (11)	58.0 (4)	**<0.001**
MLHFQ Physical *mean (SD)*	11.8 (11.3)	14.9 (11)	3.3 (5)	**<0.001**
MLHFQ Emotional *mean (SD)*	3.1 (5.1)	3.9 (6)	0.6 (2)	**<0.001**
HADS-A, *mean (SD)*	3.9 (3.4)	4.2 (4)	2.9 (2)	**0.036**
HADS-D, *mean (SD)*	4.5 (3.4)	5.0 (4)	2.7 (2)	**<0.001**
HADS-A $\geq$ 8, *n (%)*	18 (14)	17 (17)	1 (3)	0.071
HADS-D $\geq$ 8, *n (%)*	24 (18)	22 (22)	2 (7)	0.056

SD: standard deviation; PCS: physical component summary of SF-12; MCS: mental component summary of SF-12; MLHFQ: Minnesota Living with Heart Failure Questionnaire; HADS-A: Hospital Anxiety and Depression Scale, anxiety component; HADS-D: Hospital Anxiety and Depression Scale, depression component

Figure 1. Flowchart showing patient with and without aortic valve replacement participating in the study, and outcomes after 18-months follow-up for136 patients aged 35 to 95 years under conservative treatment at the time of survey. Patients were diagnosed between the years 2000 to 2012 and were invited to complete the questionnaire in year 2013.

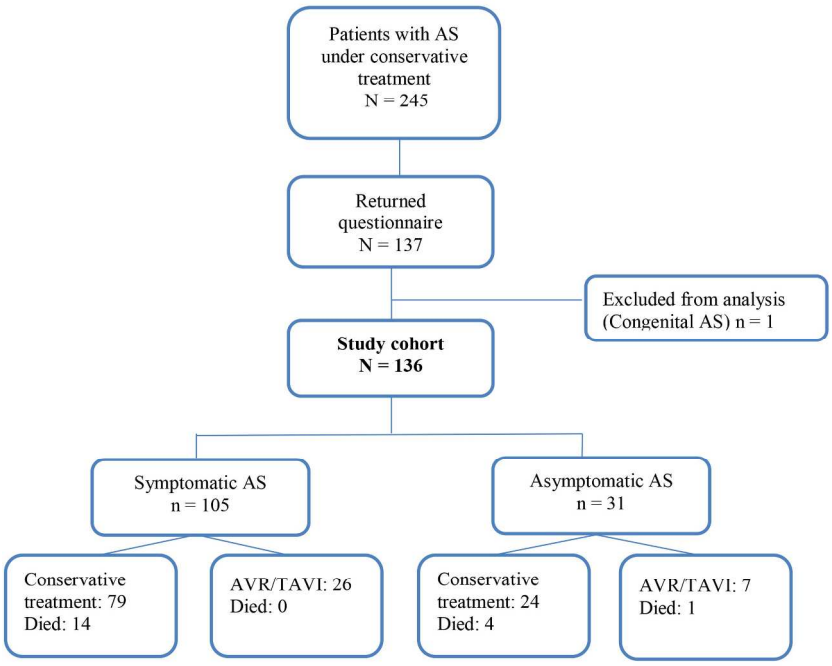
Figure 2. Number of symptomatic AS patients with overlapping symptoms (N = 105)
A: Chest pain. B: Dyspnoea. C: Dizziness/syncope

Figur 3. Reasons for not having undergone AVR at baseline in 136 patients with symptomatic and asymptomatic severe-to-moderate aortic stenosis.

Figure 4. Cumulative occurrence of AVR or TAVI from Cox model, according to EuroSCORE range (likelihood ratio p-value (LR-p) = 0.011) in patients with aortic stenosis within 18 months adjusted for gender (LR-p = 0.336); age (LR-p =0.223); symptomatic status (LR-p = 0.437); and severity of aortic stenosis (LR-p = 0.002).

Figure 5. Kaplan-Meier curves showing: A, event-free survival in patients with aortic stenosis according to self-rated general health category at baseline (log rank test: p = 0.418). B, overall

survival in patients with aortic stenosis (AVR or TAVI censored) according to numeric EuroSCORE I range (log rank test: p = 0.209).



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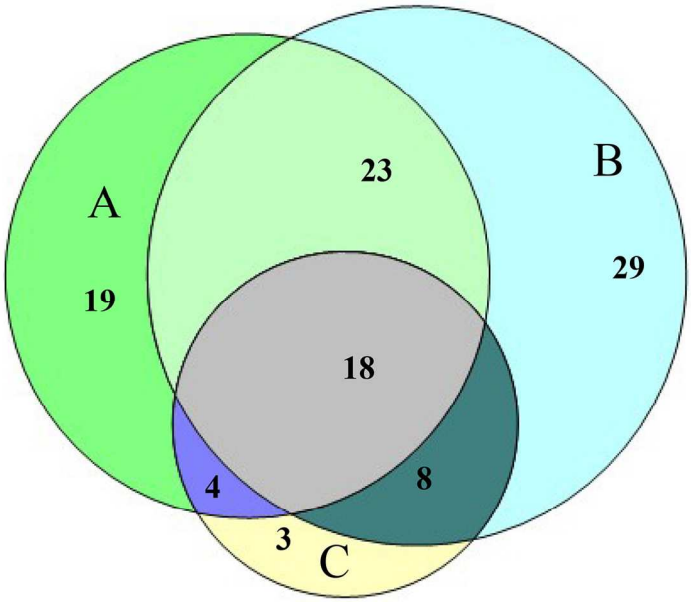

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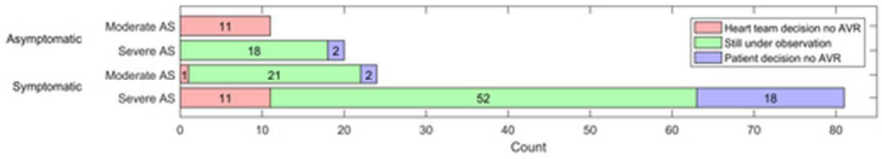

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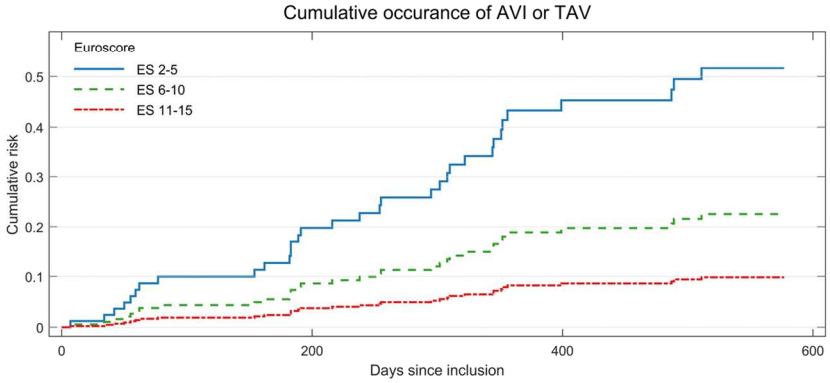

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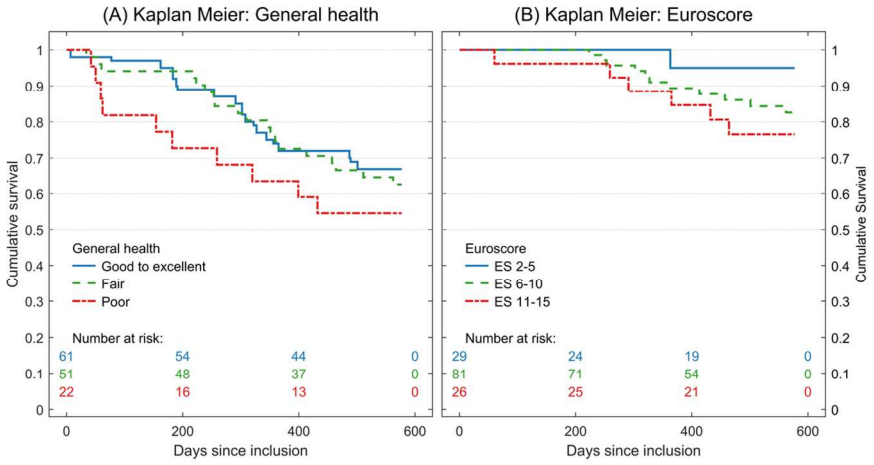

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract The study's design can be found in the title (p1) and in the abstract (p2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. This is shown in page 2.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Very few studies have investigated the disease burden of aortic stenosis placed on patients' daily life, whether symptomatic or asymptomatic. Current European guidelines recommend AVR for patients with severe symptomatic AS. Despite this many patients fulfilling these guidelines are not referred for surgery (p4).
Objectives	3	State specific objectives, including any prespecified hypotheses The objectives were to investigate symptoms and self-reported health of patients conservatively treated for aortic stenosis (AS) and to identify factors associated with treatment decision and patient outcomes. (p5)
Methods		
Study design	4	Present key elements of study design early in the paper A cross-sectional design (survey) with an 18 month follow-up regarding treatment decision and survival (p5).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Patients diagnosed with AS at a tertiary university hospital in western Norway and fulfilling inclusion criteria (p5-6) were invited to a postal survey in April 2013. 18 months after the survey, information on selection of treatment and survival were retrieved from patients' medical records (p6)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants To be included in the survey participants had to have echocardiographically verified AS in the native aortic valve, with at least a maximum transvalvular gradient of ≥40 mm Hg (p5). This information was retrieved from patients' medical records.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Primary outcome measures were symptoms and self-reported health status. Secondary outcomes were treatment decision and patient survival after 18 months (p1). Severe AS was defined according to current guidelines. Patients had to fulfil at least one of the following haemodynamic criteria: an aortic valve area (AVA) < 1 cm^2; a mean pressure gradient > 40 mmHg or a peak aortic jet velocity > 4 m/s, as demonstrated by Doppler echocardiography. Moderate AS was defined as having an AVA of 1.5-1.0 cm^2, a mean pressure gradient of 25-40 mm Hg or a peak aortic jet velocity of 3.0-4.0 m/s (p5-6). Definition of symptomatic status is described on p7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

		Socio-demographic variables, smoking status, symptoms, co-morbidities; and physical and mental health status were obtained by means of patient self-reports. Clinical variables such as date of AS diagnosis, reasons for declining an AVR or TAVI, results from Doppler echocardiography examination regarding severity of AS and AR, treatment modalities, and survival were retrieved from patient medical records. Expected operative risk was calculated using numeric and logistic EuroSCORE I classification (www.euroscore.org) (p6).
Bias	9	Describe any efforts to address potential sources of bias Analyses were performed to investigate possible differences between responders and non-responders. No statistical significant differences were found between responders and non-responders with respect to age (p = 0.157) or gender (p = 0.062) (p10).
Study size	10	Explain how the study size was arrived at All eligible patients were invited to participate in the survey.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. Descriptive statistics for continuous variables are presented as means and standard deviations (SDs). For comparisons between groups, the unpaired t-test was used. Descriptive statistics for categorical variables are presented as counts and proportions, and comparisons done using the exact chi-square test. Correlation between continuous variables was estimated by Pearson's correlation (p9).We decided to compare symptomatic and asymptomatic patients with respect to symptoms, self-reported health as well as AS severity to investigate how the variables correlated.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding This has been done in the Statistical methods section (p9). Control for confounding in the analysis of survival was done by using Cox regression.
		(*b*) Describe any methods used to examine subgroups and interactions Descriptive statistics were used for examining the subgroups with symptomatic and asymptomatic AS (Table 1 and 2). For survival analysis we used Kaplan-Meier in subgroups defined by symptomatic status, severity of AS and EUROscore.
		(*c*) Explain how missing data were addressed No imputing of missing data was performed, this is stated on p9.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy Not applicable
		(*e*) Describe any sensitivity analyses This was not applicable.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed As shown in Figure 1 (p22) 245 eligible patients were invited to participate in the survey, 137 responded, 1 was excluded due to congenital AS. Thus 136 were included in further analysis.
		(b) Give reasons for non-participation at each stage Non participants were those who did not return the questionnaire. They

		did not differ from participants with respect to age or gender.
		(c) Consider use of a flow diagram A flow diagram is used in Figure 1 to show treatment selection in patients with symptomatic and asymptomatic AS (p22).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders This is shown in Table1 (p20-21)
		(b) Indicate number of participants with missing data for each variable of interest Number of missing data on self-reported heath appears in Table 2. Non-responders are given in Figure 1. There were no missing data on treatment selection or survival data. We were able to calculate EuroSCORE in all patients. EF: 8 (5.9%) missing, mean gradient 6 (4.4%) missing, AVA 20 (14.7%) missing, V max 40 (29.4%) missing.
Outcome data	15*	Report numbers of outcome events or summary measures This is given in the Results chapter (p 9-12)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Not applicable.
		(*b*) Report category boundaries when continuous variables were categorized No continuous variables were categorized.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses All relevant results are reported.
Discussion		
Key results	18	Summarise key results with reference to study objectives One-hundred and five (77%) patients were symptomatic. The most frequently self-reported symptom was dyspnoea, 57 (71%); followed by chest pain 49 (61%) and light-headedness 26 (33%). Patients with asymptomatic AS reported better physical and mental health status compared to symptomatic patients. No associations were found between AS severity and symptoms. Eighteen months after the survey 117 (86%) were still alive. Twenty-tree (16%) had undergone AVR and 10 (7%) had undergone TAVI. Nineteen patients (14%) had died (p11). Many patients with symptomatic severe AS are not scheduled for surgery after 18 months, despite the recommendations in current guidelines. (p9-12)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Some limitations are that this was a single centre study with a moderate response rate and that some data were retrospective collected. Using EuroSCORE in AS patients might have overestimated the postoperative mortality risk. Because the data from patients' records was retrieved retrospective some missing data might have made the results less precise. See also p16

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence The present study demonstrated that AS symptoms have great impact on patients' physical and mental health status. However, this impact does not reflect the severity of AS. This is in line with previous studies. Still, many patients with symptomatic severe AS are not scheduled for surgery, despite the recommendations in current guidelines. Our results indicate that the referral practice for aortic valve surgery ought to be carefully scrutinised. Further well-designed prospective studies are needed to fully understand the disease burden of AS and to optimise the timing of surgical intervention. Recent studies indicate also patients with asymptomatic severe AS will benefit from surgical treatment, and that watch-full waiting not always is the best solution.
Generalisability	21	Discuss the generalisability (external validity) of the study results The results might be of limited value due to that the data was only collected at a single centre, but we believe that this centre is a typical representative for the population of patients in Norway.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. The study was funded by a research grant from the Western Norway Health Authority that supported the PhD education for the first author. The study also received funding from The Norwegian Nursing Association to finance expenses of carrying out the survey.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.