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Impact of aortic valve replacement in symptomatic low-risk patients with less than severe aortic stenosis

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ABSTRACT

Objective To evaluate whether transcatheter or surgical aortic valve replacement (TAVR or SAVR) affects clinical and haemodynamic outcomes in symptomatic patients with moderately-severe aortic stenosis (AS).

Methods Echocardiographic evidence of severe AS for enrolment in the Evolut Low Risk trial was based on site-reported measurements. For this post hoc analysis, core laboratory measurements identified patients with symptomatic moderately-severe AS (1.0<aortic valve area (AVA)<1.5 cm^2, 3.0<peak velocity<4.0 m/s and 20≤mean gradient (MG) <40 mm Hg). Clinical outcomes were reported through 2 years.

Results Moderately-severe AS was identified in 113 out of 1414 patients (8%). Baseline AVA was 1.1±0.1 cm^2, peak velocity 3.7±0.2 m/s, MG 32.7±4.8 mm Hg and aortic valve calcium volume 588 (364, 815) mm^3. Valve haemodynamics improved following TAVR (AVA 2.5±0.7 cm^2, peak velocity 1.9±0.5 m/s and MG 8.4±4.8 mm Hg; p<0.001 for all) and SAVR (AVA 2.0±0.6 cm^2, peak velocity 2.1±0.4 m/s and MG 10.0±3.4 mm Hg; p<0.001 for all). At 24 months, the rates of death or disabling stroke were similar (TAVR 7.7% vs SAVR 6.5%; p=0.82). Kansas City Cardiomyopathy Questionnaire overall summary score assessing quality of life improved from baseline to 30 days after TAVR (67.0±20.6 to 89.3±13.4; p<0.001) and SAVR (67.5±19.6 to 78.3±22.3; p=0.001).

Conclusions In symptomatic patients with moderately-severe AS, AVR appears to be beneficial. Determination of the clinical and haemodynamic profile of patients who can benefit from earlier isolated AVR needs further investigation in randomised clinical trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The efficacy and safety of isolated aortic valve replacement (AVR) in patients with severe aortic stenosis (AS) is well established but scarce in patients with less than severe AS.

WHAT THIS STUDY ADDS

⇒ In symptomatic patients with moderately-severe AS identified from the Evolut Low Risk trial, valve haemodynamics and health status improved following AVR, and major clinical outcomes were similar for transcatheter AVR and surgical AVR through 2 years. Patients with symptomatic moderately-severe AS appeared to have superimposed myocardial disease from comorbidities compared with patients with severe AS. Further clinical trials are necessary to prove the benefit of AVR.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Before clinical trials investigate the benefit of AVR in patients with less than severe AS, it would be appropriate to clarify the target population who can potentially benefit from earlier isolated AVR based on the patient's natural history. Since moderate AS includes a wide range of valve haemodynamics, it is probably more appropriate to first evaluate extending the current definition of severe AS rather than to prove the benefit of AVR in moderate AS, as currently defined by guidelines.

INTRODUCTION

The efficacy and safety of aortic valve replacement (AVR) is well established in patients with severe aortic stenosis (AS),[1 2] but remains unknown in those with less than severe AS. The current management of patients with less than severe AS has been a conservative approach of 'watchful waiting'. AVR is usually not formally recommended until AS becomes severe, even in symptomatic patients, or when the left ventricular ejection fraction (LVEF) <50% in asymptomatic severe AS patients.[1 2] In patients with moderate AS, AVR is only recommended when other open-heart surgery is performed. With recent findings of increased mortality[3–6] and LV maladaptation when AS severity is only moderate,[7] a subset of patients with less than severe AS may benefit from earlier AVR.

This post hoc study from the Evolut Low Risk trial (NCT02701283) aimed to investigate clinical outcomes, valve haemodynamics and health status out to 2 years following

transcatheter or surgical AVR (TAVR or SAVR) in symptomatic patients with less than severe AS.

METHODS

Patient population

The Evolut Low Risk trial evaluated the safety and efficacy of TAVR using a self-expanding, supra-annular bioprosthesis compared with SAVR in symptomatic and asymptomatic patients with severe AS at low surgical risk (<3%).[2 8] Patients assigned to TAVR were treated with a CoreValve, Evolut R or Evolut PRO valve (Medtronic, Minnesota, USA). Surgical bioprosthesis type was per operator's choice. Details of the study design and primary outcomes have been previously published.[2 8]

In the Evolut Low Risk trial, symptomatic severe AS was defined as meeting 1 of the following echocardiography criteria based the clinical sites' assessment; aortic valve area (AVA) ≤1.0 cm^2 (OR AVA Index (AVAi) ≤0.6 cm^2/m^2), OR peak velocity ≥4.0 m/s, OR mean gradient (MG) ≥40 mm Hg. Detailed trial inclusion criteria for patients with asymptomatic severe AS are provided in online supplemental table S1.

Consistent with many prospective clinical trials, site-reported echocardiographic measurements were used to select patients for trial enrolment. During echocardiographic core laboratory assessment of the same echocardiograms, differences in measurements can be revealed. Since the enrolment parameters for severe AS were based on only 1 of the above-mentioned echocardiographic measures, patients in the Evolut Low Risk who met enrolment criteria of severe AS based on the site measurements may not have met the criteria based on the core-laboratory assessment. For this post hoc analysis, an independent core laboratory (Mayo Clinic, Minnesota, USA) identified symptomatic patients with moderately-severe AS if ALL of the following baseline criteria were met: 1.0<AVA <1.5 cm^2, 3<peak velocity<4 m/s, 20≤MG<40 mm Hg, and New York Heart Association (NYHA) functional class ≥II.

Echocardiography

Echocardiographic examinations were performed according to the Evolut Low Risk trial protocol.[2] All echocardiography data were centrally analysed by the core laboratory using Digisonics workstation (Digisonics, Texas, USA). Measurements were made from an average of three cardiac cycles. Peak velocity and MG were acquired from all transducer positions to obtain the highest values.[9] The LV outflow tract (LVOT) diameter of the native valve was measured at the aortic annulus, and the AVA was calculated according to the continuity equation using the velocity time integral (VTI).[9 10] The dimensionless velocity index was calculated as the ratio between LVOT and valve VTI.[10] After TAVR, the LVOT diameter was measured from the outer-to-outer border of the stented valve at its ventricular tip.[11 12] Stroke volume (SV) was calculated as LVOT diameter^2×0.785×LVOT VTI. AVAi and SV Index (SVI) were calculated by adjusting for the body surface area (BSA).

Multidetector CT

Baseline aortic valve calcium volume from multidetector CT images was centrally assessed by Medtronic personnel using the semiautomated calcium scoring tool in 3mensio software system (Research V.8.1, Pie Medical Imaging, Maastricht, the Netherlands). The patient-specific threshold was set to the median of Hounsfield units in the contrast-enhanced blood in the aortic root plus 200 Hounsfield units. The aortic valve calcium volume included the region from the valve basal plane to the top of the leaflets.[13]

Study endpoints

The primary endpoint for this work was the composite of all-cause mortality or disabling stroke at 24 months. A secondary endpoint included the safety composite of all-cause mortality, disabling stroke, life-threatening or disabling bleeding, major vascular complication or stage 2 or 3 acute kidney injury at 24 months. The longitudinal change in quality of life (QOL) was evaluated with the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score[14] through 24 months after AVR.

Statistical analysis

The primary patient cohort for this post hoc analysis comprised patients who underwent an attempted implant (as-treated cohort). Echocardiographic outcomes are reported for the cohort of patients who underwent implantation. Haemodynamic, clinical outcomes and QOL are reported for patients with moderately-severe AS, and in those with severe AS for reference. Continuous variables are presented as mean±SD or median (quartile 1, quartile 3), and categorical variables as counts and frequencies. Student's t-test was used to assess differences between groups in continuous variables. Comparisons between categorical variables were done using the χ^2 test or Fischer's exact test where appropriate. For ordinal data, the Cochran-Mantel-Haenszel test was used. Clinical events are reported as Kaplan-Meier estimates and compared using the log-rank test. A Cox proportional hazards model was fitted and reported with HRs and 95% CIs. Due to the small sample size of the moderately-severe AS patient cohort and the unbalanced sample size compared with the severe AS cohort, a statistical comparison between these two patient populations was not performed. A two-sided $p<0.05$ was considered significant. No adjustments were made for multiple comparisons. All statistical analyses were performed using SAS V.9.4 (SAS Institute).

RESULTS

Of 1414 as-treated patients in the Evolut Low Risk trial, 113 (8%) patients were identified as having symptomatic moderately-severe AS and 1301 (92%) as severe AS

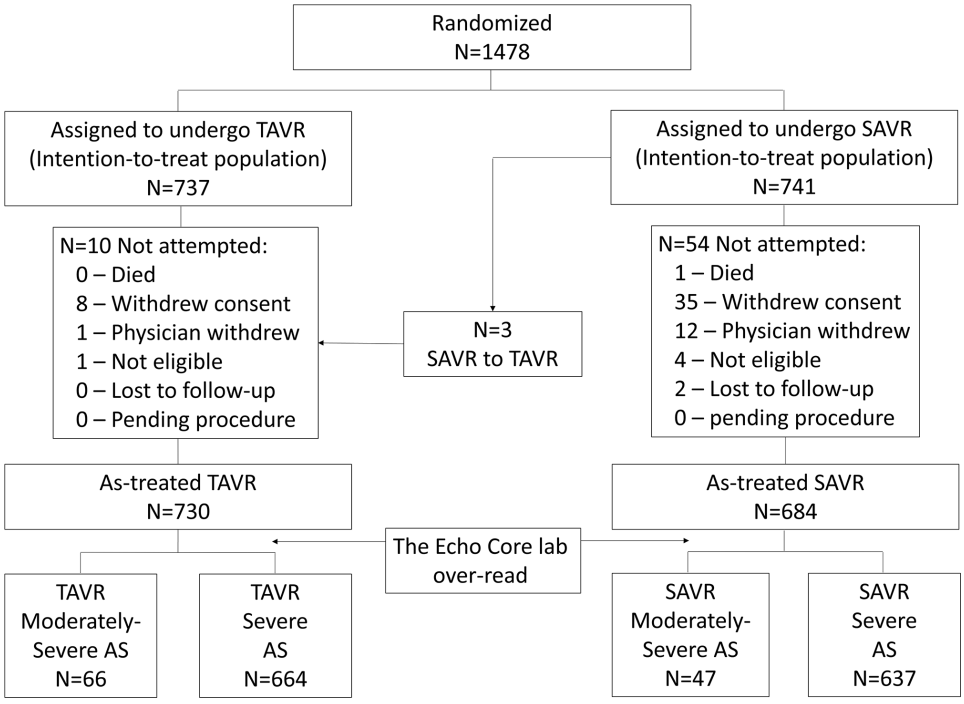

Figure 1 Patient flow diagram showing process of patient assignment. AS, aortic stenosis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

(figure 1). In patients with moderately-severe AS, TAVR was performed in 66 cases (58%) and SAVR in 47 cases (42%). In the severe AS patients, TAVR was performed in 664 cases (51%) and SAVR in 637 cases (49%).

Demographic and baseline clinical characteristics are shown in table 1. By definition, patients with moderately-severe AS had to be symptomatic (NYHA class ≥II), while all asymptomatic patients were included in the severe AS group. The STS score was 2.0±0.6 for patients with moderately-severe AS and 1.9±0.7 for those with severe AS (table 1). Although no statistical comparisons were performed between the moderately-severe AS and the severe AS patients, moderately-severe AS patients tended to be male, more commonly had diabetes, peripheral artery disease, prior percutaneous coronary intervention (PCI) and atrial fibrillation (table 1). The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score appeared to be numerically higher in the moderately-severe AS group than in the severe AS group. Moreover, patients with moderately-severe AS had less total aortic valve calcium volume than those with severe AS (558 (364, 815) vs 653 (385, 1014) mm^3).

Baseline echocardiographic measurements are presented in table 1. Compared with the severe AS patients, moderately-severe AS patients had a larger AVA (1.1±0.1 vs 0.8±0.2 cm^2) and dimensionless velocity index (0.28±0.04 vs 0.23±0.05), as well as a lower peak velocity (3.7±0.2 vs 4.3±0.5 m/s) and MG (32.7±4.8 vs 45.5±12.1 mm Hg). In addition, patients with moderately-severe AS had a higher SV (95.8±13.4 vs 82.5±20.6 mL) and SVI (47.1±8.5 vs 41.9±10.1 mL/m^2) compared with patients with severe AS. An SVI<35 mL/m^2 in the moderately-severe AS group was much less frequent (TAVR; 4.5%, SAVR; 6.4%) compared with the severe AS group (TAVR; 26.5%, SAVR; 23.7%).

Haemodynamic improvement after AVR

In patients with moderately-severe AS, valve haemodynamics significantly improved immediately after TAVR or SAVR (online supplemental table S2). At 30 days, AVA and dimensionless velocity index increased, while peak velocity and MG decreased (p<0.001 for all) (figure 2 and table 2). As expected, better postprocedure haemodynamics were observed following TAVR compared with SAVR. However, ≥mild aortic regurgitation was more frequent among TAVR versus SAVR (table 2). Similar haemodynamic improvements were observed for the severe AS cohort.

Clinical outcomes after AVR

In patients with moderately-severe AS, the primary endpoint of 24-month all-cause mortality or disabling stroke occurred in 7.7% of TAVR patients and 6.5% of SAVR patients (p=0.82) (table 3). For severe AS, rates were 4.0% for TAVR and 6.3% for SAVR (p=0.051). The secondary safety composite endpoint at 24 months in patients with moderately-severe AS occurred in 13.8% of TAVR patients and 8.7% of SAVR patients (p=0.42). For severe AS, rates were 9.2% for TAVR and 16.2% for SAVR (p<0.001). Consistent with the STS score (< 3%), all-cause mortality at 30 days for moderately-severe AS was 1.5% for TAVR and 2.1% for SAVR, respectively. For severe AS, it was 0.3% for TAVR and 1.1% for SAVR, respectively (online supplemental table S3).

Table 1 Baseline characteristics and echocardiography parameters of patients with moderate to severe AS and severe AS

	Moderate to severe AS (n=113)			Severe AS (n=1301)			All moderate to severe AS (n=113)	All severe AS (n=1301)
	TAVR (n=66)	SAVR (n=47)	P value	TAVR (n=664)	SAVR (n=637)	P value		
Baseline clinical characteristics								
Age, years	74.4±6.2	72.6±6.1	0.11	74.1±5.8	73.7±5.9	0.30	73.6±6.2	73.9±5.8
Female (%)	11 (16.7)	12 (25.5)	0.25	255 (38.4)	221 (34.7)	0.16	23 (20.4)	476 (36.6)
Body surface area, m^2	2.1±0.2	2.0±0.2	0.32	2.0±0.2	2.0±0.2	0.58	2.1±0.2	2.0±0.2
STS-PROM, %	2.0±0.5	2.0±0.7	0.67	1.9±0.7	1.9±0.6	0.38	2.0±0.6	1.9±0.7
NYHA class (%)			0.55			0.14		
I	0 (0)	0 (0)		76 (11.4)	63 (9.9)		0 (0)	139 (10.7)
II	48 (72.7)	32 (68.1)		424 (63.9)	396 (62.2)		80 (70.8)	820 (63.0)
III	18 (27.3)	14 (29.8)		163 (24.5)	176 (27.6)		32 (28.3)	339 (26.1)
IV	0 (0.0)	1 (2.1)		1 (0.2)	2 (0.3)		1 (0.9)	3 (0.2)
Diabetes mellitus (%)	31 (47.0)	17 (36.2)	0.25	198 (29.8)	193 (30.3)	0.85	48 (42.5)	391 (30.1)
Hypertension (%)	55 (84.6)	41 (87.2)	0.70	563 (84.8)	522 (82.1)	0.19	96 (85.7)	1085 (83.5)
COPD (%)	12 (19.7)	7 (15.2)	0.55	94 (14.7)	111 (18.2)	0.09	19 (17.8)	205 (16.4)
Immunosuppressive therapy (%)	2 (3.0)	0 (0.0)	0.51	13 (2.0)	7 (1.1)	0.21	2 (1.8)	20 (1.5)
Peripheral arterial disease (%)	4 (6.2)	6 (12.8)	0.32	50 (7.6)	50 (7.9)	0.86	10 (8.9)	100 (7.7)
SYNTAX score I (%)	2.4±3.9	2.5±3.9	0.84	1.9±3.7	2.1±3.8	0.32	2.5±3.9	2.0±3.8
Cerebrovascular disease (%)	8 (12.1)	5 (10.6)	0.81	66 (9.9)	77 (12.1)	0.22	13 (11.5)	143 (11.0)
Previous CABG (%)	2 (3.0)	0 (0.0)	0.51	16 (2.4)	14 (2.2)	0.80	2 (1.8)	30 (2.3)
Previous PCI (%)	13 (19.7)	11 (23.4)	0.63	90 (13.6)	77 (12.1)	0.43	24 (21.2)	167 (12.8)
Previous myocardial infarction (%)	2 (3.0)	4 (8.5)	0.23	46 (6.9)	29 (4.6)	0.07	6 (5.3)	75 (5.8)
Atrial fibrillation/atrial flutter (%)	11 (16.7)	9 (19.1)	0.73	100 (15.1)	89 (14.0)	0.57	20 (17.7)	189 (14.6)
Aortic valve calcium volume, mm^3	597 (376, 832)	556 (361, 789)	0.60	653 (390, 1050)	654 (377, 980)	0.21	588 (364, 815)	653 (385, 1014)
Baseline echocardiography	TAVR (n=66)	SAVR (n=47)	p Value	TAVR (n=661)	SAVR (n=639)	p Value	All moderate to severe AS (n=113)	All severe AS (n=1300)
Aortic valve area, cm^2	1.1±0.1	1.2±0.1	0.56	0.8±0.2 (571)	0.8±0.2 (549)	0.054	1.1±0.1	0.8±0.2 (1120)
Aortic valve area index, cm^2/m^2	0.55±0.08	0.57±0.09	0.18	0.41±0.10 (571)	0.42±0.10 (549)	0.09	0.56±0.08	0.42±0.10 (1120)
Peak velocity, m/s	3.7±0.3	3.7±0.2	0.30	4.3±0.5 (651)	4.2±0.5 (632)	0.09	3.7±0.2	4.3± 0.5 (1283)
Mean pressure gradient, mm Hg	32.6±4.8	32.8±4.8	0.79	46.0±11.9 (651)	45.1±12.3 (632)	0.17	32.7±4.8	45.5±12.1 (1283)
Dimensionless Velocity Index	0.27±0.04	0.28±0.04	0.46	0.22±0.05 (617)	0.23±0.05 (604)	0.03	0.28±0.04	0.23±0.05 (1221)
Left ventricular ejection fraction, %	63.7±7.6	63.7±8.4	0.99	64.5±7.5 (657)	64.5±7.0 (635)	0.96	63.7±7.9	64.5±7.3 (1292)
Stroke volume, mL	95.5±12.4	96.2±15.0	0.78	81.9±20.0 (574)	83.2±21.1 (552)	0.30	95.8±13.4	82.5±20.6 (1126)

Continued

Table 1 Continued

	Moderate to severe AS (n=113)			Severe AS (n=1301)			All moderate to severe AS (n=113)	All severe AS (n=1301)
	TAVR (n=66)	SAVR (n=47)	P value	TAVR (n=664)	SAVR (n=637)	P value		
Stroke volume index, mL/m^2	46.3±7.4	48.1±9.8	0.30	41.6±10.0 (574)	42.1±10.2 (552)	0.41	47.1±8.5	41.9±10.1 (1126)
Stroke Volume Index <35 mL/m^2 (%)	3 (4.5)	3 (6.4)	0.69	152 (26.5)(574)	131 (23.7)(552)	0.29	6 (5.3)	283 (25.1) (1126)
Lateral E/e' ratio	13.9±6.0 (47)	14.0±6.6 (36)	0.92	15.2±6.3 (516)	15.0±6.9 (499)	0.64	13.9±6.2 (83)	15.1±6.6 (1015)

Data shown as mean±SD, mean±SD (no of patients), no of patients (%) or median (first quartile, third quartile).
AS, aortic stenosis; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS-PROM, The Society of Thoracic Surgeons Predicted Risk of Mortality; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; TAVR, transcatheter aortic valve replacement.

Permanent pacemaker implantation at 24 months was more commonly performed following TAVR than SAVR in patients with moderately-severe AS (30.5% vs 2.3%, p<0.001) (table 3). On the other hand, the incidence of atrial fibrillation was less frequent after TAVR than SAVR in patients with moderately-severe AS (9.2% vs 29.9%, p=0.003). An exploratory univariate analysis showed that the risk for all-cause mortality at 24 months was similar in patients with moderately-severe AS compared with severe AS (HR 1.20, 95% CI 0.48 to 3.02, p=0.69) (online supplemental table S4).

QOL improvement after AVR

In patients with moderately-severe AS, a significant change in the KCCQ score was noted from baseline to 30 days following TAVR (67.0±20.6 to 89.3±13.4, p<0.001) and SAVR (67.5±19.6 to 78.3±22.3, p=0.001) (figure 3). The increase in KCCQ score from baseline to 24 months was similar for TAVR and SAVR (19.3±18.8 vs 21.9±19.2, p=0.51). A similar health status improvement was observed in patients with severe AS.

DISCUSSION

This hypothesis-generating post hoc study demonstrated that in symptomatic patients with moderately-severe AS: (1) valve haemodynamics and health status improved after TAVR or SAVR, (2) key clinical event rates were similar for TAVR and SAVR and (3) advanced coronary artery disease (CAD) and/or peripheral arterial disease associated with an underlying myocardial disease appeared to be more common than in patients with severe AS.

Efficacy and safety of earlier AVR

Among patients who were enrolled in the Evolut Low Risk trial for severe AS, 8% were found to have less than severe AS and appeared to have symptomatic moderately-severe AS (table 1). Their higher SV and lower aortic valve calcium volume compared with severe AS patients support the revised classification of their AS severity. A major reason for classifying these patients as severe AS by clinical sites was the use of AVAi≤0.6 cm^2/m^2, even in patients with a normal SVI (≥35 mL/m^2). In fact, 95% of patients with moderately-severe AS had an SVI≥35 mL/m^2 at baseline (table 1). AVAi was applied to determine severe AS only when SVI is <35 mL/m^2, as described in current guidelines. Furthermore, SVI has been reported to significantly increase the prevalence of severe AS without improving the predictive accuracy for AS-related events.[15] Therefore, we did not consider AVAi≤0.6 cm^2/m^2 for defining severe AS in the current study. Other reasons for the potential overestimation of the AS severity at trial enrolment by the sites could be related to the over tracing of the valve gradient and/or the under tracing of the LVOT diameter. Stress echocardiography may be helpful to reveal severe AS in the moderate to severe AS group, however, patients had well-preserved SV at baseline, thus its utility may be limited in our cohort.

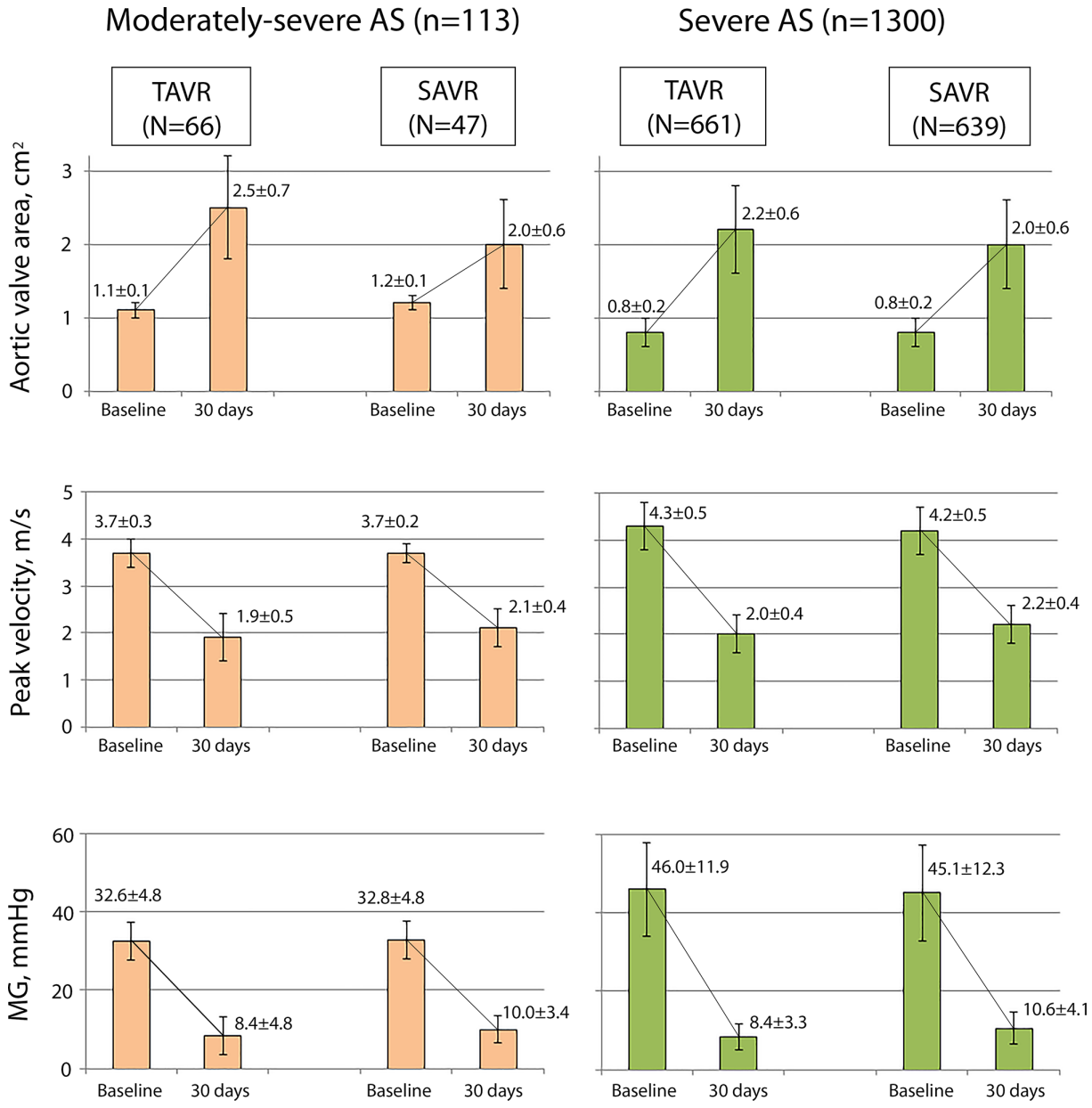

Figure 2 Valve haemodynamics (core laboratory) before and after AVR for patients with moderate to severe AS and severe AS. Change of aortic valve area, peak velocity and mean pressure gradient (MG) from baseline to 30 days for transcatheter and surgical aortic valve replacement (TAVR and SAVR) groups. Patients with moderately-severe AS are shown in the left panel and patients with severe AS in the right panel. Longitudinal changes for all parameters are significant (p<0.001). Error bars represent SD. AS, aortic stenosis; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

TAVR has revolutionised the management of severe AS, offering an efficacious, safe and less invasive alternative to surgery. The indications for TAVR have continued to expand but not yet for patients with less than severe AS.[16 17] Although unfavourable survival outcomes in the moderate AS population have been well documented,[3–6] the current management strategy for patients with less than severe AS has been 'watchful waiting', as prospective data to support earlier isolated AVR are not yet available. A recent retrospective study demonstrated a significant reduction in mortality by AVR in patients with moderate AS and a reduced LVEF.[18] Currently, the TAVR UNLOAD trial (TAVR to Unload the Left Ventricle in Patients with Advanced Heart Failure, NCT02661451), the PROGRESS trial (Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR, NCT04889872) and EXPAND trial (Evolut EXPAND TAVR II Pivotal Trial, NCT05149755) are evaluating the efficacy of TAVR among patients with moderate AS and cardiac dysfunction,[17] but results will not be available for some time. Our findings that TAVR and SAVR significantly improved QOL and valve haemodynamics in patients with symptomatic moderately-severe AS at low surgical risk support further investigations via randomised trials comparing isolated AVR with watchful

Table 2 Echocardiography parameters at 30 days for patients with moderately-severe AS and severe AS

	Moderately-severe AS (n=113)			Severe AS (n=1300)		
	TAVR (n=66)	SAVR (n=47)	P value	TAVR (n=661)	SAVR (n=639)	P value
Aortic valve area, cm^2	2.5±0.7 (56)	2.0±0.6 (41)	<0.001	2.2±0.6 (558)	2.0±0.6 (509)	<0.001
Aortic Valve Area Index, cm^2/m^2	1.23±0.39 (56)	0.98±0.27 (41)	<0.001	1.10±0.28 (557)	1.04±0.29 (509)	<0.001
Peak velocity, m/s	1.9±0.5 (65)	2.1±0.4 (44)	0.03	2.0±0.4 (641)	2.2±0.4 (600)	<0.001
Mean pressure gradient, mm Hg	8.4±4.8 (65)	10.0±3.4 (44)	0.04	8.4±3.3 (641)	10.6±4.1 (600)	<0.001
Dimensionless Velocity Index	0.61±0.14 (61)	0.51±0.08 (43)	<0.001	0.58±0.13 (612)	0.51±0.11 (569)	<0.001
Left ventricular ejection fraction, %	63.1±5.7 (65)	60.7±11.5 (44)	0.20	64.0±6.9 (656)	62.6±8.0 (604)	0.01
Stroke volume, mL	94.4±21.6 (56)	80.2±20.8 (41)	0.002	82.5±21.4 (568)	82.0±23.3 (511)	0.74
Stroke Volume Index, mL/m^2	45.6±10.4 (56)	39.5±10.2 (41)	0.005	41.8±10.2 (567)	41.8±11.3 (511)	0.97
Total aortic regurgitation (%)			<0.001			<0.001
None	14 (21.5)	33 (75.0)		130 (20.0)	436 (73.6)	
Trace	28 (43.1)	8 (18.2)		261 (40.1)	124 (20.9)	
Mild/mild to moderate	22 (33.8)	3 (6.8)		235 (36.1)	29 (4.9)	
Moderate/moderate to severe	1 (1.5)	0 (0.0)		23 (3.5)	2 (0.3)	
Severe	0 (0.0)	0 (0.0)		2 (0.3)	1 (0.2)	

Data shown as mean±SD, mean±SD (no of patients) or no of patients (%).
AS, aortic stenosis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

waiting in patients with symptomatic moderate AS and a preserved LVEF.

Consistent with the STS score, all-cause mortality rate at 30 days was less than 3% for all patients, but appeared to be slightly higher in the moderately-severe AS group than the severe AS group (online supplemental table S3). Nevertheless, this work shows the efficacy and safety of TAVR throughout 24 months in patients with moderately-severe AS, with major clinical event rates at acceptable levels. To note, a direct comparison between severe AS and moderately-severe AS patients lacks statistical power due to the small sample size of the moderate to severe AS cohort and the unbalanced sample size between the two patient groups. Nevertheless, patients with moderately-severe AS appeared to have more comorbidities (eg, diabetes mellitus, PCI, higher SYNTAX score, atrial fibrillation and peripheral artery disease) than those with severe AS (table 1). The STS score of moderately-severe AS patients was 2.0±0.6and 1.9±0.7 for patients with severe AS. Advanced CAD and/or peripheral artery disease associated with myocardial ischaemia and high afterload probably contribute to patient symptoms in addition to the stenotic aortic valve. Although comorbidities were not associated with adverse survival outcomes (online supplemental table S4), it is likely that symptomatic patients with less than severe AS do have superimposed myocardial disease from comorbidities. Studies have consistently shown that myocardial dysfunction demonstrated by global longitudinal strain, diastolic dysfunction or myocardial fibrosis on cardiac imaging is associated with worse clinical outcomes in patients with moderate AS, even after AVR.[6 19 20]

A high incidence of atrial fibrillation following SAVR and frequent pacemaker implantation following TAVR in patients with moderately-severe AS should be also acknowledged. However, recent studies have suggested reductions in pacemaker implantation rates following TAVR with the Evolut platform,[21 22] therefore, the frequency of this clinical event is expected to decrease with continued refinement of procedural techniques and improved implantation experience and care pathways.

Symptomatic AS

Symptomatic status is currently one of the most important indications for AVR in patients with severe AS and has been well described.[23] Isolated AVR has not been indicated in patients with moderate AS based on the assumption that they seldom have purely AS-related symptoms. However, our data showed that some patients with moderately-severe AS are symptomatic and their KCCQ score significantly increases after TAVR or SAVR (figure 3). Even with the underlying myocardial disease, these findings indicate that symptoms in these patients with less than severe AS are primarily associated with AS. Symptomatic status might be more common than previously estimated in the moderate AS population. Our data from a retrospective study showed that symptoms were present in 45% of moderate AS patients.[6]

Since symptoms can be considered a subjective parameter, functional assessment is sometimes difficult because of the sedentary status in elderly patients. Although a recent multicentre trial showed the benefit of AVR in asymptomatic patients with 'very' severe AS (ie, peak velocity >4.5 m/s),[24] it is uncertain that symptomatic status should be an

Table 3 Clinical outcomes at 24 months for patients with moderately-severe AS and severe AS

	Moderately-severe AS (n=113)			Severe AS (n=1301)		
	TAVR (n=66)	SAVR (n=47)	P value	TAVR (n=664)	SAVR (n=637)	P value
All-cause mortality or disabling stroke	5 (7.7)	3 (6.5)	0.82	26 (4.0)	39 (6.3)	0.05
All-cause mortality	3 (4.6)	2 (4.4)	0.95	22 (3.3)	27 (4.4)	0.32
Reintervention	1 (1.5)	0 (0.0)	0.40	5 (0.8)	5 (0.8)	0.91
All stroke and TIA	8 (12.6)	2 (4.3)	0.15	52 (7.9)	49 (8.0)	0.99
Bleed	6 (9.5)	3 (6.4)	0.62	70 (10.6)	88 (14.0)	0.05
Life-threatening or disabling	3 (4.7)	2 (4.3)	0.96	28 (4.2)	61 (9.7)	<0.001
Major bleed	3 (4.8)	1 (2.1)	0.49	42 (6.4)	33 (5.3)	0.42
Major vascular complication	2 (3.0)	1 (2.1)	0.77	26 (3.9)	23 (3.6)	0.78
Acute kidney injury	2 (3.0)	5 (10.6)	0.10	13 (2.0)	64 (10.1)	<0.001
Myocardial infarction	1 (1.6)	2 (4.3)	0.37	15 (2.3)	9 (1.4)	0.27
Valve endocarditis	0 (0.0)	0 (0.0)	NA	3 (0.5)	6 (1.0)	0.26
Valve thrombosis	1 (1.5)	0 (0)	0.40	1 (0.2)	1 (0.2)	0.96
Valve thrombosis (subclinical)	0 (0.0)	0 (0.0)	NA	4 (0.6)	3 (0.5)	0.78
Permanent pacemaker implant*	19 (30.1)	1 (2.1)	<0.001	134 (20.3)	52 (8.3)	<0.001
Permanent pacemaker implant†	19 (30.5)	1 (2.3)	<0.001	134 (21.0)	52 (8.6)	<0.001
Atrial fibrillation	6 (9.2)	14 (29.9)	0.003	79 (12.0)	255 (40.3)	<0.001
Coronary artery obstruction	1 (1.5)	0 (0.0)	0.40	5 (0.8)	2 (0.3)	0.28
Composite event‡	9 (13.8)	4 (8.7)	0.42	61 (9.2)	102 (16.2)	<0.001

Data shown as number of patients with an event (%), where Kaplan-Meier estimates are provided as percentages. The corresponding p values were calculated by the log-rank test for all data through 24 months.
*Subjects with pacemaker or implantable cardioverter defibrillator (ICD) at baseline are included.
†Subjects with pacemaker or ICD at baseline are excluded.
‡Composite event includes all-cause mortality, disabling stroke, life threatening or disabling bleeding, major vascular complication, acute kidney injury stage 2 or 3.
AS, aortic stenosis; NA, not available; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TIA, transient ischaemic attack.

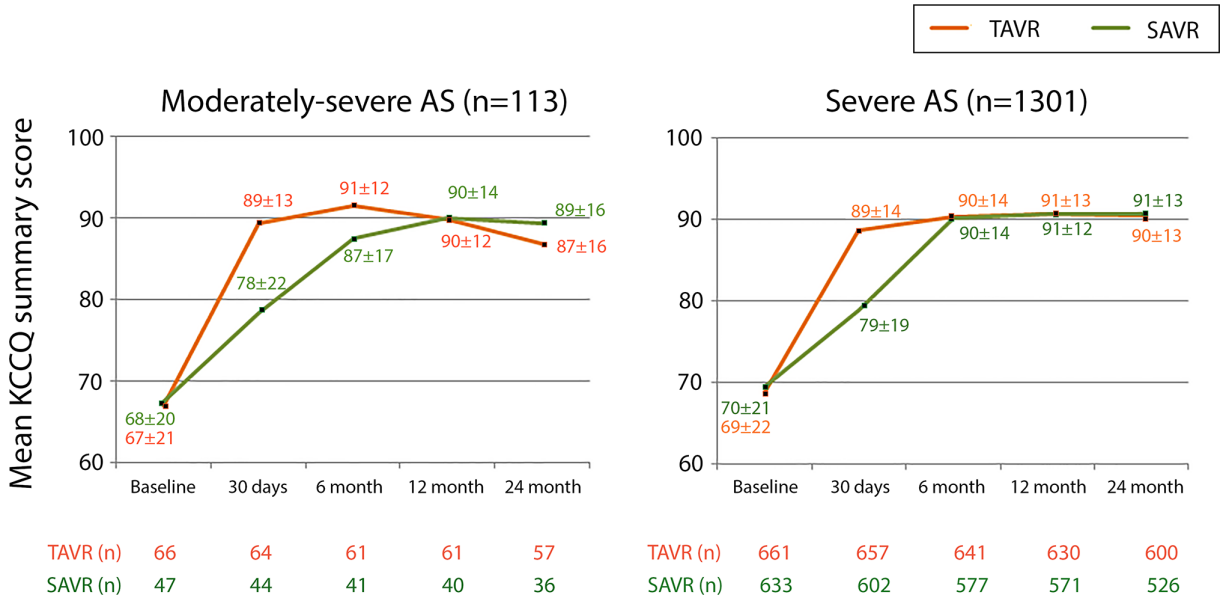

Figure 3 Longitudinal change of KCCQ summary score for patients with moderately-severe AS and severe AS. Longitudinal change of quality of life evaluated with the KCCQ overall score in patients with moderately-severe AS (left panel) and severe AS (right panel). The number of patients (n) at each time point is shown. AS, aortic stenosis; KCCQ, Kansas City Cardiomyopathy Questionnaire.

indicator for AVR in the advanced disease.[25] Risk stratification using objective parameters with Doppler echocardiography data and/or biological markers such as N-terminal pro b-type natriuretic peptide (NT-pro-BNP) should play an important role, especially in those with less than severe AS.[6 25 26] Our group has reported that an LVEF<50%, SVI<35 mL/m^2, averaged E/e' >15, LV global longitudinal strain >−15.2%, and NT-pro-BNP>888 pg/mL are associated with poor survival outcomes in patients with moderate AS.[6 19 26] Their overall survival was better in patients with AVR compared with those without AVR. Long-term survival and valve durability data from patients with moderately-severe ASwill be key to follow. A recent study found that in patients with severe AS at intermediate or high surgical risk, the 5-year rate of structural valve deterioration was 4.4% in SAVR patients and 2.2% in self-expandable TAVR patients (p=0.004).[27] Further investigations are necessary to determine valve durability in younger, lower risk patients, even more in those treated for less than severe AS.

Significant AS: definition of severe AS in the TAVR era

This study showed the potential advantage of earlier intervention for symptomatic patients with AS classified as less than severe. However, moderate AS includes a wide range of valve haemodynamics.[1 2] In fact, the patients evaluated in this study had borderline severe AS (so-called moderately-severe AS); with a baseline mean AVA of 1.1 cm^2, peak velocity 3.7 m/s and MG 32.7 mm Hg. Our findings suggest that the current definition of severe AS or criteria for AVR may need to be relaxed or extended to a lower severity than currently recommended. In longitudinal data investigating the natural history or progression of AS, LV systolic function and SV were shown to significantly deteriorate when the AVA reached 1.2 cm^2.[7 28] From a large dataset of AS patients from Australia, a lower SVI in patients with severe AS compared with those with moderate AS was demonstrated (41.9±13.9 vs 49.8±14.6 mL/m^2).[5] Similarly, this study showed that patients with severe AS had a lower SV and SVI at baseline compared with those with moderate to severe AS (table 1). An AVR procedure may be reasonable for those symptomatic patients with an AVA≤1.2±0.1 cm^2; as LV dysfunction was found to deteriorate more precipitously at that severity.[7 28] Prognostic data are necessary to support this hypothesis and further work is required.

Future directions

In this study, the possible benefit of earlier AVR in symptomatic patients with less than severe AS was evaluated. Since the current definition of moderate AS is extremely wide, it is difficult to apply our findings to the entire moderate AS population. However, this study challenges us to identify such a population who can benefit from AVR among patients with less than severe AS. When AS is not severe, symptoms may be related to an underlying myocardial disease rather than to the stenotic aortic valve alone, thus, there is a need to investigate objective cardiac parameters to guide patient management. Can AVR benefit patients with combined myocardial disease and less than severe AS? According to our data, further investigations and randomised clinical trials that compare the benefit with adverse events related to earlier AVR in patients with less than severe AS are needed.

Limitations

The post hoc nature of the study limited the ability to explore the benefit of AVR in patients with moderately-severe AS. It is of utmost importance to stress that our findings are merely hypothesis generating. Data were collected from a randomised trial with patients considered having severe AS based on individual clinical sites' echocardiographic analysis. However, the designation of less than severe AS for 113 patients by the echocardiography core laboratory over read is supported by the patients' lower aortic valve calcium volume and haemodynamics compared with those with severe AS. Given the relatively small number of patients in the moderately-severe AS group and the retrospective nature of the analysis, a direct statistical comparison with the severe AS group was not considered appropriate. Moreover, event rates reported for the moderately-severe AS cohort compared with the severe AS cohort may be a differential effect or characteristic of the small sample size. Lastly, the assessment of symptoms was limited to heart failure, and data for angina or syncope were not collected. Further studies are warranted since our data can be only generalised to the low surgical risk population with symptomatic moderately-severe AS.

CONCLUSIONS

In patients with symptomatic moderately-severe AS, major clinical outcomes were similar for TAVR and SAVR, and valve haemodynamics and health status significantly improved following AVR. Earlier intervention in symptomatic patients with less than severe AS may be beneficial. However, compared with patients with severe AS, patients with moderately-severe AS appeared to have a higher prevalence of advanced CAD and/or peripheral arterial disease at baseline, potentially due to their underlying superimposed myocardial disease. Further research is needed to elaborate on our hypothesis-generating findings, and to identify the patient population with less than severe AS that could benefit from earlier isolated AVR.

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