ORIGINAL ARTICLE

Impact of transcatheter aortic valve implantation in symptomatic patients with very severe aortic stenosis

Semptomatik çok ciddi aort darlıklı hastalarda transkateter aort kapak implantasyonun etkisi

Bilge Duran Karaduman, M.D.[1], Hüseyin Ayhan, M.D.[1], Telat Keleş, M.D.[2], Engin Bozkurt, M.D.[3]

[1]Department of Cardiology, Atılım University School of Medicine, Medicana International Ankara Hospital, Ankara, Turkey
[2]Department of Cardiology, Ankara Yıldırım Beyazıt University School of Medicine, Ankara City Hospital, Ankara, Turkey
[3]Department of Cardiology, Medicana International Ankara Hospital, Ankara, Turkey

ABSTRACT

Objective: Aortic stenosis (AS) is a progressive disease, and valve replacement—the only treatment option—should be performed after it becomes symptomatic and before irreversible myocardial damages develop. Surgical valve replacement is recommended in patients with very severe AS (VSAS), even if they are asymptomatic. However, there is no detailed study on the effect of transcatheter aortic valve implantation (TAVI) in patients with VSAS. Our aim in this study is to show the feasibility and safety of TAVI in symptomatic patients with VSAS.

Methods: A total of 505 consecutive patients with symptomatic AD who underwent TAVI in our center were retrospectively studied. The mean age of the patients was 77.8±7.6 years, and 56.4% of them were women. The patients were divided into 2 groups: a group with VSAS (n=134 patients) and a group with high-gradient AS (HGAS) (n=371 patients).

Results: Female sex, left ventricular ejection fraction, small left ventricle, hypertrophic left ventricle were more common in the group with VSAS; on the other hand, histories of coronary artery disease bypass surgery, myocardial infarction, and atrial fibrillation were less frequent. Predilatation and Edwards SAPIEN 3 were less used in the group with VSAS. There was no statistical difference in major complications and in-hospital mortality (group with VSAS: 5 patients, group with HGAS: 16 patients; p=0.769) according to the Valve Academic Research Consortium-2 criteria. There was a significant difference between the 2 groups in favor of the group with VSAS on the Cox regression model survival curve (p<0.001).

Conclusion: In this study, it has been shown that TAVI can be feasible and safe in symptomatic VSAS, with acceptable complications and higher survival rates. Currently, further randomized studies are required to perform TAVI in patients with asymptomatic VSAS currently indicated for surgical aortic valve replacement.

ÖZET

Amaç: Aort darlığı (AD) ilerleyici bir hastalıktır ve tek tedavi seçeneği olan kapak replasmanı semptomatik hale geldikten sonra ve geri dönüşümsüz miyokardiyal hasar gelişmeden önce yapılmalıdır. Çok ciddi aort darlığı (ÇCAD) hastalarında cerrahi kapak replasmanı asemptomatik olsa bile önerilmektedir. Ancak ÇCAD hastalarında transkateter aortik kapak implantasyonunun (TAVI) etkisi hakkında ayrıntılı bir çalışma yoktur. Bu çalışmada amacımız, semptomatik ÇCAD hastalarında TAVI'nin uygulanabilirliğini ve güvenilirliğini göstermektir.

Yöntemler: Merkezimizde TAVI uygulanan toplam 505 ardışık semptomatik AD hastası retrospektif olarak incelendi. Hastaların ortalama yaşı 77.8±7.6 yıl ve %56.4 kadın idi. Hastalar ÇCAD grubu (n: 134 hasta) ve yüksek gradyentli AD grubu (YGAD, n: 371 hasta) olarak iki gruba ayrıldı.

Bulgular: ÇCAD grubunda daha fazla kadın cinsiyet, daha yüksek sol ventrikül ejeksiyon (SV) fraksiyonu, daha fazla küçük SV, hipertrofik SV, daha fazla normal koronerler ve daha az koroner arter hastalığı, bypas cerrahisi, miyokard enfarktüsü ve atriyal fibrilasyon öyküsü vardı. Predilatasyon ve Edwards SAPIEN 3 ÇCAD grubunda olarak daha az kullanıldı. VARC-2 kriterlerine göre majör komplikasyonlar ve hastane içi mortalitede (ÇCAD grubu; 5 hasta, YG AD grubu; 16 hasta, p: 0.769) istatistiksel fark saptanmadı. İki grup arasında Cox regresyon modeli sağ kalım eğrisinde ÇCAD lehine istatistiksel olarak anlamlı fark vardı (p<0.001).

Sonuç: Bu çalışmamız ile semptomatik çok ciddi aort darlığında TAVI'nin kabul edilebilir komplikasyon ve daha yüksek sağ kalım oranları ile uygulanabilir ve güvenli olduğu gösterilmiştir. Hâlihazırda cerrahi kapak replasmanı endikasyonu olan asemptomatik ÇCAD hastalarında TAVI uygulanabilmesi için daha fazla randomize büyük çalışma gereklidir.

Received: May 23, 2020 *Accepted:* September 21, 2020
Correspondence: Engin Bozkurt, M.D. Söğütözü Mah. 2176. Cad. No.3 06520 Ankara – Türkiye
Tel: +9005306945353 e-mail: drebozkurt@yahoo.com.tr

Aortic stenosis (AS) is the most common valve disease for which aortic valve replacement (AVR) is the only effective therapy, and its prevalence is increasing owing to the aging population.[1] According to the current European and United States (US) guidelines, AVR indications in severe AS are present as follows:[1,2]

1. In symptomatic patients with a classical high gradient AS (HGAS); low-flow low-gradient (LFLG) severe AS with or without contractile reserve; and paradoxically LFLG with confirmed severity of AS; and
2. In asymptomatic patients with left ventricular (LV) ejection fraction (LVEF) <50%, with abnormal response to exercise, and whose surgical risk is low and with 1 of these abnormalities: very severe AS (VSAS), severe valve calcification with a rate of progression ≥0.3 m/s/year, markedly elevated brain natriuretic peptide, and severe pulmonary hypertension.

The development of transcatheter aortic valve implantation (TAVI), which was first introduced by Cribier et al.[3] in 2002, has revolutionized AS treatment in the last decade. After TAVI was gradually and rapidly accepted in high-risk and inoperable patients, it has been approved by guidelines as a result of recent studies suggesting that it can be used safely and effectively in intermediate-risk patients.[4–7] Advances in transcatheter techniques and valve prostheses may change the risk-to-benefit ratio of AVR in low-risk patients, especially after TAVI has become the standard of treatment in intermediate-risk and high-risk patients. Besides, as far as we know, no detailed impact of TAVI has been performed in symptomatic or asymptomatic patients with VSAS. Although surgical aortic valve replacement (SAVR) is recommended in asymptomatic patients with VSAS owing to the risk of sudden cardiac death and irreversible myocardial damage, TAVI performed with lower morbidity and mortality than SAVR in most patient groups should be considered in these patients. However, because TAVI's efficacy and safety have not been studied in asymptomatic patients, it is recommended not to perform TAVI in asymptomatic patients with AS. The results of the ongoing randomized trials (Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients With Asymptomatic Severe Aortic Stenosis [EARLY-TAVR] and the Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe AS [EVoLVeD]), which is about TAVI in asymptomatic patients with severe AS, are expected.[8,9]

Our aim in this study is to determine the impact and safety of TAVI in symptomatic patients with VSAS. We hope that this study will inspire large randomized TAVI studies in symptomatic and asymptomatic patients with VSAS.

Abbreviations:

AF	*Atrial fibrillation*
AS	*Aortic stenosis*
AVA	*Aortic valve area*
AVAi	*Aortic valve area indexed*
AVR	*Aortic valve replacement*
CABG	*Coronary artery bypass grafting*
CAD	*coronary artery disease*
CI	*Confidence interval*
EARLY-TAVR	*Evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis*
EVoLVeD	*Early valve replacement guided by biomarkers of left ventricular decompensation in asymptomatic patients with severe AS*
HGAS	*High-gradient aortic stenosis*
LFLG	*Low-flow low-gradient*
LV	*Left ventricular*
LVEF	*Left ventricular ejection fraction*
MI	*Myocardial infarction*
MSCT	*Multislice computed tomography*
PCI	*Percutaneous coronary intervention*
PVL	*Paravalvular leakage*
SAVR	*Surgical aortic valve replacement*
STS	*Society of Thoracic Surgeons*
TAVI	*Transcatheter aortic valve implantation*
TEE	*Transesophageal echocardiography*
THV	*Transcatheter heart valve*
TTE	*Transthoracic echocardiography*
US	*United States*
VARC-2	*Valve Academic Research Consortium-2*
Vmax	*Velocity maximum*
VSAS	*Very severe aortic stenosis*

METHODS

Patient population and study design

After the LFLG and paradoxical LFLG AS were excluded, 505 consecutive symptomatic patients with severe AS who underwent TAVI between 2011 and 2019 were included in this retrospective single-center study. These patients were divided into 2 groups: VSAS and HGAS groups. The group with HGAS included patients defined as having classical severe AS with aortic valve area (AVA) <1.0 cm^2, mean gradient >40 mm Hg, or maximum jet velocity >4.0 m/s. According to the traditional definition of severe AS, VSAS was defined as critical stenosis in the aortic valve fulfilling the following criteria regardless of LVEF: a peak aortic velocity ≥5 m/s and a mean transaortic pressure gradient ≥60 mm Hg on Doppler echocardiography. The diagnosis and severity of AS are mainly evaluated by imaging cardiologists with transthoracic echocardiography (TTE), transesoph-

ageal echocardiography (TEE), dobutamine stress TTE, and valve calcium score. Considering comorbid conditions, irrespective of whether AS caused the clinical cardiologist to evaluate the symptoms, TAVI was not performed on asymptomatic patients. Patients underwent TAVI if they had symptomatic AS and were at high or prohibitive surgical risk owing to comorbidities after a consensus within the dedicated heart team. Informed consent was obtained from all patients, and Ankara Atatürk Training and Research Hospital (Approval Date: March 1, 2011; Approval Number: 068) granted permission for the study.

Procedure

All patients underwent TTE, TEE (initial cases and when needed), multislice computed tomography (MSCT) (for a proper assessment of the aortic annulus, prosthesis size, and morphology of the access route and, in some patients, for coronary evaluation), and coronary angiography as a part of multimodality preprocedural planning. In the first 74 patients, TAVI was performed under general anesthesia with predilatation and intraprocedural TEE. In subsequent patients, TAVI was performed with a minimalist approach—without sedation and intraprocedural TEE—and only in selected patients with predilattaion. Transfemoral access was used in 96.4% of the patients, and SAPIEN XT, Edwards Sapien 3 valve (Edwards Lifesciences, Irvine, CA, USA); LOTUS valve system (Boston Scientific, Marlborough, MA, USA), or ACURATE neo (Boston Scientific) transcatheter heart valves (THVs) were selected according to the aortic annulus, calcification degree, and operators preference. All outcomes were defined according to the consensus document of the Valve Academic Research Consortium-2 (VARC-2).[10]

Follow up

All patients regularly visited their attending physicians at 30-day, 6-month, and 1-year intervals for a clinical examination at our hospital outpatient clinic. Data were collected during visits to the echocardiographic laboratory and from a detailed review of all patients from our database or from telephone interviews.

Statistical analysis

Categorical variables are presented as numbers and percentages and were compared using the Chi-square test and Fisher exact test. Continuous variables are expressed as mean±standard deviation, and normally distributed variables were compared with the Student *t*-test and non-normally distributed variables were compared with the Wilcoxon rank-sum test. Survival curves were created with Kaplan–Meier analyses and compared with the log-rank test. Simple and multiple Cox regression models studied the effect of potential prognostic factors (sex, baseline total cholesterol level, baseline creatinine level, previous coronary artery bypass grafting [CABG], previous percutaneous coronary intervention [PCI], previous myocardial infarction [MI], atrial fibrillation [AF] history, coronary artery disease [CAD] severity, valve type used, and baseline LVEF) on the chance of event-free survival. All statistical analyses were conducted using the Statistical Package for the Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA). A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

There were 134 patients with VSAS (26.5%) and 371 patients with HGAS (73.5%). The mean age of the patients was 77.8±7.6 years, and 56.4% were women. A comparison of baseline clinical and echocardiographic characteristics between the group with VSAS and the group with HGAS is shown in Table 1. There were no significant differences in terms of age, body mass index, Society of Thoracic Surgeons (STS) score, and bicuspid aortic valve between the groups. However, there was a statistically significantly higher number of female sex in patients with VSAS (51.2% vs 70.6%, respectively, p<0.001). In addition, CABG (26.1% vs 15.7, p=0.014), previous MI (11.9% vs 5.2%, p=0.029), PCI (22.7% vs 13.4%, p=0.022), and AF (25.7% vs 15.7%, p=0.018) were statistically more frequently among the patients with HGAS. Although the ratio of the normal coronary artery was found numerically higher in the group with VSAS (VSAS 41.0% vs HGAS 29.7%), the severity of CAD was significantly higher in the group with HGAS (p=0.022). When the laboratory parameters were evaluated, the baseline creatinine level was lower, whereas the total cholesterol level was higher in the group with VSAS (p=0.012 and p=0.008, respectively). When we compared the echocardiographic parameters between the 2 groups, as seen in Table 2, LVEF, aortic velocity, maximum gradient, mean gradient, LV hypertrophy, and LV septal and

Table 1. Baseline clinical and laboratory parameters

Parameters	All patients n=505	Group 1 (HGAS) n=371	Group 2 (VSAS) n=134	*p*
Age (years)	77.8±7.6	77.6±7.3	78.4±8.4	0.281
Female, n (%)	285 (56.4)	190 (51.2)	95 (70.6)	<0.001
BMI (kg/m^2)	27.6±6.1	27.6±6.5	27.7±4.9	0.838
NYHA, n (%)				
2	131 (25.9)	93 (25.1)	38 (28.4)	0.506
3	291 (57.6)	221 (59.6)	70 (52.2)	
4	71 (14.1)	49 (13.2)	22 (16.4)	
Pulmonary edema	12 (2.4)	8 (2.2)	4 (3.0)	
DM, n (%)	148 (29.3)	114 (30.7)	34 (25.4)	0.243
HT, n (%)	418 (82.8)	304 (81.9)	114 (85.1)	0.410
HL, n (%)	249 (49.3)	192 (51.8)	57 (42.5)	0.067
Previous PCI, n (%)	102 (20.2)	84 (22.7)	18 (13.4)	0.022
Previous CABG, n (%)	118 (23.4)	97 (26.1)	21 (15.7)	0.014
Previous MI, n (%)	51.0 (10.1)	44 (11.9)	7 (5.2)	0.029
Moderate to severe COPD, n (%)	153 (40.2)	145 (39.1)	58 (43.3)	0.679
AF, n (%)	116 (23.0)	95 (25.7)	21 (15.7)	0.018
Stroke, n (%)	29 (5.7)	24 (6.5)	5 (3.7)	0.243
Bicuspid, n (%)	65 (13.1)	45 (12.3)	20 (15.2)	0.404
STS score, n (%)	5.9±3.4	5.9±3.3	5.9±3.4	0.963
EuroSCORE II, n (%)	8.7±5.6	9.0±5.6	8.1±5.7	0.217
Logistic EuroSCORE, n (%)	21.9±14.0	21.8±13.4	22.1±15.5	0.914
CAD				
Normal	165 (32.7)	110 (29.7)	55 (41.0)	0.057
Nonobstructive	216 (42.9)	166 (44.9)	50 (37.3)	
Obstructive	123 (24.4)	94 (25.4)	29 (21.6)	
CAD severity				
1 vessel disease	68 (55.7)	47 (49.5)	21 (77.8)	0.022
2 vessel disease	45 (36.9)	40 (42.1)	5 (18.5)	
3 vessel disease	9 (7.4)	8 (8.4)	1 (3.7)	
Laboratory parameters				
Serum glucose, mg/dL	126.2±51.3	127.5±51.5	123.7±50.9	0.309
Creatinine, mg/dL	1.05±0.53	1.09±0.59	0.95±0.30	0.012
Hemoglobin, mg/dL	11.6±1.9	11.6±1.9	11.5±1.7	0.433
Platelets, ×10^9 /L	239.8±83.7	242.7±85.3	230.5±77.9	0.198
Total cholesterol (mg/dL)	168.9±44.3	166.1±44.1	178.1±44.5	0.008
Triglyceride (mg/dL)	121.5±63.9	118.8±63.4	130.3±68.7	0.079
LDL cholesterol (mg/dL)	102.8±36.1	105.6±43.6	117.1±28.5	0.058
HDL cholesterol (mg/dL)	45.0±13.6	44.4±13.6	46.4±13.6	0.156

AF: atrial fibrillation; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; EuroSCORE: European System for Cardiac Operative Risk Evaluation; HDL: high-density lipoprotein; HGAS: high-gradient aortic stenosis; HL: hyperlipidemia; HT: hypertension; LDL: low-density lipoprotein; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons; VSAS: very severe aortic stenosis.

Table 2. Comparison of baseline echocardiographic parameters

Parameters	All patients n=505	Group 1 (HGAS) n=371	Group 2 (VSAS) n=134	*p*
LVEF (%)	53.2±13.0	51.9±13.8	56.8±9.5	0.001
LVEDD (cm)	4.70±0.62	4.77±0.63	4.49±0.54	<0.001
LVESD (cm)	3.07±0.79	3.14±0.81	2.82±0.67	<0.001
Septal wall thickness (cm)	1.38±0.23	1.36±0.23	1.48±0.23	<0.001
Posterior wall thickness (cm)	1.29±0.18	1.28±0.18	1.36±0.17	<0.001
LVH, n (%)	436 (86.7)	307 (83.0)	129 (97.0)	<0.001
LA (cm)	4.65±0.63	4.65±0.64	4.62±0.60	0.588
Aortic peak velocity (m/s)	4.5±0.5	4.3±0.2	5.2±0.4	<0.001
Aortic maximum gradient (mm Hg)	84.9±21.2	75.2±10.1	112.1±20.6	<0.001
Aortic mean gradient (mm Hg)	52.4±13.9	45.6±5.6	71.3±12.8	<0.001
AVA (cm²)	0.66±0.16	0.71±0.14	0.52±0.12	<0.001
AVA index (cm²)	0.36±0.09	0.40±0.08	0.29±0.07	<0.001
sPAP (mm Hg)	44.0±16.9	43.7±16.8	44.7±17.3	0.548
Moderate to severe aortic regurgitation (%)	22 (4.4)	14 (3.8)	8 (6.0)	0.659
Mitral regurgitation severe (%)	4 (0.8)	4 (1.1)	—	0.049

AVA: aortic valve area; HGAS: high-gradient aortic stenosis; LA: left atrium; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVH: left ventricular hypertrophy; sPAP: systolic pulmonary artery pressure; VSAS: very severe aortic stenosis.

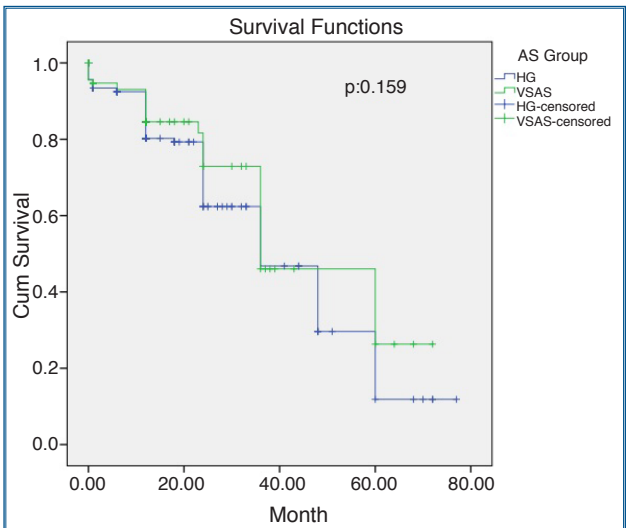

Figure 1. Kaplan–Meier analysis of survival curves between the 2 groups. Cumulative survival probability was not significantly different between the groups (VSAS: 44.3±3.5, 95% CI: 51.2-37.4; HGAS: 39.4±2.0, 95% CI: 35.4-43.3; Log-rank p=0.159). CI: confidence interval; HGAS: high-gradient aortic stenosis; VSAS: very severe aortic stenosis.

posterior wall thickness were significantly higher in the group with VSAS. The LV diameters, AVA, AVA indexed (AVAi), and severe mitral regurgitation were lower in the group with VSAS.

Procedural characteristics and clinical outcomes are presented in Table 3. Without a statistical difference, 96.4% of the cases were performed transfemorally in both groups, and percutaneous closure device (Prostar XL [Abbott Vascular, Santa Clara, CA, USA] or Perclose ProGlide 6Fr suture devices [Abbott Vascular]) was used in 97.9% of the cases. With similar rates in both groups, a total of 18 patients (3.6%) were able to undergo TAVI by the transaxillary route. There was a significant difference in the type and size of the valves used between the 2 groups, and the smaller THV and lesser Edwards SAPIEN 3 and higher LOTUS and SAPIEN XT valves were used in patients with VSAS. The need for predilatation was significantly higher in the group with VSAS (84.1% vs 69.4%, p=0.001), but the need for postdilatation was similar in both groups (VSAS 2.3% vs HGAS 3.6%, p=0.475). Successful device implantation during the index procedure was similar in both groups (p=0.166) and was achieved in 96% of the cases (n=486) according to the VARC-2 criteria. In addition, major vascular complications (p=0.304), major bleeding (p=0.956), and permanent pacemaker rates (p=0.746) were comparable between groups. While 1 patient in the group with VSAS had an an-

Table 3. Procedural characteristics and clinical outcomes

Parameters	All patients n=505	Group 1 (HGAS) n=371	Group 2 (VSAS) n=134	*p*
Access site, n (%)				
Transfemoral	482 (96.4)	354 (96.2)	128 (97.0)	0.682
Transaxillary	18 (3.6)	14 (3.8)	4 (3.0)	
Closure method n (%)				
Prostar	168 (34.9)	115 (32.6)	53 (41.4)	0.181
Proglide	303 (63.0)	231 (65.4)	72 (56.3)	
Cut-down	10 (2.1)	7 (2.0)	3 (2.3)	
Valve size, mm, n (%)				
20	1 (0.2)	—	1 (0.8)	0.049
23	214 (42.5)	146 (39.4)	68 (51.1)	
25	12 (2.4)	9 (2.4)	3 (2.3)	
26	210 (41.7)	160 (43.1)	50 (37.6)	
27	6 (1.2)	4 (1.1)	2 (1.5)	
29	61 (12.1)	52 (14.0)	9 (6.8)	
Valve type, n (%)				
SAPIEN XT	439 (86.9)	318 (85.7)	121 (91.0)	0.016
Edwards SAPIEN 3	38 (7.5)	35 (9.4)	3 (2.3)	
LOTUS	23 (4.6)	14 (3.8)	9 (6.8)	
ACURATE neo	4 (0.8)	4 (1.1)	—	
Predilatation (%)	365 (73.3)	254 (69.4)	111 (84.1)	0.001
Postdilatation (%)	16 (3.2)	13 (3.6)	3 (2.3)	0.475
Device Success (%)	486 (96.0)	358 (96.8)	126 (94.0)	0.166
Procedural outcomes				
Pace maker, n (%)	37 (7.3)	28 (7.6)	9 (6.7)	0.746
Stroke, n (%)	4 (0.8)	4 (1.1)	—	0.227
Pericardial effusion, n (%)	9 (1.8)	4 (1.1)	5 (3.7)	0.137
New AF, n (%)	18 (3.6)	11 (3.0)	7 (5.2)	0.718
New LBBB, n (%)	12 (2.4)	10 (2.7)	2 (1.5)	0.682
Acute renal failure, n (%)	3 (0.6)	3 (0.8)	—	0.215
Annular rupture, n (%)	1 (0.2)	—	1 (0.7)	0.186
Major bleeding, n (%)	4 (0.8)	3 (0.8)	1 (0.7)	0.956
Major vascular complication, n (%)	30 (5.9)	27 (7.0)	3 (2.5)	0.304
Discharge time (day)	4.5±2.2	4.5±2.2	4.4±2.3	0.731
In-hospital mortality, n (%)	21 (4.2)	16 (4.3)	5 (3.7)	0.769

AF: atrial fibrillation; HGAS: high-gradient aortic stenosis; LBBB: left bundle branch block; VSAS: very severe aortic stenosis.

nular rupture, 4 patients had a stroke and 3 patients had an acute kidney injury in the group with HGAS.

The median length of hospital stay for the entire cohort was 4.5±2.2 days. In-hospital mortality occurred in 5 patients (3.7%) in the group with VSAS and in 16 patients (4.3%) in the group with HGAS; however, statistical difference was not observed between the 2 groups (p=0.769). Follow-up outcomes

Table 4. Follow up outcomes

Parameters	All patients n=505	Group 1 (HGAS) n=371	Group 2 (VSAS) n=134	*p*
Mean follow up time (month)	15.5±14.9	15.2±15.0	16.2±14.8	0.537
Post-TAVI LVEF (%)	55.6±11.6	54.3±12.3	59.1±8.6	<0.001
Post-TAVI aortic mean gradient (mm Hg)	10.5±3.9	10.2±3.7	11.4±4.4	0.002
Post-TAVI PVL, n (%)				
Mild	84 (17.4)	58 (16.5)	26 (19.8)	0.671
Moderate	5 (1.0)	4 (1.1)	1 (0.8)	
30-day mortality, n (%)	11 (2.4)	9 (2.7)	2 (1.7)	0.528
30-day NYHA, n (%)				
1	131 (43.1)	95 (43.6)	36 (41.9)	0.620
2	153 (50.3)	107 (49.1)	46 (53.5)	
3	20 (6.6)	16 (7.3)	4 (4.7)	
30-day LVEF (%)	56.5±10.4	55.1±11.1	59.5±7.8	0.002
30-day aortic mean gradient (mm Hg)	11.0±4.2	10.4±3.9	12.4±4.6	<0.001
30-day PVL (%)				
Mild	46 (16.7)	31 (15.9)	15 (18.8)	0.411
Moderate	6 (2.2)	3 (1.5)	3 (3.8)	
6-month mortality, n (%)	5 (1.2)	3 (1.0)	2 (1.8)	0.540
6-month LVEF (%)	59.5±7.4	59.1±7.3	59.8±7.7	0.648
6-month aortic mean gradient (mm Hg)	11.0±4.2	11.4±5.2	13.4±5.0	0.052
1-year mortality, n (%)	48 (12.3)	38 (13.6)	10 (9.1)	0.226
1-year NYHA, n (%)				
1	83 (64.3)	54 (61.4)	29 (70.7)	
2	44 (34.1)	32 (36.4)	12 (29.3)	
3	2 (1.6)	2 (2.3)	—	0.422
1-year LVEF (%)	59.4±7.6	58.7±7.9	61.1±6.6	0.170
1-year aortic mean gradient (mm Hg)	12.8±4.3	12.4±4.3	13.8±3.8	0.084
Total mortality, n (%)	145 (28.8)	112 (30.3)	33 (24.6)	0.216

AVA: aortic valve area; EOA: effective orifice area; HGAS: high-gradient aortic stenosis; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PVL: paravalvular leakage; TAVI: transcatheter aortic valve implantation; VSAS: very severe aortic stenosis.

and echocardiographic parameters are shown in Table 4. After TAVI, there was a significant improvement in functional capacities during follow-up. At an average of 15.5±14.9 months of follow-up, no severe paravalvular leakage (PVL) was observed in any patient in both groups, and there was no difference in mild and moderate PVL rates. The LVEF and transaortic mean gradients were statistically higher in patients with VSAS from baseline and continued through the follow-up visits until the end of the 30-day follow-up. There was no statistical difference in 30-day, 6-month, 1-year mortality and in overall mortality in both groups (p=0.528, p=0.540, p-0.226, and p=0.216, respectively). The Kaplan–Meier survival curve is presented in Fig. 1, and it shows no statistical difference between the 2 groups (VSAS: 44.3±3.5, 95% confidence interval [CI]: 51.2–37.4; HGAS: 39.4±2.0, 95% CI: 35.4–43.3, log-rank p=0.159). Simple and multiple Cox regression models studied the effect of potential prognostic factors (sex, baseline total cholesterol level, baseline creatinine level, previous CABG, previous PCI, previous MI, AF history, CAD severity, valve type, and baseline LVEF) on the chance of event-free survival; after the stud-

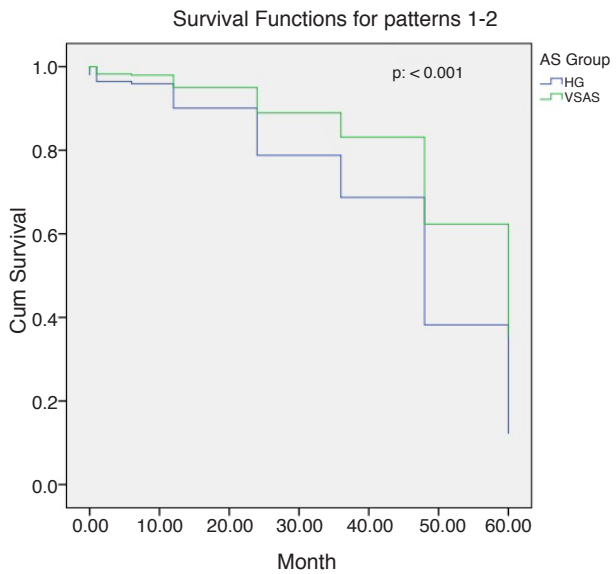

Figure 2. Cox regression adjusted analysis (sex, baseline total cholesterol level, baseline creatinine level, previous CABG, previous PCI, previous MI, AF history, CAD severity, valve type, and baseline LVEF) of survival curves in patients with VSAS and those with HGAS. Overall survival probability was significantly different in these patients (p<0.001). AF: atrial fibrillation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; HGAS: high-gradient aortic stenosis; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; VSAS: very severe aortic stenosis.

ies, there was a significant difference between the 2 groups in favor of the group with VSAS on Kaplan–Meier survival curve (p<0.001, Fig. 2).

DISCUSSION

This is the first study to precisely assess the impact of TAVI in a subset of symptomatic patients with VSAS. This study shows that TAVI can be performed efficiently and safely in symptomatic patients with VSAS with intermediate and high surgical risk. The frequency of VSAS was determined at the rate of 26.5% in our study group. Major complications, PVL, and mortality rates were comparable with those in patients with HGAS, and higher survival rates were identified in the group with VSAS. As a procedural difference, predilatation was performed more than in the group with VSAS. In addition, according to the findings from our study, the following clinical characteristics of patients with VSAS were observed: higher number of females and normal coronary arteries, less severe CAD and MI, fewer coronary revascularization history, and fewer history of AF. In the echocardiographic comparison of patients with VSAS, higher LVEF, LV hypertrophy, transaortic maximum, and mean gradients were found in the group with VSAS. In contrast, these patients had a smaller left ventricle, a smaller AVA, and severe mitral regurgitation.

AS is a progressive disease, and there is no medication to reverse the stenosis. When it becomes symptomatic or when irreversible myocardial injury begins occurs, its prognosis is very poor, and the only available treatment is valve replacement. When evaluating patients with AS, the most critical parameter is whether the patient is symptomatic; so, exercise testing is recommended for patients with unclear symptom status. Other parameters evaluated in the valve replacement decision are the degree of severity of AS and LVEF. AVR should theoretically be performed when the risks of the disease process outweigh the risks of AVR. Patients with VSAS appear to have an especially poor prognosis, similar to that of patients with symptomatic severe AS.[11] There is no clear definition of VSAS so far, and there are differences in definitions between the 2 guidelines. According to the European guideline, VSAS is defined by an aortic valve velocity maximum (Vmax) ≥5.5 m/s, but it is defined by a peak aortic jet velocity ≥5.0 m/s or a mean gradient ≥60 mm Hg according to the US guideline.[1,2] In this study, we defined VSAS as having both criteria; a peak aortic velocity ≥5 m/s and a mean transaortic pressure gradient ≥60 mm Hg on Doppler echocardiography. However, in recent studies, it has been revealed that AVA, AVAi, and dimensionless index are also prognostic factors in addition to aortic velocity and mean gradient in patients with AS.[12–15] Rosenhek et al.[16] have shown that maximum aortic velocity is a significant predictor of outcome in patients with severe AS. They emphasized that the >5.0 and >5.5 m/s show a 2-year event-free survival of 43% and 25%, respectively, compared with 70% in those with Vmax of 4.0–4.9 m/s. The criteria suggested by Tribouilloy et al. for VSAS with the results obtained from these studies are as follows: Vmax >5 m/s, mean transaortic pressure gradient ≥60 mm Hg, AVA <0.6 cm^2, AVAi <0.4 cm^2/m^2 (<0.45 cm^2/m), or dimensionless index <0.20.[17] Regardless of the criteria, it is clear that without valve replacement, patients with VSAS have high morbidity and mortality. Although the decision for SAVR is made more easily in patients with asymp-

tomatic VSAS with low surgical risk, SAVR is not considered first in intermediate- and high-risk patients. TAVI is not currently approved for asymptomatic severe AS. Besides, patients with VSAS have not been studied in detail in TAVI studies from the beginning to now. Similar to our study, if TAVI can be confirmed with large randomized studies to be effective and safe in symptomatic intermediate- and high-risk patients with VSAS, TAVI will come to the fore in asymptomatic and low-risk VSAS in the future. The outcomes of continuous randomized studies in low-risk and the use of TAVI in asymptomatic patients with VSAS may be a solution for these patients.

With the newly published and upcoming studies, TAVI's next expanding indication is its use in low-risk patients. Medtronic Evolut Low Risk and Placement of AoRTic TraNscathetER Valve (PARTNER) 3 have been published in the past year, and 850 patients in the first and 1,000 patients in the latter were randomized to TAVI and SAVR.[18,19] In the Evolut Low-Risk study, 1 of the valves of CoreValve, Evolut R, or Evolut PRO was used, and the study reported noninferiority of TAVI to SAVR for the primary composite endpoint of allcause death or disabling stroke at 24 months.[18] However, the PARTNER 3 study, using a balloon-expandable SAPIEN 3 THV, showed that the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than with SAVR.[19] These studies predict that TAVI can be applied safely and effectively in low-risk patients with new generation THVs by transfemoral access. Although our research was on symptomatic and intermediate- to high-risk patients, our complication and mortality rates were similar or better than those of the registry. In our study, PVL was similar in both groups, and no severe PLV was observed in any group. The low complication rate in our cohort may be due to the time and effort spent on a careful and detailed evaluation of the aortic valve and peripheral arteries with multimodality imaging.

It is not easy to assess symptoms in the elderly group, and symptoms can be masked, and stress tests are not routinely performed owing to multiple comorbid conditions. Even if the patients are asymptomatic, the annual risk of sudden death is approximately 1.5%.[20] However, 2 studies evaluated the effect of early SAVR in asymptomatic patients with VSAS. The definition was done as follows: an aortic valve area ≤0.75 cm^2 with either a peak aortic jet velocity ≥4.5 m/s or a mean transaortic gradient ≥50 mm Hg.[21,22] In addition, there are not enough data in the literature regarding baseline characteristics, echocardiography, and laboratory parameters of patients with VSAS. As mentioned earlier, more females, higher LVEF and smaller hypertrophic left ventricles, less atrial fibrillation (15.7%), fewer CAD (59.0%), fewer CABG (15.7%), fewer PCI (15.4%), and fewer history of MI (5.2%) were observed among patients with VSAS. Although there is not much evidence regarding the clinical and echocardiographic features of patients with VSAS, CAD was detected in 22% of the patients with a mean age of 67.0±15.0 years in the study conducted by Rosenhek et al.[16] In our study, although CAD was found to be fewer and less severe in the group with VSAS compared with that in the group with HGAS, the higher CAD than that reported in this study was due to our patients being older and having a higher risk. In the study performed by Kang et al.,[20] SAVR and conventional treatment were compared. There were no CAD data, but AF was found in 7% and 8% in the 2 groups, respectively. In the study of Kanamori et al.,[11] in which patients were grouped according to AVA (group 1 AVA: >0.80 cm^2, group 2 AVA: 0.6–0.6 cm2, and group 3 AVA: ≤0.6 cm^2), with similar results to those of our study, group 3 more often were older, were female, had smaller LV dimension, and higher LV hypertrophy.

In previous observational studies of asymptomatic VSAS, the main differences between unpaired treatment groups (selection bias to AVR or conservative treatment and some parameters that were not considered) may have affected the results.[11,21,22] The meta-analysis of 4 studies in asymptomatic patients indicated that patients with severe asymptomatic AS have a 3.5-fold higher rate of all-cause death with a watchful-waiting strategy than with AVR.[23] However, the most recently published The Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis trial is a randomized multicenter study comparing SAVR with a conservative approach in patients with asymptomatic VSAS.[21] This study was randomized to patients with an average age of 64.2±9.4 years: 145 patients with asymptomatic VSAS, including those who underwent early surgery (73 patients) and those who received conservative treatment (72 patients). However, instead of the VSAS criteria in the guidelines, the criteria formed by the au-

thors (AVA ≤0.75 cm^2 with either a peak aortic jet velocity ≥4.5 m/s or a mean aortic gradient ≥50 mm Hg) were used. In this study, authors found a lower incidence of the primary endpoint of operative mortality or death from cardiovascular causes among patients who underwent early surgery than among those who received conservative care. Another result obtained from this study is in the conservative care group. The majority of the patients (74%) needed AVR during follow-up, and postponement of surgery until symptoms occurred increased the cardiovascular events that occurred after surgery. In contrast to this study, in our research, VSAS was defined according to a peak aortic velocity ≥5 m/s and a mean transaortic pressure gradient ≥60 mm Hg. Patients were symptomatic in the intermediate- or high-risk group, according to the STS. However, similar to the group with HGAS, the group with VSAS even had numerically fewer major complications and mortality rates. TAVI is not currently recommended in asymptomatic patients in any guidelines, and there are further studies in this group of patients. Randomized controlled trials (EARLY-TAVR, EVoLVeD, Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis, and Early Surgery for Patients With Asymptomatic Aortic Stenosis (ESTIMATE)) are currently ongoing, which will determine whether valve replacement (TAVI or SAVR) in asymptomatic patients with severe AS can improve clinical outcomes.[8,9,24,25]

Limitations

Our study has some limitations that need to be discussed. Our research is a single-center retrospective observational study. Differences in baseline characteristics between groups may have affected the results. Owing to the retrospective design, the absence of aortic calcification rate and aortic valve calcification scores in MSCT may have limited a better understanding of the nature of VSAS.

Conclusion

In this study, it has been shown that TAVI can be feasible and safe in symptomatic VSAS with acceptable complications and higher survival rates. Currently, further randomized large studies are required to perform TAVI in patients with asymptomatic VSAS who are currently indicated for SAVR.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ankara Atatürk Training and Research Hospital (Approval Date: March 1, 2011; Approval Number: 068).

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - E.B., B.D.K., H.A.; Design - H.A., B.D.K.; Supervision - T.K., E.B.; Materials - B.D.K., H.A.; Data - B.D.K., H.A.; Analysis - H.A.; Literature search - H.A., B.D.K.; Writing - H.A., B.D.K.; Critical revision - E.B., T.K.

Funding: No funding was received for this research.

Conflict-of-interest: None.

REFERENCES

1. Baumgartner H, Falk V, Bax JJ, Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91. [Crossref]
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol 2017;70:252-89. [Crossref]
3. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006-8. [Crossref]
4. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic- valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607. [Crossref]
5. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98. [Crossref]
6. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609-20. [Crossref]
7. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321-31. [Crossref]
8. US National Library of Medicine. ClinicalTrials.gov. 2019. Available at: https://ClinicalTrials.gov/show/NCT03042104
9. Bing R, Everett RJ, Tuck C, Semple S, Lewis S, Harkess R, et al. Rationale and design of the randomized, controlled early valve replacement guided by biomarkers of left ventricular decompensation in asymptomatic patients with severe aortic stenosis (EVOLVED) trial. Am Heart J 2019;212:91-100. [Crossref]
10. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Valve Academic Research Consortium-2. Updated standardized endpoint definitions for

transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document (VARC-2). J Thorac Cardiovasc Surg 2013;145:6-23. [Crossref]
11. Kanamori N, Tomohiko T, Morimoto T, Watanabe H, Shiomi H, Ando K, et al. Prognostic impact of aortic valve area in conservatively managed patients with asymptomatic severe aortic stenosis with preserved ejection fraction. J Am Heart Assoc 2019;8:e010198.
12. Marechaux S, Ringle A, Rusinaru D, Debry N, Bohbot Y, Tribouilloy C. Prognostic value of aortic valve area by Doppler echocardiography in patients with severe asymptomatic aortic stenosis. J Am Heart Assoc 2016;5:e003146. [Crossref]
13. Tribouilloy C, Bohbot Y, Marechaux S, Debry N, Delpierre Q, Peltier M, et al. Outcome implication of aortic valve area normalized to body size in asymptomatic aortic stenosis. Circ Cardiovasc Imaging 2016;9:e005121. [Crossref]
14. Rusinaru D, Malaquin D, Marechaux S, Debry N, Tribouilloy C. Relation of dimensionless index to long-term outcome in aortic stenosis with preserved LVEF. JACC Cardiovasc Imaging 2015;8:766-75. [Crossref]
15. Kitai T, Honda S, Okada Y, Tani T, Kim K, Kaji S, et al. Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. Heart 2011;97:2029-32. [Crossref]
16. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151-6. [Crossref]
17. Tribouilloy C, Rusinaru D, Bohbot Y, Maréchaux S, Vanoverschelde JL, Enriquez–Sarano M. How should very severe aortic stenosis be defined in asymptomatic individuals? J Am Heart Assoc 2019;8:e011724. [Crossref]
18. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706-15. [Crossref]
19. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705. [Crossref]
20. Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation 2010;121:1502-9. [Crossref]
21. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, et al. Early surgery or conservative care for asymptomatic aortic stenosis. New N Engl J Med 2020;382:111-9. [Crossref]
22. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2015;66:2827-38. [Crossref]
23. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, et al. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2016;67:2263-88. [Crossref]
24. Banovic M, Iung B, Bartunek J, Asanin M, Beleslin B, Biocina B, et al. Rationale and design of the Aortic Valve replacement versus conservative treatment in asymptomatic severe aortic stenosis (AVATAR trial): a randomized multicenter controlled event-driven trial. Am Heart J 2016;174:147-53. [Crossref]
25. Early surgery for patients with asymptomatic aortic stenosis (ESTIMATE). ClinicalTrials.gov. December 10, 2015. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02627391

Keywords: Aortic stenosis; TAVI; symptomatic; high gradient

Anahtar Kelimeler: Aort darlığı; TAVI; semptomatik; yüksek gradient