Original Investigation

Comparison of Balloon-Expandable vs Self-expandable Valves in Patients Undergoing Transcatheter Aortic Valve Replacement
The CHOICE Randomized Clinical Trial

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IMPORTANCE Transcatheter aortic valve replacement (TAVR) is an effective treatment option for high-risk patients with severe aortic stenosis. Different from surgery, transcatheter deployment of valves requires either a balloon-expandable or self-expandable system. A randomized comparison of these 2 systems has not been performed.

OBJECTIVE To determine whether the balloon-expandable device is associated with a better success rate than the self-expandable device.

DESIGN, SETTING, AND PATIENTS The CHOICE study was an investigator-initiated trial in high-risk patients with severe aortic stenosis and an anatomy suitable for the transfemoral TAVR procedure. One hundred twenty-one patients were randomly assigned to receive a balloon-expandable valve (Edwards Sapien XT) and 120 were assigned to receive a self-expandable valve (Medtronic CoreValve). Patients were enrolled between March 2012 and December 2013 at 5 centers in Germany.

INTERVENTIONS Transfemoral TAVR with a balloon-expandable or self-expandable device.

MAIN OUTCOMES AND MEASURES The primary end point was device success, which is a composite end point including successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only 1 valve implanted in the proper anatomical location. Secondary end points included cardiovascular mortality, bleeding and vascular complications, postprocedural pacemaker placement, and a combined safety end point at 30 days, including all-cause mortality, major stroke, and other serious complications.

RESULTS Device success occurred in 116 of 121 patients (95.9%) in the balloon-expandable valve group and 93 of 120 patients (77.5%) in the self-expandable valve group (relative risk [RR], 1.24, 95% CI, 1.12-1.37, $P < .001$). This was attributed to a significantly lower frequency of residual more-than-mild aortic regurgitation (4.1% vs 18.3%; RR, 0.23; 95% CI, 0.09-0.58; $P < .001$) and the less frequent need for implanting more than 1 valve (0.8% vs 5.8%, $P = .03$) in the balloon-expandable valve group. Cardiovascular mortality at 30 days was 4.1% in the balloon-expandable valve group and 4.3% in the self-expandable valve group (RR, 0.97; 95% CI, 0.29-3.25; $P = .99$). Bleeding and vascular complications were not significantly different, and the combined safety end point occurred in 18.2% of those in the balloon-expandable valve group and 23.1% of the self-expandable valve group (RR, 0.79; 95% CI, 0.48-1.30; $P = .42$). Placement of a new permanent pacemaker was less frequent in the balloon-expandable valve group (17.3% vs 37.6%, $P = .001$).

CONCLUSIONS AND RELEVANCE Among patients with high-risk aortic stenosis undergoing TAVR, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable valve.

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Editorial

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Transcatheter aortic valve replacement (TAVR) has emerged as a new therapeutic option for inoperable patients with severe aortic stenosis and as an effective alternative treatment modality to surgical aortic valve replacement in selected high-risk patients.[1,2] Different from surgery, transcatheter deployment of aortic prostheses requires either a self-expandable or balloon-expandable system. Among the early generation transcatheter heart valves, 2 device types have been in widespread use: the self-expandable Medtronic CoreValve (Medtronic Inc) and the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences). Numerous studies have been published on the safety and efficacy of both devices, and both valves have been reported to have excellent flow characteristics.[1-4]

However, recent reports have suggested differences in the hemodynamic performance of both valves, with the self-expandable valve associated with a higher rate of residual paravalvular aortic regurgitation.[5-8] Because the frequency of use of each device depends strongly on operators' familiarity with the device and anatomical and clinical suitability of the patient, these findings derived from observational registries might be hampered by bias and confounding factors. In addition, recent improvements in preprocedural imaging and device size selection, refinements in implantation technique, and the recognition of paravalvular leaks as a relevant clinical complication,[9-11] might affect the functional outcome of both valves. However, a randomized comparison of both devices is lacking.

Therefore, we designed the randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve vs Edwards SAPIEN XT (CHOICE) trial, aiming to assess the comparative performance of both technologies regarding overall device success.

Methods

Study Design and Population

The CHOICE trial was an investigator-initiated, open-label, multicenter, randomized trial. The study was approved by the local ethics committees of all participating centers, and each patient provided written informed consent for inclusion in the trial.

Patients scheduled to undergo TAVR were considered for inclusion in the trial if they met all inclusion and none of the exclusion criteria. Inclusion criteria were severe aortic stenosis defined as an aortic valve area (AVA) of 1 cm^2 or less or an indexed AVA of 0.6 cm^2/m^2 or less; presence of clinical symptoms defined as a New York Heart Association (NYHA) functional class of 2 or more; high risk of surgical aortic valve replacement defined as older than 75 years, a logistic EuroSCORE of 20% or more, a Society of Thoracic Surgeons score of 10% or more, contraindications to conventional surgical valve replacement, or all 4; anatomic suitability for either transcatheter device defined as a native aortic valve annulus measuring 20 to 27 mm in diameter; and suitability for a transfemoral vascular access.

Principal exclusion criteria were a native aortic valve annulus of less than 20 mm or more than 27 mm; a preexisting aortic bioprosthesis; hemodynamic instability; history of or active endocarditis; and contraindications for a transfemoral access. Additional exclusion criteria were a life expectancy of less than 12 months due to comorbid conditions; active peptic ulcer or upper gastrointestinal bleeding within the prior 3 months; hypersensitivity or contraindication to aspirin, heparin or clopidogrel; active infection requiring antibiotic treatment; planned elective surgery that would necessitate interruption of thienopyridines during the first 3 months; and active participation in another drug or device investigational study that has yet to complete the primary end point follow-up period.

Preinterventional Assessment

Patients were assessed using transthoracic echocardiography, transesophageal echocardiography, multidetector computed tomography (CT), selective coronary angiography, left ventriculography, and angiography of the aortic root and iliofemoral vessels for detailed assessment of the aortic valve as well as aortic root anatomy. All multidetector CT examinations were locally evaluated by experienced cardiac CT readers. Three-dimensional multidetector CT annular measurements included minimum, maximum, and mean diameter, area, and perimeter. Annular eccentricity was described using the eccentricity index, defined as: 1 −minimum diameter/maximum diameter.[12] Aortic valve calcification was graded semiquantitatively as follows: grade 1, no calcification; grade 2, mildly calcified (small isolated spots); grade 3, moderately calcified (multiple larger spots); and grade 4, heavily calcified (extensive calcifications of all cusps).[13] The left ventricular outflow tract was separately analyzed for the presence, amount, and location of calcification in a semiquantitative fashion as previously described.[14] The final decision to perform TAVR was made by a multidisciplinary team consisting of an interventional cardiologist, a conservative cardiologist, a cardiac surgeon, and an anesthesiologist, as suggested by current recommendations.[15]

Randomization and Treatment

Randomization was carried out through computer-generated block randomization forms for each participating center. After the patient provided a written informed consent form, a numbered envelope was opened, assigning the patient to either valve device in a 1:1 randomization fashion. The date of randomization marked the patient's entry into the study, and the assigned intervention had to be performed as soon as possible.

The self-expandable system consists of porcine pericardial tissue sewn to form a trileaflet valve mounted within a self-expanding hourglass-shaped nitinol frame. The prosthetic size is determined by the external diameter of the ventricular end. Four sizes were available during the study period: 23-, 26-, 29-, and 31-mm prostheses. Device size selection was based on sizing charts provided by the manufacturer, but the steering committee strongly recommended sizing to be based on 3-dimensional imaging, preferably multidetector CT-based annular perimeter.[16] The delivery system of the self-expandable device is currently 18-F catheters. Details of the implantation technique have been previously reported.[3,4]

The balloon-expandable valve system includes a cylindrical cobalt-chromium stent onto which 3 leaflets made of bovine pericardium are mounted. During the study period, the valve was available in 3 sizes: 23-, 26-, and 29-mm prostheses. Device size selection was based on sizing charts provided by the manufacturer, but the steering committee strongly recommended sizing to be based on 3-dimensional imaging, preferably the multidetector CT-based annular area.[16,17] The current transfemoral delivery system has 16-F through 20-F catheters. Details of the implantation technique have been previously reported.[18]

All procedures were performed by highly experienced operators in centers with an established multidisciplinary TAVR program (trial operators had an overall experience of performing 790 self-expandable valve and 695 balloon-expandable valve implants prior to trial initiation). The procedure was mainly performed under analgosedation (without endotracheal intubation) using fluoroscopic guidance and in selected cases using transesophageal echocardiography guidance as appropriate. The self-expandable valve was positioned in a controlled manner either without pacing or under slow-rapid pacing with allowance for limited repositioning. The balloon-expandable valve was deployed under rapid pacing without cardiopulmonary support. In patients with significant coronary artery disease, complete preprocedural revascularization—preferably using second-generation drug-eluting stents—was recommended. Antithrombotic treatment consisted of 100 mg of aspirin daily indefinitely and 75 mg of clopidogrel for at least 3 months. Patients taking oral anticoagulants received clopidogrel for 3 months and no aspirin.

Assessment of Valve Function

Following valve deployment, assessment of valve function was performed using angiography, transthoracic echocardiography, and invasive hemodynamic measurements.

Angiographic assessment was performed after wire retrieval from the ventricle using a 5- or 6-F pigtail catheter placed in the upper part of the implanted valve above the leaflets in the ascending aorta. Aortography in the 30° right anterior oblique projection and the 50° left anterior oblique projection was recorded over several cardiac cycles. The amount of contrast was standardized to allow adequate angiographic evaluation (at least 30 mL with a flow rate of 16 mL/s). Angiographic assessment of the severity of aortic regurgitation was performed by visual estimation of the concentration of contrast medium in the left ventricle, using the method of Sellers et al.[19] Aortic regurgitation was classified into the following grades: absent or trace, 0; mild, 1; moderate, 2; and severe, 3; the latter comprised grades 3 and 4 according to Sellers. Angiograms were digitally recorded and assessed off-line in the angiographic core laboratory (Intracoronary Stenting and Antithrombosis Research, Munich, Germany).

Echocardiographic assessment was performed in accordance with the Valve Academic Research Consortium recommendations. Aortic regurgitation was semiquantitatively assessed by estimating the proportion of the circumference of the valved stent occupied by the jet: less than 10% was graded as mild, 10% to 20% as moderate, and more than 20% as severe paravalvular aortic regurgitation.[20,21] Evaluation was performed on site by an experienced interventional echocardiographer.

Invasive hemodynamic assessment included measurement of the residual transprosthetic gradient, left-ventricular end-diastolic pressure, and aortic diastolic pressure. The dimensionless aortic regurgitation index was calculated as ([diastolic blood pressure –left ventricular end diastolic pressure]/systolic blood pressure) × 100.[22]

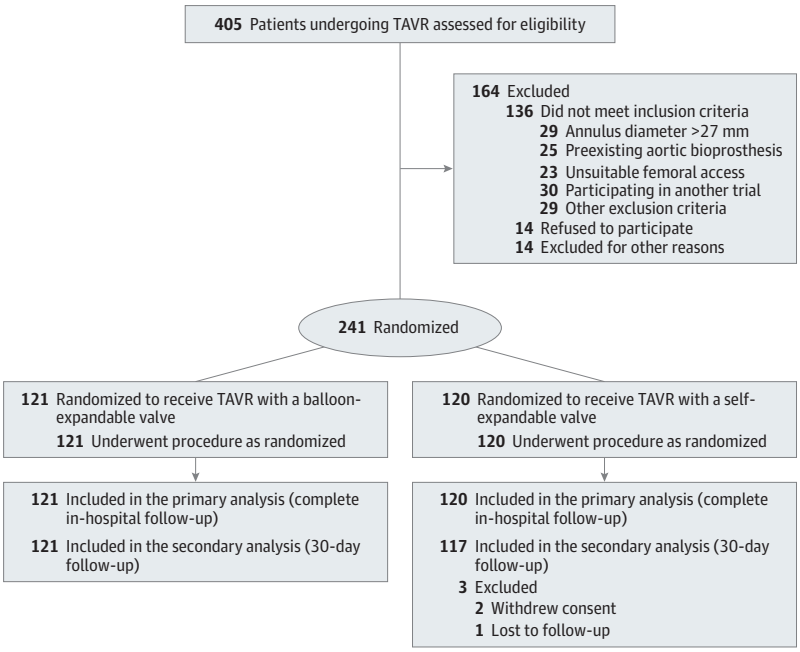
During follow-up, valve function was assessed by transthoracic echocardiography at prespecified time points (48 hours and 30 days) and will be further assessed at intermediate and long-term follow-up. In addition, a prespecified subgroup of patients was examined using cardiac magnetic resonance imaging (MRI) within 7 to 14 days after valve replacement. Using an electrocardiogram-gated cardiac MRI with a 5-element cardiac phased-array coil, flow measurements were obtained as previously described.[23] The forward and reverse volumes across the prosthesis were determined, and the regurgitant fraction (RF) was calculated. An RF of 15% or less was graded 1 (mild), 16% to 30% was graded 2 (moderate), 31% to 50% was graded 3 (moderate to severe), and more than 50% was graded 4 (severe) aortic regurgitation according to the standard grading criteria.[23] The MRI data were analyzed by 2 independent and experienced observers.

Follow-up and End Points

An electrocardiogram was performed 60 minutes after valve implant, 12 and 24 hours after the procedure, daily for the first week, and prior to discharge. In addition, blood tests, including a full blood count, and liver and renal function tests were performed between 12 and 24 hours after the procedure and on day 3. Patients were clinically monitored for the occurrence of adverse events while in the hospital and at 30 days. Additional follow-up visits are planned for 6 months and for years 1, 2, and 5.

The primary end point of the trial was *device success* as defined by the first Valve Academic Research Consortium consensus document, which is a technical composite end point including (1) successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system; (2) correct position of the device in the proper anatomical location; (3) intended performance of the prosthetic heart valve (AVA >1.2 cm^2, mean aortic valve gradient <20 mm Hg, or peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation); and (4) only 1 valve implanted in the proper anatomical location.[20] Echocardiographic assessment of the severity of aortic regurgitation is the standard tool in native aortic valves. Nevertheless, due to the lack of validation of the echocardiographic grading criteria suggested by Valve Academic Research Consortium and the challenges proposed by extremely eccentric paravalvular aortic regurgitation jets in a setting of a prosthetic valve implanted in a native valve,[24] assessment of immediate postprocedural aortic regurgitation as a criterion of the composite primary end point of this study was performed using angiography.

Figure 1. Study Flow Chart



Secondary end points at 30 days included cardiovascular mortality, major and minor vascular complications, major and minor bleeding, postprocedural pacemaker implant, NYHA class improvement (by at least 1 functional class), a 30-day combined safety end point (a composite of all-cause mortality, major stroke, life-threatening or disabling bleeding, acute stage 3 kidney injury including renal replacement therapy, periprocedural myocardial infarction, major vascular complications, and repeat procedure for valve-related dysfunction); and major adverse cardiovascular and cerebrovascular events (a composite of myocardial infarction, cardiac or vascular surgery, and stroke). All end points and adverse events were predefined in accordance with the first Valve Academic Research Consortium consensus document[20] and adjudicated by a clinical events committee blinded to treatment assignment. A detailed definition of all secondary end points is provided in the eAppendix in the Supplement. Quality of life was assessed as a self-rating of health status analogous to the EuroQol visual analogue scale,[25] anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

Statistical Analysis

The power calculation was based on the following assumptions: an incidence of device success of 70% in the self-expandable valve group[5-8] and an incidence of 85% in the balloon-expandable valve group,[5-8] a power of 80% and an α level of .05. The calculated sample size was a total of 240 patients (120 patients per group). An independent statistician performed all statistical analyses.

Primary and secondary end points were analyzed on an intention-to-treat basis. Categorical outcome measures were compared using a χ^2 test or Fisher exact test as required. Continuous variables were compared using a 2-sided unpaired *t* test or a Mann-Whitney test, as appropriate. The estimated relative risk (RR) is the ratio of the risk probabilities, and a confidence interval was constructed based on a logarithmic transformation. Missing data were assumed to be missing at random, and there were no missing data for the primary end point.

Prespecified subgroup analyses (stratified by sex, coronary artery disease status, and left ventricular ejection fraction) and post hoc subgroup analyses were performed, with RRs and 95% confidence intervals calculated by logistic regression, together with formal tests for interaction.

All tests were 2-sided and a *P* value <.05 was considered statistically significant. No adjustment was made for the primary and secondary end point comparisons. Statistical analyses were performed using Minitab, Version 15, and R, Version 2.14.

Results

Baseline Characteristics

Two hundred forty-one patients with severe symptomatic aortic stenosis undergoing transfemoral TAVR were enrolled at 5 centers in Germany between March 2012 and December 2013. One hundred twenty-one patients were randomized to receive the balloon-expandable valve and 120, the self-expandable valve. All patients received the assigned TAVR device with no crossovers. All patients underwent follow-up until hospital discharge, and 30-day clinical follow-up data were obtained for all but 3 patients (**Figure 1**).

The groups were well balanced in terms of baseline characteristics (**Table 1**), except for sex (43.0% men in the balloon-

expandable valve group vs 28.3% in the self-expandable valve group, $P = .02$). Most patients were severely symptomatic (NYHA class III or IV among 81.2% of the balloon-expandable valve group and 81.7% of the self-expandable valve group). Patients had a high surgical risk as predicted by the logistic EuroSCORE (21.5; 95% CI, 19.2-23.8 in the balloon-expandable valve group and 22.1; 95% CI, 19.5-24.8 in the self-expandable valve group), and an intermediate risk as predicted by the STS score (5.6; 95% CI, 5.0-6.1 in the balloon-expandable valve group and 6.2; 95% CI, 5.5-6.9 in the self-expandable valve group).

Echocardiographic characteristics are shown in **Table 2**. There were no significant differences in the hemodynamic severity of aortic stenosis between both groups, and the mean aortic annulus diameter as assessed by transesophageal echocardiography was comparable: 23.3 mm (95% CI, 22.8-23.7) in the balloon-expandable valve group vs 23.1 mm (95% CI, 22.7-23.4) in the self-expandable valve group ($P = .46$).

Preprocedural multidetector CT examinations were performed in 191 patients (97 of the balloon-expandable valve group and 94 of the self-expandable valve group; Table 2). Three-dimensional annular measurements (area and perimeter) were larger in the balloon-expandable valve group, probably due to the higher percentage of male patients, but annular diameters, eccentricity, the amount and location of calcification, and the distance to the coronary ostia were comparable.

Procedural Details and Outcome

Details of the procedures and procedural outcome are shown in **Table 3**. The most common valve used in the balloon-expandable group was the 26-mm valve (58.7%), whereas the most frequently implanted valve in the self-expandable group was the 29-mm valve (63.3%). Percent prosthesis oversizing was significantly higher in the self-expandable group in relation to all echocardiographic- and multidetector CT-based annular measurements. Balloon predilatation was performed in all the balloon-expandable valve procedures and was not performed for 14 (11.7%) of the self-expandable valve procedures. The mean implantation depth of the self-expandable valve group was 5.2 mm (95% CI, 4.6-5.8) from the noncoronary cusp and 6.0 mm (95% CI, 5.5-6.6) from the left coronary cusp.

Postdilatation was less frequently performed in the balloon-expandable valve group (19.8% vs 49.2%, $P < .001$), due to a lower incidence of any aortic regurgitation (40.5% vs 74.2%, $P < .001$), and more-than-mild aortic regurgitation (12.4% vs 42.5%, $P < .001$) after initial implant. The implantation of a second valve (transcatheter valve-in-valve) was also less frequent in the balloon-expandable group (1 patient, 0.8%) than the self-expandable valve group (7 patients, 5.8%, $P = .03$). The indication for a second valve was significant aortic regurgitation due to device malpositioning (too high or too low) in 1 in the balloon-expandable group and 5 in the self-expandable valve group, and device embolization (prosthesis moved during or after deployment such that it lost contact with the aortic annulus) in the remaining 2 patients in the self-expandable valve group.

Table 1. Baseline Clinical Characteristics

	No./Total No. (%) of Patients	
	Balloon-Expandable Valve (n = 121)	Self-expandable Valve (n = 120)
Age, mean (SD), y	81.9 (6.7)	79.6 (15.8)
Women	69/121 (57.0)	86/120 (71.7)
Logistic EuroSCORE, mean (SD)	21.5 (12.9)	22.1 (14.7)
EuroSCORE II, median (IQR)	4.6 (2.9-7.9)	4.4 (2.4-7.2)
Society of Thoracic Surgeons score, mean (SD)	5.6 (2.9)	6.2 (3.9)
NYHA Class		
I	7/121 (5.8)	4/120 (3.3)
II	17/121 (14.1)	18/120 (15.0)
III	73/121 (60.3)	74/120 (61.7)
IV	24/121 (19.8)	24/120 (20.0)
Quality of life score, mean (SD)	54.4 (22.2)	54.1 (20.6)
Diabetes mellitus	38/121 (31.4)	32/120 (26.7)
Coronary artery disease	73/121 (60.3)	79/120 (65.8)
Previous cardiac event		
Myocardial infarction	14/121 (11.6)	16/120 (13.3)
CABG	19/121 (15.7)	15/120 (12.5)
PCI	44/121 (36.4)	51/120 (42.5)
Vascular disease		
Cerebral	26/121 (21.5)	22/120 (18.3)
Peripheral	20/121 (16.5)	22/120 (18.3)
Pulmonary disease	27/121 (22.3)	24/120 (20.0)
Creatinine level, mean (SD), mg/dL	1.1 (0.4)	1.2 (0.5)
Severe chronic renal failure[a]	7/121 (5.8)	10/120 (8.3)
Atrial fibrillation	39/117 (33.3)	29/117 (24.8)
Permanent pacemaker	7/117 (5.9)	9/117 (7.7)

Abbreviations: CABG, coronary artery bypass grafting; IQR, interquartile range; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

SI conversion fraction: to convert creatinine from mg/dL to μmol/L, multiply by 88.4.

[a] Defined as a glomerular filtration rate <30 mL/min/1.73 m^2.

Final angiographic, echocardiographic, and hemodynamic assessments of post-TAVR aortic regurgitation are shown in **Table 4**; aortic regurgitation was paravalvular in origin in all observed cases. The occurrence of any degree of aortic regurgitation as assessed by the angiographic core laboratory was lower in the balloon-expandable valve group (38.0% vs 65.0%; RR, 0.58; 95% CI, 0.45-0.76; $P < .001$). Fewer patients in the balloon-expandable group experienced more-than-mild aortic regurgitation after valve placement than those in the self-expandable valve group (4.1% vs 18.3%; RR, 0.23; 95% CI, 0.09-0.58; $P < .001$). The interobserver κ correlation coefficient for the diagnosis of more-than-mild aortic regurgitation in the angiographic core laboratory was 0.81. Similar results were seen when aortic regurgitation was assessed by echocardiography, although the incidence was lower for both devices than was angiography. The aortic regurgitation index was not significantly different between groups with a mean of 29.0 (95% CI,

27.7-30.3) in balloon-expandable group vs 27.3 (95% CI, 26.0-28.7) in self-expandable valve group (P = .08). The invasively measured mean residual gradient was negligible with both devices (1.5 mm Hg; 95% CI, 0.9-2.1 vs 1.4 mm Hg; 95% CI, 0.7-2.1; P = .80). The mean echocardiographic transvalvular pressure gradient was higher in the balloon-expandable valve group

Table 2. Echocardiography and Multidetector Computed Tomography Characteristics

	No./Total No. (%) of Patients		
	Balloon-Expandable Valve (n = 121)	Self-expandable Valve (n = 120)	*P* Value
Transthoracic echocardiography, No.	120	116	
Aortic valve area, mean (SD), cm^2	0.7 (0.2)	0.7 (0.2)	.71
Indexed aortic valve area, mean (SD), cm^2/m^2	0.4 (0.1)	0.4 (0.1)	.34
Mean gradient, mean (SD), mmHg	43.3 (15.4)	43.0 (13.9)	.90
Left ventricle			
Ejection fraction, mean (SD), %	52.5 (13.8)	54.9 (11.9)	.15
Ejection fraction ≤35%	18/120 (15.0)	11/115 (9.6)	.21
End-diastolic diameter, mean (SD), mm	47.7 (8.4)	46.2 (8.5)	.28
End-systolic diameter, mean (SD), mm	34.7 (8.9)	32.3 (9.9)	.17
Regurgitation, moderate or severe			
Aortic[a]	17/118 (14.4)	24/115 (20.9)	.19
Mitral	44/119 (36.9)	38/116 (32.7)	.49
Tricuspid	35/118 (29.6)	35/115 (30.4)	.89
Systolic pulmonary artery pressure, mean (SD), mmHg	37.3 (13.1)	39.2 (13.6)	.34
Transesophageal echocardiography, No.	107	102	
Annulus diameter, mean (SD), mm	23.3 (2.2)	23.1 (1.9)	.46
Diameter at mid-sinus level, mean (SD), mm	31.1 (3.4)	30.1 (3.2)	.05
Degree of leaflet calcification[b]			.60
Moderate	31/106 (29.2)	33/101 (32.7)	
Severe	75/106 (70.8)	68/101 (67.3)	
Asymmetric calcification	26/94 (27.7)	26/101 (25.7)	.76
Eccentric valve orifice	9/97 (9.3)	12/100 (12.0)	.54
Bicuspid aortic valve	0/107 (0)	0/102 (0)	
Multidetector CT, No.	97	94	
Aortic annulus diameter, mean (SD), mm			
Maximum	26.5 (2.1)	26.0 (2.3)	.14
Minimum	21.7 (1.8)	21.2 (2.1)	.09
Mean	24.1 (1.7)	23.6 (2.0)	.09
Area, mm^2	456.6 (70.2)	432.3 (75.3)	.03
Perimeter	78.1 (5.9)	75.3 (6.6)	.004
Eccentricity index[c]	0.17 (0.06)	0.18 (0.07)	.75
Degree of aortic cusp calcification[d]			
Mild	9/94 (9.6)	20/93 (21.5)	.99
Moderate	52/94 (55.3)	33/93 (35.5)	
Severe	33/94 (35.1)	40/93 (43.0)	
Degree of LVOT calcification[e]			
None	45/94 (47.9)	56/93 (60.2)	.15
Mild	21/94 (22.3)	15/93 (16.1)	
Moderate	23/94 (24.5)	16/93 (17.2)	
Severe	5/94 (5.3)	6/93 (6.5)	
Height, mean (SD), mm			
Coronary artery			
Left	13.7 (2.2)	13.3 (1.9)	.20
Right	13.5 (2.9)	13.0 (2.8)	.23
Common femoral artery diameter, mean (SD), mm			
Right	8.0 (1.4)	7.6 (1.3)	.14
Left	8.0 (1.5)	7.6 (1.5)	.11

Abbreviation: CT, computed tomography; LVOT, left ventricular outflow tract.

[a] Baseline aortic regurgitation was graded using color Doppler (mainly jet width and vena contracta) and pulsed-wave Doppler (diastolic flow reversal in the descending aorta), and was classified as absent, mild, moderate, or severe.

[b] Relied on visualization of bright echoes at the base of the aortic valve leaflets and was graded as mild (small isolated spots), moderate (multiple larger spots), and severe (extensive thickening and calcification of all cusp).

[c] Eccentricity index = 1 −minimum diameter/maximum diameter.

[d] Aortic cusp calcification was graded semiquantitatively as follows: grade 1, no calcification; grade 2, mildly calcified (small isolated spots); grade 3, moderately calcified (multiple larger spots); and grade 4, severely calcified (extensive calcifications of all cusps).

[e] The LVOT calcification was graded semiquantitatively as follows: grade 1, no calcification; grade 2, mildly calcified (1 nodule of calcium extending <5 mm in any dimension and covering <10% of the perimeter of the LVOT); grade 3, moderately calcified (2 nodules of calcification or 1 extending >5 mm in any direction or covering >10% of the perimeter of the LVOT); and grade 4, severely calcified (multiple nodules of calcification or single focus extending >1 cm in length or covering >20% of the perimeter of the LVOT).

Table 3. Procedural Details

	No./Total No. (%) of Patients		P Value
	Balloon-Expandable Valve (n = 121)	Self-expandable Valve (n = 120)	
Balloon predilatation	121/121 (100)	106/120 (88.3)	<.001
Valve size, mm			
23	12/121 (9.9)	2/120 (1.7)	<.001
26	71/121 (58.7)	36/120 (30)	
29	38/121 (31.4)	76/120 (63.3)	
31	-	6/120 (5)	
Percent oversizing, mean (95% CI)			
TEE diameter (cover index)[a]	12.8 (11.8-13.8)	17.7 (16.5-18.9)	<.001
Multidetector computed tomography, mean (95% CI)			
Diameter	9.6 (8.5-10.8)	15.8 (14.9-16.7)	<.001
Area	19.5 (17.8-21.2)	30.8 (29.1-32.6)	<.001
Perimeter	7.2 (6.2-8.2)	14.8 (13.7-15.9)	<.001
Aortic regurgitation after initial valve placement[b]			
None/trace	72/121 (59.5)	31/120 (25.8)	<.001
Mild	34/121 (28.1)	38/120 (31.7)	
Moderate	10/121 (8.3)	33/120 (27.5)	
Severe	5/121 (4.1)	18/120 (15.0)	
Balloon postdilatation	24/121 (19.8)	59/120 (49.2)	<.001
Valve snaring due to deep implant	0/121 (0.0)	2/120 (1.7)	.24
Implant of ≥2 valves	1/121 (0.8)	7/120 (5.8)	.03
Adjunctive percutaneous coronary intervention	7/121 (5.8)	10/120 (8.3)	.44
Procedural duration, mean (95% CI), min	74.5 (69.2-79.9)	80.5 (72.9-88.0)	.20
Fluoroscopy time, mean (95% CI), min	19.5 (17.9-21.2)	22.5 (19.1-26.1)	.12
Contrast amount, mean (95% CI), mL	208.6 (195.6-221.7)	223.1 (205.1-241.3)	.19

Abbreviation: TEE, transesophageal echocardiography.

[a] Cover index = 100 × (prosthesis diameter −transesophageal echocardiography annulus diameter)/prosthesis diameter.

[b] Assessed by angiography using the method of Sellers et al.[19] Aortic regurgitation was classified into the following grades: absent or trace, mild, moderate, and severe, the latter comprised grades 3 and 4 according to Sellers.

Table 4. Procedural Outcome

	No./Total No. (%)		Relative Risk (95%CI)	P Value
	Balloon-Expandable Valve (n = 121)	Self-expandable Valve (n = 120)		
Immediate procedural mortality	0 /121 (0)	0/120 (0)	-	-
Final aortic regurgitation				
Angiography[a]				
None/trace	75/121 (62.0)	42/120 (35.0)	1.77 (1.34-2.35)	<.001
Mild	41/121 (33.9)	56/120 (46.7)	0.73 (0.53-0.99)	
Moderate	4/121 (3.3)	17/120 (14.1)	0.23 (0.08-0.67)	
Severe	1/121 (0.8)	5/120 (4.2)	0.20 (0.02-1.67)	
Echocardiography[b]				
None/trace	88/121 (66.1)	59/120 (49.2)	1.48 (1.20-1.83)	.005
Mild	39/121 (32.2)	54/120 (45.0)	0.72 (0.52-0.99)	
Moderate	1/121 (0.8)	7/120 (5.8)	0.14 (0.02-1.13)	
Severe	1/121 (0.8)	0/120 (0)		
Aortic regurgitation index, mean (95% CI)[c]	29.0 (27.7-30.3)	27.3 (26.0-28.7)		.08
Coronary obstruction	2/121 (1.6)	0/120 (0.0)		.49
Annular rupture	0/121 (0)	0/120 (0)		
Left-to-right shunt	2/121 (1.6)	2/120 (1.7)	0.99 (0.14-6.93)	.99
Device success (primary endpoint)	116/121 (95.9)	93/120 (77.5)	1.24 (1.12-1.37)	<.001

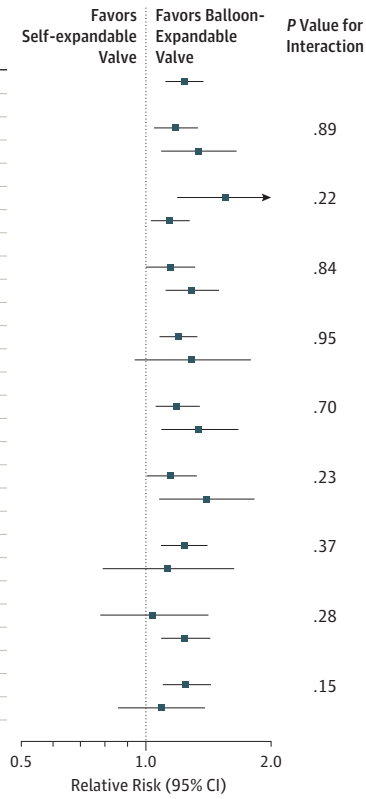
[a] Assessed by angiography using the method of Sellers et al.[19] Aortic regurgitation was classified into the following grades: absent or trace, mild, moderate, and severe, the latter comprised grades 3 and 4 according to Sellers.

[b] Semiquantitatively assessed using echocardiography. For paravalvular regurgitation, grading was performed by estimating the proportion of the circumference of the valved stent occupied by the jet: less than 10% was graded as mild, 10% to 20% as moderate, and more than 20% as severe regurgitation.[20,21]

[c] Calculated as ([diastolic blood pressure −left ventricular end diastolic pressure]/systolic blood pressure) × 100 in 114 patients in self-expandable valve group and 116 in the balloon expandable valve group.

Figure 2. Subgroup Analyses for Device Success

Subgroup	Device Success: Balloon-Expandable Valve No./Total (%)	Device Success: Self-expandable Valve No./Total (%)	Relative Risk (95% CI)	*P* Value for Interaction
Overall	116/121 (95.9)	93/120 (77.5)	1.24 (1.12-1.37)	
Age, y				
≥80	82/85 (96.5)	62/76 (81.6)	1.18 (1.05-1.33)	.89
<80	34/36 (94.4)	31/44 (70.4)	1.34 (1.09-1.65)	
Sex				
Men	50/52 (96.1)	21/34 (61.8)	1.56 (1.19-2.04)	.22
Women	66/69 (95.6)	72/86 (83.7)	1.14 (1.03-1.27)	
Coronary artery disease				
No	47/48 (97.9)	35/41 (85.4)	1.15 (1.00-1.31)	.84
Yes	69/73 (94.5)	58/79 (73.4)	1.29 (1.12-1.49)	
LV ejection fraction, %				
>35	97/101 (96.0)	80/100 (80.0)	1.20 (1.08-1.33)	.95
≤35	18/19 (94.7)	11/15 (73.3)	1.29 (0.94-1.78)	
Mitral regurgitation				
None/mild	72/75 (96.0)	63/78 (80.8)	1.19 (1.06-1.34)	.70
Moderate/severe	42/44 (95.5)	27/38 (71.1)	1.34 (1.09-1.66)	
CT annulus diameter, mm				
<25	56/60 (93.3)	55/68 (80.9)	1.15 (1.01-1.32)	.23
≥25	34/35 (97.1)	18/26 (69.2)	1.40 (1.08-1.82)	
Aortic valve eccentricity index				
≤0.25	81/84 (96.4)	60/77 (77.9)	1.24 (1.09-1.40)	.37
>0.25	8/9 (88.9)	11/14 (78.6)	1.13 (0.79-1.62)	
Aortic leaflet calcification				
None/mild	8/9 (88.9)	17/20 (85.0)	1.04 (0.78-1.41)	.28
Moderate/severe	81/85 (95.3)	56/73 (76.7)	1.24 (1.09-1.42)	
LVOT calcification				
None/mild	64/66 (97.0)	55/71 (77.5)	1.25 (1.10-1.43)	.15
Moderate/severe	25/28 (89.3)	18/22 (81.8)	1.09 (0.86-1.38)	



Subgroup analyses are shown for the primary end point of device success among patients who were randomly assigned to undergo transfemoral transcatheter aortic valve replacement with either a self-expandable or balloon-expandable prosthesis. The *P* value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. Risk ratios are for the balloon-expandable vs self-expandable valve. CT indicates computed tomography; LVOT, left ventricular outflow tract. Aortic cusp (leaflet) and LVOT calcifications have been graded as described in Table 2.

(8.4 mm Hg; 95% CI, 7.9-9.1 vs 6.4 mm Hg; 95% CI, 5.9-7.0; $P < .001$), but the valve area was comparable (2.0 cm^2; 95% CI, 1.9-2.1 vs 2.0 cm^2; 95% CI, 1.9-2.1, $P = .86$).

Consequently, the primary end point of device success was significantly higher in the balloon-expandable valve group (95.9%) than in the self-expandable valve group (77.5%; RR, 1.24; 95% CI, 1.12-1.37; $P < .001$). Detailed causes of device failure are listed in eTable 1 in the Supplement. Immediate procedural mortality did not occur in any patient.

Results with respect to the primary end point were consistent in all prespecified and post hoc subgroups (**Figure 2**), even though the difference between both devices was attenuated in patients with small anatomies (annulus diameter, <25 mm), mild leaflet calcification, severe left ventricular outflow tract calcification, and extremely eccentric annuli. Device success remained higher with the balloon-expandable valve group when accounting for sex (*P* for interaction, .22).

Postprocedural Valve Function

Echocardiographic follow-up data during index hospitalization and at 30 days are shown in eTable 2 and the eFigure in the Supplement. No significant changes were observed in the evolution of aortic regurgitation over time, and the incidence of more-than-mild paravalvular and total aortic regurgitation remained significantly lower in the balloon-expandable valve group at 30 days (0.0% vs 7.2%, $P = .009$ for paravalvular aortic regurgitation; and 2.1% vs 9.6%, $P = .04$ for total aortic regurgitation). On the other hand, the mean transvalvular gradient was slightly but significantly higher in the balloon-expandable valve group (8.9 mm Hg; 95% CI, 8.3-9.7 vs 6.6 mm Hg; 95% CI, 6.0-7.3; $P < .001$).

Absolute regurgitant fraction was not significantly different in a subgroup of 90 patients who underwent cardiac MRI scanning during the index hospitalization, 56 patients in the balloon-expandable and 34 in the self-expandable valve groups, (mean, 4.2%; 95% CI, 3.1%-5.2% vs 7.1; 95% CI, 4.2%-10.03%; $P = .06$), but the proportion of patients with more-than-mild aortic regurgitation (RF>15%) was significantly lower in the balloon-expandable group (1.8% vs 18.2%, $P = .01$).

Clinical Outcome at 30 Days

At 30 days, 11 patients (4.6%) had died, 5 (4.1%) in the balloon-expandable group and 6 (5.1%) in the self-expandable valve group (RR, 0.81; 95%CI, 0.25-2.57; **Table 5**). Cardiovascular mortality was 4.1% in the balloon-expandable group and 4.3% in the self-expandable valve group (RR, 0.97; 95% CI, 0.29-3.25). Stroke occurred in 7 patients (5.8%) in the balloon-expandable valve group (3 major and 4 minor strokes) and 3 patients (2.6%) in the self-expandable valve group (all major strokes, RR, 2.26; 95% CI,

Table 5. Thirty-Day Clinical Outcome

Variable	No./Total No. (%) Balloon-Expandable Valve (n = 121)	No./Total No. (%) Self-expandable Valve (n = 117)	Relative Risk (95% CI)	*P* Value
Death				
Any cause	5/121 (4.1)	6/117 (5.1)	0.81 (0.25-2.57)	.77
Cardiovascular causes	5/121 (4.1)	5/117 (4.3)	0.97 (0.29-3.25)	.99
Stroke	7/121 (5.8)	3/117 (2.6)	2.26 (0.60-8.52)	.33
Myocardial infarction	1/121 (0.8)	0/117 (0.0)		.99
Bleeding				
Life threatening	10/121 (8.3)	14/117 (12.0)	0.69 (0.32-1.49)	.35
Major	23/121 (19.0)	17/117 (14.5)	1.31 (0.74-2.32)	.36
Minor	11/121 (9.1)	9/117 (7.7)	1.18 (0.51-2.74)	.70
Major or minor	34/121 (28.1)	26/117 (22.2)	1.26 (0.81-1.97)	.30
Vascular complications				
All	17/121 (14.0)	15/117 (12.8)	1.10 (0.57-2.09)	.78
Major	12/121 (9.9)	13/117 (11.1)	0.89 (0.42-1.88)	.76
Minor	5/121 (4.1)	2/117 (1.7)	2.42 (0.48-12.21)	.28
Acute kidney injury	5/121 (4.1)	11/117 (9.4)	0.44 (0.16-1.23)	.13
Repeat procedure for valve-related dysfunction	1/121 (0.8)	2/117 (1.7)	0.48 (0.04-5.26)	.62
Combined safety end point[a]	22/121 (18.2)	27/117 (23.1)	0.79 (0.48-1.30)	.42
Major adverse cardiovascular and cerebrovascular events[b]	8/121 (6.6)	4/117 (3.4)	1.93 (0.60-6.25)	.38
Rehospitalization for heart failure	0/119 (0.0)	5/117 (4.3)		.02
NYHA class improvement	100/106 (94.3)	91/105 (86.7)	1.09 (1.00-1.19)	.06
Quality of life				
Score, mean (95% CI)	71.0 (68.2-73.9)	65.9 (62.4-69.5)		.02
Score change, median (IQR)	12.5 (0-20)	10 (0-20)		.19
New permanent pacemaker	19/110 (17.3)	38/101 (37.6)	0.46 (0.28-0.74)	.001

Abbreviations: IQR, interquartile range; NYHA, New York Heart Association.

[a] Defined as a composite of all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury stage 3 including renal replacement therapy, periprocedural myocardial infarction, major vascular complications, and repeat procedure for valve-related dysfunction.

[b] Defined as a composite of myocardial infarction, cardiac or vascular surgery and stroke.

0.60-8.52). Predefined secondary end points such as vascular complications and bleeding were not different between groups. Consequently, the Valve Academic Research Consortium-defined combined safety end point at 30 days was also comparable (18.2% in the balloon-expandable vs 23.1% in the self-expandable valve group; RR, 0.79; 95% CI, 0.48-1.30). Symptomatic (NYHA class) improvement occurred in the majority of patients: 94.3% in the balloon-expandable valve group and 86.5% in the self-expandable valve group (RR, 1.09; 95% CI, 1.00-1.19). Patients in the balloon-expandable valve group had a significantly higher quality of life score (on a scale from 0-100) at 30 days despite a comparable baseline score, but the median change from baseline to 30-day was not significantly different (Table 5). The exploratory end point of rehospitalization for heart failure at 30 days occurred only in 5 patients (4.3%) in the self-expandable valve group. Implantation of a new permanent pacemaker was lower in the balloon-expandable valve group (17.3% vs 37.6%; RR, 0.46; 95% CI, 0.28-0.74).

Discussion

To our knowledge, the CHOICE trial is the first randomized clinical trial to compare 2 different transcatheter heart valve technologies in high-risk patients with severe aortic stenosis. In this contemporary German study involving patients who had undergone TAVR at 5 experienced centers, clinical outcome at 30 days was excellent with both valves and with low and comparable mortality and major stroke rates. The composite primary end point of device success was higher with the balloon-expandable device, which was attributed to a lower frequency of more-than-mild paravalvular aortic regurgitation, and the less frequent need for implanting 2 devices to achieve an acceptable hemodynamic outcome. Device success is a well-defined outcome measure endorsed by the Valve Academic Research Consortium as a clinically relevant composite end point. It is meant to characterize the acute device and procedural factors that underlie vascular access, delivery, and performance of a TAVR system, and is thus an ideal end point for a comparative evaluation of different systems. Nevertheless, only a few studies have reported the frequency of device success by both prostheses in accordance with the Valve Academic Research Consortium definition, which includes the absence of moderate or severe prosthesis regurgitation.[20]

The incidence of more-than-mild aortic regurgitation after TAVR with both devices varies widely in the published literature. Frequencies between 2% and 40% have been reported for the self-expandable device,[5-8,26] and between 0.6%

and 22% for the balloon-expandable valve.[1,2,5-8,27] In a recently published meta-analysis, the incidence of more-than-mild aortic regurgitation was 16.0% after placement of the self-expandable valve compared with 9.1% after placing the balloon-expandable valve (P = .005).[28] On the other hand, a recently published multicenter collaborative study reported a very low and comparable incidence of more-than-mild aortic regurgitation with both devices (2.0%, self-expandable valve; and 1.8%, balloon expandable).[26] This discrepancy in outcomes may be related in part to the challenges in identification and quantification of aortic regurgitation after TAVR but also to the observational and nonrandomized nature of all reported comparisons.

In our study, a significant difference was observed in the frequency of any aortic regurgitation and more-than-mild aortic regurgitation favoring the balloon-expandable valve. Sizing in 80% of cases was based on 3-dimensional multidetector CT measurements, and the implanted self-expandable devices were significantly oversized (≈ 31% area oversizing and ≈ 15% perimeter oversizing), making it unlikely that device undersizing has contributed to difference. Proper device positioning is another important factor related to the occurrence of aortic regurgitation with both devices, and the self-expandable valve is a long device allowing for a wide range of implant depths. Current practice trends favor a high implantation depth of the self-expandable device,[29] and this was adopted by the implanting operators, achieving one of the highest reported implant depths for the self-expanding device (5 mm below the annular plane). The significant oversizing, the achieved depth of the implant, and the liberal use of balloon postdilatation (≈ 50%) should have allowed an adequate interference of the large inflow portion of the self-expandable valve device with the aortic annulus minimizing paravalvular leaks. The observed incidence of aortic regurgitation was much lower than anticipated and comparable with the reported 11.5% more-than-mild aortic regurgitation rate at 30 days in the recently presented CoreValve US Pivotal Extreme Risk Trial.[30] However, some concerns have been generally raised concerning the radial strength of the nitinol framework of self-expanding devices,[31] and Tzamtzis et al[32] have recently reported that the radial forces obtained in an experimental model with the same left ventricular outflow tract diameter were lower with the self-expandable valve than with the balloon-expandable valve. These experimental data are supported by the favorable performance of the balloon-expandable valve in patients with large anatomies and those with heavily calcified leaflets in the current study, for which the limitations of a self-expandable device cannot be overcome by extreme oversizing. There are conflicting data about the evolution of paravalvular aortic regurgitation after implanting a self-expandable device,[23,30] and some recent data have suggested a reduction in aortic regurgitation over time.[30] This has not been observed in our study up to 30 days after valve placement.

A further finding in the CHOICE trial was the more frequent need for a second valve in the self-expandable valve group. An optimal TAVR device should allow predictable and precise deployment in a wide range of aortic root anatomies. However, even for very experienced operators, exact placement of a self-expandable device is often difficult, particularly in challenging scenarios. For correction of a malpositioned self-expandable valve device, which commonly causes significant aortic regurgitation, a second valve is usually needed. This is considered a device failure, according to Valve Academic Research Consortium, and has been recently described to be associated with worse outcomes.[33] The results of CHOICE in this aspect support the development of delivery catheters allowing recapturing and repositioning of self-expandable devices to minimize the consequences of device malpositioning,[34] which is less frequently encountered with balloon-expandable valves.

With an accumulating body of evidence linking more-than-mild aortic regurgitation and consequently device failure with a worse clinical outcome after TAVR,[9-11] the findings of the CHOICE trial may have important clinical implications. Notably, at short-term follow-up, improvement of heart failure symptoms was more frequently observed with the balloon-expandable valve, whereas minor stroke rates were numerically higher. Nevertheless, long-term follow-up of the CHOICE population should be awaited to determine whether differences in device success will translate into a clinically relevant overall benefit for the balloon-expandable valve.

Study Limitations

The assessment of postprocedural aortic regurgitation as a criterion of the primary end point of this study using core laboratory–adjudicated angiography and the lack of an echocardiographic core laboratory are potential study limitations. We decided to choose the angiography to evaluate aortic regurgitation because it is an established tool for qualitative and semiquantitative assessment of aortic regurgitation, is readily available during the procedure, and can provide essential information to initiate further management.[35] In addition, the timing, angiographic views, and amount and flow-rate of contrast were standardized to allow adequate image analysis and off-line core laboratory assessment. The angiographic findings in our study were also confirmed by a wide range of assessment tools, including echocardiography, hemodynamic measurements, and cardiac MRI analysis in a predefined patient subgroup. On the other hand, evaluation of the severity of aortic regurgitation post-TAVR using echocardiography remains complex and challenging, may underestimate aortic regurgitation severity,[24] and the suggested Valve Academic Research Consortium criteria have not been validated in this setting.

Conclusions

Among patients with high-risk aortic stenosis undergoing transfemoral TAVR, the use of a balloon-expandable valve prosthesis compared with a self-expandable valve prosthesis resulted in a greater rate of device success.

ARTICLE INFORMATION

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