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CLINICAL RESEARCH
TAVI

Comparison of newer generation self-expandable vs. balloon-expandable valves in transcatheter aortic valve implantation: the randomized SOLVE-TAVI trial

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Aims Transcatheter aortic valve implantation (TAVI) has emerged as established treatment option in patients with symptomatic aortic stenosis. Technical developments in valve design have addressed previous limitations such as suboptimal deployment, conduction disturbances, and paravalvular leakage. However, there are only limited data available for the comparison of newer generation self-expandable valve (SEV) and balloon-expandable valve (BEV).

Methods and results SOLVE-TAVI is a multicentre, open-label, 2 × 2 factorial, randomized trial of 447 patients with aortic stenosis undergoing transfemoral TAVI comparing SEV (Evolut R, Medtronic Inc., Minneapolis, MN, USA) with BEV (Sapien 3, Edwards Lifesciences, Irvine, CA, USA). The primary efficacy composite endpoint of all-cause mortality, stroke, moderate/severe prosthetic valve regurgitation, and permanent pacemaker implantation at 30 days was powered for equivalence (equivalence margin 10% with significance level 0.05). The primary composite endpoint occurred in 28.4% of SEV patients and 26.1% of BEV patients meeting the prespecified criteria of equivalence [rate difference -2.39 (90% confidence interval, CI -9.45 to 4.66); $P_{equivalence} = 0.04$]. Event rates for the individual components were as follows: all-cause mortality 3.2% vs. 2.3% [rate difference -0.93 (90% CI -4.78 to 2.92); $P_{equivalence} < 0.001$], stroke 0.5% vs. 4.7% [rate difference 4.20 (90% CI 0.12 to 8.27); $P_{equivalence} = 0.003$], moderate/severe paravalvular leak 3.4% vs. 1.5% [rate difference -1.89 (90% CI -5.86 to 2.08); $P_{equivalence} = 0.0001$], and permanent pacemaker implantation 23.0% vs. 19.2% [rate difference -3.85 (90% CI -10.41 to 2.72) in SEV vs. BEV patients; $P_{equivalence} = 0.06$].

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Conclusion In patients with aortic stenosis undergoing transfemoral TAVI, newer generation SEV and BEV are equivalent for the primary valve-related efficacy endpoint. These findings support the safe application of these newer generation percutaneous valves in the majority of patients with some specific preferences based on individual valve anatomy.

Keywords Transcatheter aortic valve implantation • Transcatheter aortic valve replacement • Aortic stenosis • Pacemaker implantation • Stroke • Prognosis

Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a valuable and effective alternative to surgical aortic valve replacement (SAVR) in symptomatic aortic stenosis in the spectrum from high to intermediate and most recently also low surgical risk.[1–3] Based on several randomized trials in inoperable, high- and intermediate surgical risk patients several TAVI devices have gained European and US approval. In particular, two valve types have been widely used: self-expandable valve (SEV) and balloon-expandable valve (BEV).

Despite advances, initial TAVI devices had limitations, including the inability of retrieval or repositioning after full expansion, haemodynamic compromise during implantation or large access sheath size. The need for permanent pacemaker implantation is another important limitation in particular for SEV although the impact on outcome is undetermined.[4] Furthermore, paravalvular leakage (PVL) can occur and there is a higher mortality associated with moderate or severe PVL.[5] Accordingly, the current challenge is to further decrease rates in mortality, stroke, bleeding, need for permanent pacemaker implantation, and also PVL among other complications. Even though newer generation SEV[6] and BEV[7] devices have been developed to address possible drawbacks of first-generation devices which led to a frequent adoption of these devices in clinical practice,[8] randomized trials evaluating outcomes in patients treated with newer generation SEV and BEV are very limited. The current available evidence comparing different valve types includes only two small to modestly sized randomized controlled trials ($n = 240$ comparing first-generation SEV and BEV[9]; and $n = 912$ comparing a mechanically expanded valve with first- and second-generation SEV).[10]

Accordingly, aim of this randomized trial was to compare the newer generation SEV (Evolut R, Medtronic Inc., Minneapolis, MN, USA) and BEV (Sapien 3, Edwards Lifesciences, Irvine, CA, USA) in a multicentre trial with respect to equivalence in safety and efficacy in high-risk patients with symptomatic aortic stenosis undergoing transfemoral TAVI.

Methods

Study design and oversight

The compariSon of secOnd-generation seLf-expandable vs. balloon-expandable Valves and gEneral vs. local anaesthesia in Transcatheter Aortic Valve Implantation (SOLVE-TAVI) trial is an investigator-initiated 2 × 2 factorial, open-label, randomized, multicentre study conducted at seven German sites to compare newer generation SEV (Evolut R, Medtronic Inc., Minneapolis, MN, USA) vs. BEV (Sapien 3, Edwards Lifesciences, Irvine, CA, USA). Results of the concurrent, interlaced trials of the valve and anaesthesia strategy are reported separately based on different primary endpoints in both trials. SOLVE-TAVI is co-ordinated by the Heart Center Leipzig at University of Leipzig in co-operation with the Leipzig Heart Institute, Germany and the Center for Clinical Trials at University of Lübeck, Germany. The trial was designed by the first and senior authors and modified by the steering committee. Funding was partially provided by the German Heart Research Foundation and the Leipzig Heart Institute, Germany and by all participating sites.

The study was approved by ethics committees of all participating centres and national regulatory authorities. The trial organization included a steering committee, an independent data safety monitoring board, and a clinical event committee adjudicating all major clinical events. Echocardiographic data were analysed by the individual centres. In addition, PVL was also analysed by an independent core laboratory (blinded to treatment allocation). The first author had full access to all data and takes responsibility for integrity and data analysis. Data were maintained at the Center for Clinical Trials and the Institute for Medical Biometry and Statistics (IMBS), University of Lübeck, Lübeck, Germany, which performed all statistical analyses independently. All sites were monitored on site before and during the trial using the risk-based approach, and central data management queried frequently about implausible or missing values. The trial is registered at www.clinicaltrials.gov (NCT02737150).

Patient selection

Patients with symptomatic aortic stenosis, age ≥75 years and high risk for conventional SAVR were eligible for enrolment. High risk was defined by logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) ≥20% and/or Society of Thoracic Surgeons (STS) risk score ≥10% or other high-risk criteria by heart team consensus. A native aortic valve annulus size (18–29 mm) appropriate for the available valve sizes and suitability for transfemoral vascular access were also required.

Exclusion criteria were contraindication for a specific valve type; cardiogenic shock or haemodynamic instability; history of or active endocarditis; active infection requiring antibiotic treatment; life expectancy <12 months; active peptic ulcer or upper gastrointestinal bleeding <3 months; hypersensitivity or contraindication to aspirin, heparin, or clopidogrel; and participation in another trial. Written informed consent was provided by all patients.

By means of opaque sealed envelopes randomization was performed using permuted blocks of variable size and stratification for centre. The valves differ by design and instructions for use; therefore, the investigators performing the procedure were unblinded to the assigned treatment. However, clinical endpoint assessment was performed in a blinded manner.

Treatment and follow-up

Apart from the valve type, all other interventions did not differ between groups. The technical aspects of the TAVI procedures followed the accepted standards and the implantation techniques of the specific valves. A pre-procedure computed tomography scan was standard in all institutions for native annulus measurement and also assessment of vascular access. All procedures have been performed by highly experienced

operators with a minimum overall experience of 50 TAVI procedures. The study was also performed in accordance with current national German recommendations on quality criteria for implementation of TAVI.[11]

Clinical follow-up was performed at discharge and 30 days and by protocol will also be continued at 6, 12, 24, and 60 months. Neurological assessments were performed after TAVI by neurologists and/or certified physicians to administer the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale.

Study endpoints

The primary endpoint for the valve comparison was a composite of all-cause mortality, stroke, moderate or severe PVL, and permanent pacemaker implantation at 30-day follow-up.

Secondary endpoints of the current valve analysis included device success, early safety, clinical efficacy, time-related safety, and cardiovascular mortality according to the Valve Academic Research Consortium (VARC)-2 criteria.[12] In addition, the cardiovascular mortality at 30 days, individual components of the primary endpoint, mean length of primary hospital stay, quality of life according to the EuroQuol-5 questionnaire (EQ-5D), device time, and total procedural time were assessed.

Statistical analysis

The study was powered for equivalence of the composite primary endpoint.[13] Based on clinical experience, an interaction between the valve and anaesthesia strategy was not expected. Thus, independent sample size calculations were performed with no adjustment for essentially conducting two studies. The final sample size was defined by the larger of these, i.e. the valve strategy, to be powered to detect the main effect of each intervention. Sample size calculations were performed using established sample size calculation software (nQuery 6.01) and were based on the available results of the CoreValve Evolut R CE study[14] and the Safety and Performance Study of the Edwards Sapien 3 Transcatheter Heart Valve trial.[15] Based on these data, an overall incidence of the combined endpoint of 15.0% had been anticipated in both groups. Equivalence of SEV and BEV was assumed within an equivalence margin of 10%. A difference >10% was judged to be clinically relevant for the primary endpoint. To reject the equivalence null hypothesis (two-sided χ^2 test; power 90%, significance level 0.05) $2 \times 219 = 438$ evaluable patients were needed. The drop-out rate for the primary study endpoint assessment was assumed to be 1.0% resulting in a final study cohort consisting of 444 patients.

All analyses were performed according to the intention-to-treat principle. A per-protocol analysis was performed in case of cross-over. The full analysis set is the operationalization of the intention-to-treat principle which was defined as all randomized and treated patients regardless of protocol deviations. Randomized patients were not included in case of withdrawal of informed consent prior to treatment or if there was no treatment attempt (e.g. because of prior death) to avoid bias and to sharpen generalization. The denominator of proportions may differ because of missing values which were not imputed. The per-protocol set was defined as all randomized patients fulfilling all in- and no exclusion criteria receiving the allocated intervention.

Pre-specified subgroup analyses for the valve strategy were performed for sex, age (<80 vs. ≥80 years), presence or absence of coronary artery disease, left ventricular ejection fraction (≤35 vs. >35%), frailty (non/mild vs. moderate/severe), presence or absence of chronic renal insufficiency, body mass index (<25 kg/m^2 vs. ≥25 to 30 kg/m^2 vs. ≥30 kg/m^2); STS score (<10% vs. ≥10%); logistic EuroSCORE I (<20% vs. ≥20%); aortic valve stenosis haemodynamic type (normal flow, high gradient vs. low flow, low gradient with reduced ejection fraction vs. paradoxical low flow, low gradient, with normal ejection fraction); saturation of cerebral oxygen at start of TAVI procedure <50% vs. ≥50%, and general vs. local anaesthesia.

Results

Patients

From April 2016 to April 2018, 447 patients were randomized (*Figure 1*). A total of 225 patients were randomly assigned to SEV and 222 to BEV implantation. Of these, 438 patients underwent the TAVI procedure and were thus eligible for further analysis (*Figure 1*).

Patients were at high to intermediate risk with a mean age of over 80 years and a median logistic EuroSCORE I of 14.8% [interquartile range (IQR) 8.7–23.8%] and STS score of 4.7% (IQR 3.0–9.8%). Baseline characteristics are displayed in *Table 1* and were well balanced between the two valve treatment groups (*Table 1*).

Treatment

Procedural characteristics are shown in *Table 2*. Cross-over from SEV to BEV occurred in two patients (0.9%); to other valves in two patients and in the opposite direction in one patient (*Figure 1*). The use of transoesophageal echocardiography was infrequent and similar between both treatment groups (*Table 2*).

Primary and secondary endpoints

Three patients in the BEV group were lost to follow-up with respect to the primary endpoint and one patient per group withdrew informed consent after TAVI (*Figure 1*). Consequently, 218 patients in the SEV and 215 patients in the BEV group were included in the primary endpoint analysis.

At 30 days, the rate of the composite primary endpoint of all-cause mortality, stroke, moderate or severe PVL, and permanent pacemaker implantation was equivalent between SEV and BEV [28.4% vs. 25.9%; rate difference -2.51 (90% confidence interval, CI -9.65 to 4.53); $P_{equivalence} = 0.04$]. Only minor variation in the rate difference was observed when the analysis was performed in the per-protocol population [27.0% for SEV vs. 25.5% for BEV; rate difference: 1.48; 90% CI -8.61 to 5.65; $P_{equivalence} = 0.03$]. Prespecified subgroup analyses revealed consistent results across all subgroups (*Figure 2*).

Analysis of the individual components of the primary endpoint were as follows (*Take home figure*): all-cause mortality 3.2% for SEV vs. 2.3% for BEV [rate difference -0.94 (90% CI -4.79 to 2.91); $P_{equivalence} < 0.001$], stroke 0.5% for SEV vs. 4.7% for BEV [rate difference 4.20 (90% CI 0.11 to 8.28); $P_{equivalence} = 0.003$], moderate/severe paravalvular leak 3.4% for SEV vs. 1.5% for BEV [rate difference -1.92 (90% CI -5.88 to 2.05); $P_{equivalence} = 0.0001$], permanent pacemaker implantation 23.0% for SEV vs. 19.2% for BEV [rate difference -3.85 (90% CI -10.41 to 2.72); $P_{equivalence} = 0.06$] (*Table 3*). Altogether, permanent pacemaker implantation rates were relatively high with similar indications between groups (*Table 3*).

Device time and total procedural time were similar between both treatment groups. However, fluoroscopy time and overall doses of contrast agent were higher in the SEV group in comparison to the BEV group (*Table 2*). There were no differences in major bleeding complications, acute kidney injury or the need and doses of vasopressors and inotropes between groups (*Table 4*).

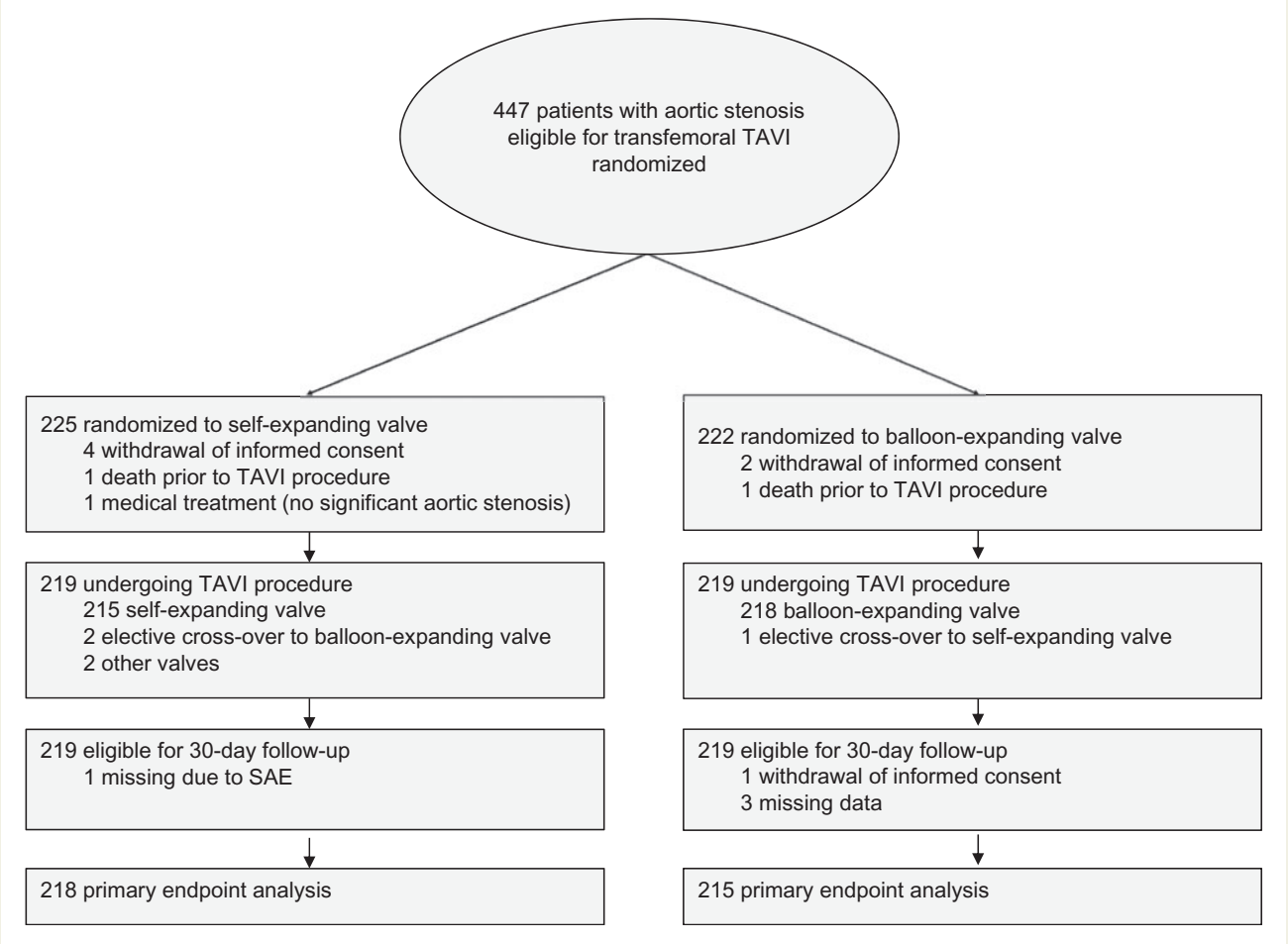


Figure 1 Diagram of patient flow. TAVI, transcatheter aortic valve implantation. The total number of patients with aortic stenosis who were screened but not enrolled and the reasons for their exclusion are not available.

Valve-related outcomes according to VARC-2 criteria with respect to device success and early safety fulfilled the criteria of equivalence (*Table 4*). However, clinical efficacy and time-related safety did not show equivalence (*Table 4*). Time-related safety was significantly better for the SEV (*Table 4*) which was mainly driven by a higher rate of patients with a gradient ≥20 mmHg in the BEV group at 30-day follow-up.

Overall quality of life according to the EQ-5D questionnaire was not statistically different between the two treatment groups. Pain was relieved by a median of one point compared with baseline in both groups in parallel (95% CI -1 to -0.5), while median self-care worsened by one point (95% CI 0.5–1) at 30 days in both groups. Little change was observed in mobility, anxiety, and usual activities (*Figure 3*).

Discussion

In this randomized multicentre trial among high- to intermediate-risk aortic stenosis patients undergoing transfemoral TAVI, newer generation SEV in comparison to BEV met criteria for equivalence for the composite primary efficacy endpoint at 30 days. All-cause mortality, stroke rates, and PVL were low. However, permanent pacemaker implantation in this specific high-risk population is still high with both valve types.

The number of TAVI procedures performed is steadily growing.[17,18] With the latest trials in low-risk patients showing superiority and non-inferiority of TAVI in comparison to SAVR,[2,3] valve design, device-related complications, and valve durability become even more important. Multiple companies continue to develop new valves in order to further reduce clinical complications. However, evidence on valve comparisons is limited. Currently, there are only two randomized trials comparing different valve types.[9,10] One trial was conducted in the early years of TAVI comparing first-generation SEV (CoreValve, Medtronic) and BEV (Sapien XT, Edwards)[9,19]; the second trial compared a mechanical expanding valve (Lotus, Boston Scientific Corp.) to mixed first- and second-generation SEV (CoreValve and Evolut R, Medtronic).[10] Similar to the SOLVE-TAVI trial, both trials also used a composite clinical endpoint. In the CHOICE trial ($n = 241$) device success—according to the previous VARC criteria[20]—was superior with BEV vs. SEV mainly driven by less PVL.[9] In the REPRISE III (Repositionable Percutaneous

Table 1 Baseline characteristics

	Self-expanding valve (Evolut R) (*n* = 219)	Balloon-expandable valve (Sapien 3) (*n* = 219)
Age (years), mean ± SD	81.7 ± 5.3	81.5 ± 5.7
Male sex, *n*/total (%)	105/219 (47.9)	109/219 (49.8)
Risk scores		
STS score (%), median (IQR)	4.9 (2.9–9.9)	4.7 (3.1–9.4)
Log. EuroSCORE I (%), median (IQR)	14.9 (8.9–23.8)	14.8 (8.6–24.4)
EuroSCORE II (%), median (IQR)	4.1 (2.5–7.5)	3.8 (2.4–6.1)
Frailty, *n*/total (%)	93/216 (43.1)	80/217 (36.9)
Peripheral arterial disease, *n*/total (%)	29/218 (13.3)	26/220 (11.8)
Coronary artery disease, *n*/total (%)	127/219 (58.0)	116/219 (52.7)
Prior myocardial infarction, *n*/total (%)	19/219 (8.7)	22/219 (10.0)
Prior PCI, *n*/total (%)	84/219 (38.4)	79/219 (36.1)
Prior CABG, *n*/total (%)	26/219 (11.9)	18/219 (8.2)
Atrial fibrillation, *n*/total (%)	103/219 (47.0)	93/219 (42.5)
Prior pacemaker/implantable cardioverter defibrillator, *n*/total (%)	24/218 (11.0)	23/219 (10.5)
Prior stroke, *n*/total (%)	25/219 (11.4)	26/219 (11.9)
Renal insufficiency, *n*/total (%)	177/216 (81.9)	184/214 (86.0)
Pulmonary hypertension, *n*/total (%)	106/216 (49.1)	105/218 (48.2)
Chronic obstructive pulmonary disease, *n*/total (%)	30/219 (13.7)	29/217 (13.4)
Cardiovascular risk factors		
Diabetes, *n*/total (%)	79/218 (36.2)	68/219 (31.1)
Arterial hypertension, *n*/total (%)	193/219 (88.1)	204/219 (93.2)
Hyperlipoproteinemia, *n*/total (%)	100/218 (45.9)	80/217 (36.9)
Current smoking, *n*/total (%)	8/218 (3.7)	10/219 (4.6)
New York Heart Association class, *n*/total (%)		
I	25/216 (11.6)	17/218 (7.8)
II	50/216 (23.2)	56/218 (25.7)
III	122/216 (56.5)	130/218 (59.6)
IV	19/216 (8.8)	15/218 (6.9)
Baseline echocardiographic findings		
Aortic valve area (cm^2), median (IQR)	0.7 (0.6–0.9)	0.8 (0.6–0.9)
Mean aortic valve gradient (mmHg), median (IQR)	38.5 (30.0–50.5)	37.0 (26.5–47.5)
≥40 mmHg, *n*/total (%)	91/192 (52.6)	86/196 (43.9)
Left ventricular ejection fraction, *n*/total (%)		
>55%	120/211 (56.9)	119/208 (57.2)
45–55%	58/211 (27.5)	52/208 (25.0)
35–44%	21/211 (10.0)	18/208 (8.7)
<35%	12/211 (5.7)	19/208 (9.1)
Quality of life EuroQoL 5D 5L, median (IQR)		
Mobility	2 (1–3)	2 (1–4)
Self-care	1 (1–2)	1 (1–2)
Usual activities	2 (1–3)	2 (1–3)
Pain	2 (1–3)	3 (1–3)
Anxiety	1 (1–2)	1 (1–2)
VAS	60 (50–75)	60 (50–75)
Index	0.81 (0.68–0.91)	0.81 (0.60–0.91)

CABG, coronary artery bypass grafting; IQR, interquartile range; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; VAS, visual analogue scale.

Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System—Randomized Clinical Evaluation) trial (*n* = 912), all-cause mortality, disabling stroke, and moderate to severe PVL showed non-inferiority between both valve types.[9,10] However, significantly more permanent pacemaker implantations were required with the mechanical expanding valve. In the current trial, permanent pacemaker implantation was added to the composite endpoint because of its clinical relevance. An equivalence design was

Table 2 Procedural characteristics

	Self-expanding valve (Evolut R) ($n = 219$)	Balloon-expandable valve (Sapien 3) ($n = 219$)	*P*-value
Transoesophageal echocardiography, *n*/total (%)	41/214 (19.2)	38/213 (17.8)	0.73
Catecholamines, *n*/total (%)			
Norepinephrine	114/219 (52.1)	115/219 (52.5)	0.93
Epinephrine	19/219 (8.7)	18/219 (8.2)	0.86
Dobutamine	1/219 (0.5)	2/219 (0.9)	0.56
Duration of anaesthesia (min), median (IQR)	134 (110–155)	125 (102–154)	0.57
Anaesthesia type, *n*/total (%)			
Local anaesthesia	107/219 (48.9)	111/219 (50.7)	0.70
General anaesthesia	112/219 (51.1)	108/219 (49.3)	0.70
Final gradient after TAVI			
Invasive peak-to-peak (mmHg), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.52
Invasive mean (mmHg), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.31
≥20 mmHg after one day at TOE, *n*/total (%)	2/185 (1.1%)	7/189 (3.7%)	0.17
≥20 mmHg after one month at TOE, *n*/total (%)	3/154 (2.0%)	10/159 (3.3%)	0.09
Device time (min), median (IQR)	57 (44–69)	57 (43–73)	0.80
Total procedural time (min), median (IQR)	110 (86–142)	107 (85–135)	0.40
Fluoroscopy time (min), median (IQR)	12 (9–16)	11 (8–15)	0.02
Contrast agent (ml), median (IQR)	110 (90–130)	90 (80–105)	<0.001
Major vascular complication, *n*/total (%)	11/218 (5.1)	14/219 (6.4)	0.54
Access site percutaneous closure device failure, *n*/total (%)	15/217 (6.9)	12/217 (5.5)	0.55
Life-threatening or disabling bleeding, *n*/total (%)	3/218 (1.4)	9/219 (4.1)	0.08
Major bleeding, *n*/total (%)	5/218 (2.3)	7/218 (3.2)	0.56
Time to echocardiography (days), median (IQR)	34.5 (27–55)	34 (28–50)	0.95

IQR, interquartile range; TAVI, transcatheter aortic valve implantation.

chosen because both newer generation valves were considered to have similar performance for the combined clinical endpoint.[13]

In addition to the above-mentioned two randomized trials, there are two registry-based trials with propensity matching to assess possible differences with SEV vs. BEV in 408 and 12 381 patients.[8,21] Therefore, the present randomized study significantly adds to the body of evidence of newer generation SEV vs. BEV by showing equivalence for a combined clinical endpoint consisting of four clinically relevant components. Currently, one other randomized trial has recently been published. In the SCOPE I trial, the SEV ACURATE neo did not show non-inferiority in comparison to the BAV Sapien 3 valve using a modified combined 30-day early safety and clinical efficacy endpoint. Results were mainly driven by higher rates of acute kidney injury and more PVL in the ACURATE neo SEV arm.[22] Furthermore, the SCOPE II trial (NCT03192813) compares the SEV ACURATE neo with the CoreValve Evolut R with respect to the primary composite endpoint of all-cause mortality or stroke at 1-year follow-up. This trial also has a non-inferiority design.

The lack of any difference in 30-day mortality rates between both valve types comes to no surprise based on the two previous randomized trials.[9,10] Interestingly, the 30-day all-cause mortality was low despite inclusion of a high-risk population and lower than in the CENTER matched comparison which also showed no difference in 30-day mortality between SEV and BEV.[8]

The low rate of moderate or severe PVL is in line with the expected rates based on registry studies of these new generation devices.[14,15,23] Moderate or severe PVL has been associated with an increased risk of mortality.[24] Therefore, PVL was included in the primary endpoint and was carefully assessed by a core lab. PVL can be a result of (i) under-sizing, (ii) malpositioning, or (iii) lack of a sealing zone due to calcification or irregularities from compression of the native valve. The advent of new sealing mechanisms in these new generation devices addresses the latter mechanism which led to a significant improvement in comparison to the first-generation comparison in the CHOICE trial.[9] The latest development in the CoreValve family (Evolut R Pro) has an additional external pericardial wrap to enhance annular sealing. However, no direct valve comparisons are available for this new device and PVL rates were similar to other devices and historical comparisons.[25]

Aortic valve area was increased and transvalvular pressure gradients were decreased with both valve types. However, gradients were smaller with the SEV because the leaflets reside in a less constrained supra-annular location. This is the reason why the secondary endpoint time-related safety according to VARC-2 criteria did not meet equivalence. The same finding has recently been observed in the low-risk trials comparing TAVI vs. conventional SAVR where the SEV Evolut R had larger valve area in comparison to surgical valves, whereas the BEV Sapien 3 valve had smaller valve areas in

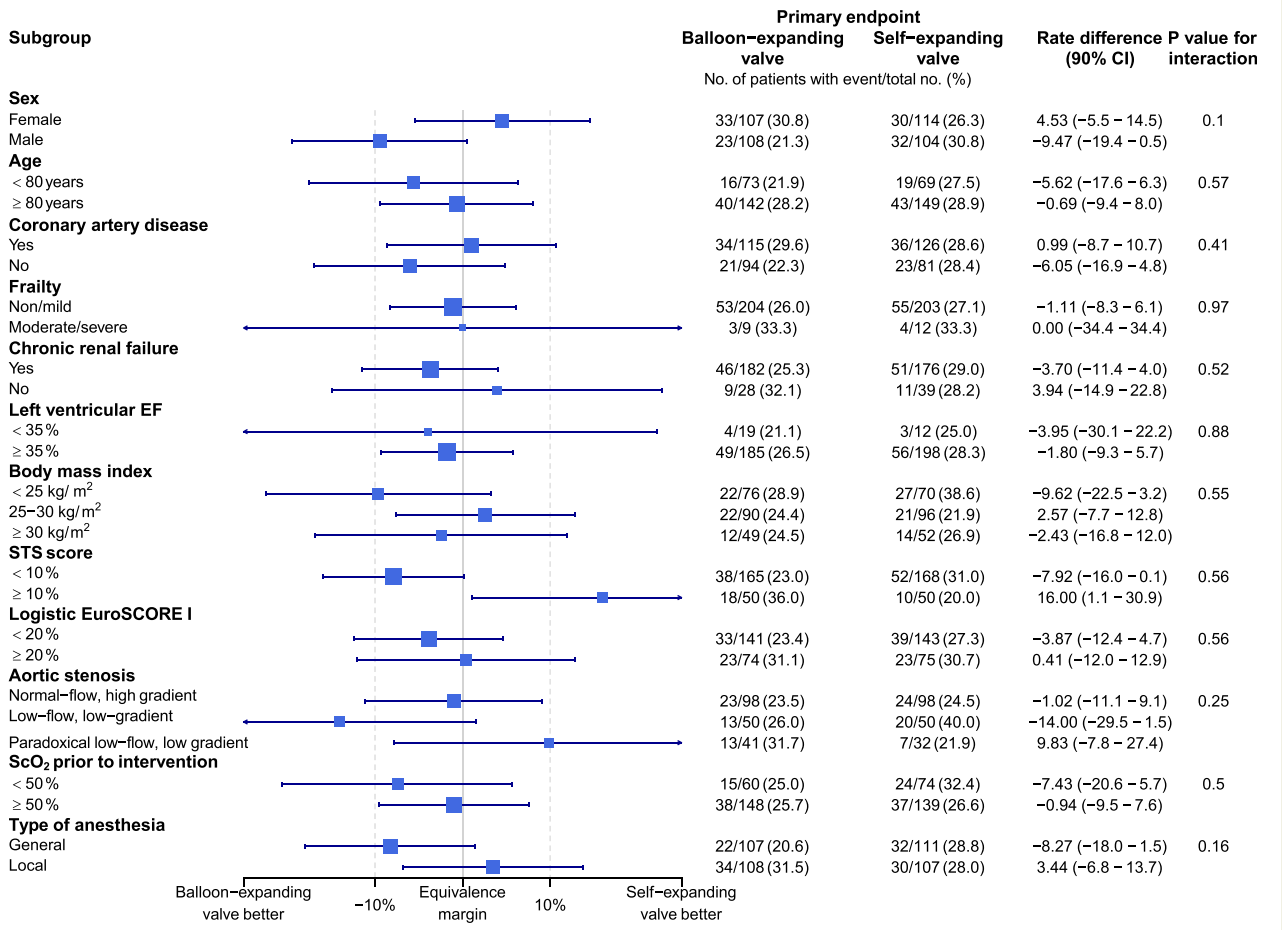


Figure 2 Forest plot for predefined subgroup analyses. EF, ejection fraction; ScO_2, saturation cerebral oxygen at start of TAVI procedure; STS, Society of Thoracic Surgeons.

Table 3 Primary endpoint and its components

	Self-expanding valve (Evolut R)	Balloon-expandable valve (Sapien 3)	Rate difference (90% CI)	*P*-value equivalence
Composite primary endpoint,[a] % (*n*/total)	28.4 (62/218)	25.9 (56/216)	-2.51 (-9.56 to 4.53)	0.04
All-cause mortality, % (*n*/total)	3.2 (7/217)	2.3 (5/219)	-0.94 (-4.79 to 2.91)	<0.0001
Stroke, % (*n*/total)	0.5 (1/210)	4.7 (10/214)	4.2 (0.11 to 8.28)	0.003
Moderate or severe prosthetic valve regurgitation,[b] % (*n*/total)	3.4 (7/208)	1.5 (3/207)	-1.92 (-5.88 to 2.05)	0.0002
Permanent pacemaker, % (*n*/total)	23.0 (49/213)	19.2 (41/214)	-3.85 (-10.4 to 2.72)	0.06

Results are displayed for the prespecified hierarchical testing against the equivalence margin 10% for the primary endpoint and its components.
[a]Composite of all-cause mortality, stroke, moderate or severe prosthetic valve regurgitation; permanent pacemaker implantation at 30-day follow-up.
[b]Moderate or severe paravalvular leak (PVL) based on core laboratory assessment.

comparison to surgical valves.[2,3] The long-term effect of haemodynamic differences between the SEV and BEV is unknown and the planned long-term follow-up will help elucidate this.

Stroke rates differ in TAVI trials mainly based on different patient cohorts and also intensity of follow-up and also if assessment by neurologists is performed. In the current trial, stroke rates were numerically higher with BEV compared with SEV without reaching statistical significance in superiority testing. However, overall stroke rates in the SEV group were extremely low and much lower than reported in some high-risk studies, whereas the stroke rates in the BEV group were also in the lower range of these trials (range 6–10%).[26–28] Previous randomized trials did not

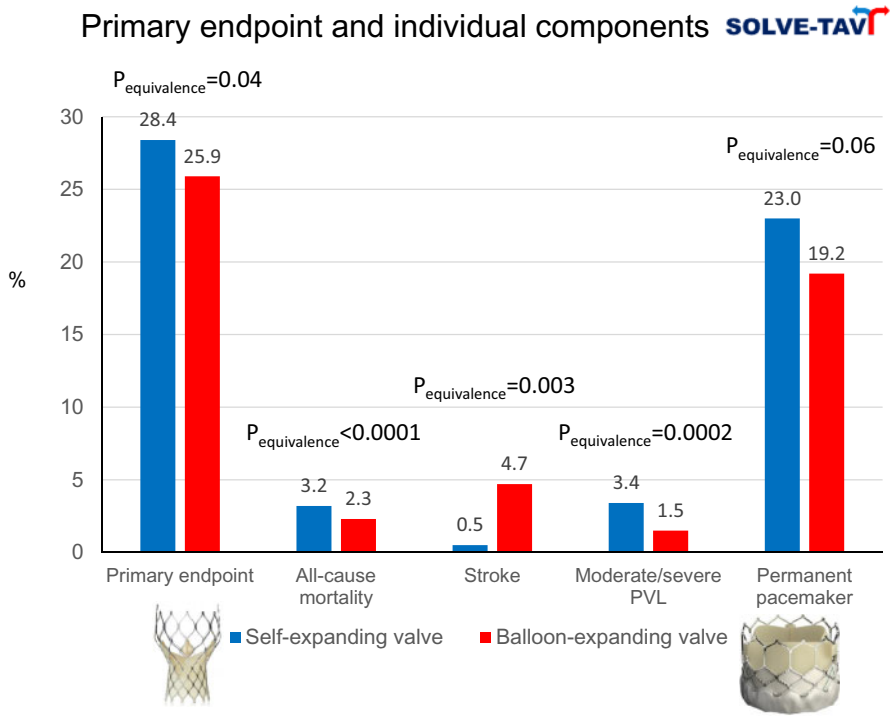
Table 4 Clinical outcome at 30 days for other clinical endpoints

	Self-expanding valve (Evolut R)	Balloon-expandable valve (Sapien 3)	Rate difference (90% CI)
Indication for permanent pacemaker			
AV block III.°, % (*n*/total)	14.7 (32/218)	11.4 (25/219)	-3.26 (-8.81 to 2.28)
AV block II.° type Mobitz, % (*n*/total)	0.46 (1/ 218)	1.83 (4/219)	1.37 (-2.26 to 4.99)
AV block II.° type Wenckebach, % (*n*/total)	0.46 (1/218)	0.46 (1/219)	0 (-3.42 to 3.41)
AV block I.°, % (*n*/total)	2.75 (6/218)	4.11 (9/219)	1.36 (-2.64 to 5.35)
Left bundle branch block, % (*n*/total)	6.88 (15/218)	6.39 (14/219)	-0.49 (-4.98 to 4.00)
Sinus node arrest/higher degree SA-block, % (*n*/total)	0.92 (2/218)	0.91 (2/219)	0 (-3.49 to 3.49)
Bradyarrhythmias, % (*n*/total)	3.67 (8/218)	3.2 (7/219)	-0.47 (-4.41 to 3.46)
Valve-related outcome according to VARC-2 criteria[a,12]			
Device success, % (*n*/total)	93.6 (189/202)	91.0 (183/201)	2.52 (-2.42 to 7.45)
Early safety, % (*n*/total)	11.9 (26/219)	16.0 (35/219)	4.11 (-1.57 to 9.79)
Clinical efficacy, % (*n*/total)	33.8 (74/219)	37.0 (81/219)	-3.20 (-10.7 to 4.30)
Time-related safety, % (*n*/total)	17.8 (39/219)	26.0 (57/219)	8.22 (1.62 to 14.8)
Acute kidney injury[b], % (*n*/total)	9.39 (20/213)	8.84 (19/215)	-0.55 (-5.50 to 4.39)
Delirium at 24 h or 48 h[c], % (*n*/total)	10.4 (22/212)	13.6 (29/214)	3.22 (-2.24 to 8.69)
Need for inotropes, % (*n*/total)	78.5 (172/219)	80.4 (176/219)	-1.83 (-8.24 to 4.59)
Need for vasopressors, % (*n*/total)	79 (173/219)	80.8 (177/219)	-1.83 (-8.20 to 4.54)
Need for inotropes or vasopressors, % (*n*/total)	79 (173/219)	81.3 (178/219)	-2.28 (-8.63 to 4.07)

[a]Device success according to VARC-2 criteria[12]: absence of procedural mortality AND correct positioning of a single prosthetic heart valve into the proper anatomical location AND intended performance of the prosthetic heart valve (no prosthesis–patient mismatch) and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation. Early safety according to VARC-2 criteria[12]: composite of all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury (Stage 2 or 3, including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure. Clinical efficacy according to VARC-2 criteria[12]: composite of all-cause mortality, all stroke (disabling and non-disabling), requiring hospitalizations for valve-related symptoms or worsening congestive heart failure, New York Heart Association (NYHA) Class III or IV, valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area (EOA) ≤0.9–1.1 cm^2 and/or Doppler velocity index (DVI) <0.35 m/s, and/or moderate or severe prosthetic valve regurgitation). Time-related safety according to VARC-2 criteria[12]: structural valve deterioration such as valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9–1.1 cm^2 and/or DVI <0.35 m/s), and/or moderate or severe prosthetic valve regurgitation requiring repeat procedure, prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g. stroke), bleeding, unless clearly unrelated to valve therapy (e.g. trauma).
[b]Acute kidney injury according to VARC-2 criteria Stage 2 or 3.[12]
[c]Delirium assessed by Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) criteria.[16]

find differences in stroke rates between different valve types.[9,10] In contrast, the CENTER large-scale, propensity-matched study observed lower stroke rates with BEV compared with SEV and hypothesized that the implantation mechanism of SEV may generate more periprocedural strokes.[8] Therefore, the current finding may also be a chance finding. Intraprocedural strokes are potentially modifiable by the use of cerebral embolic protection devices. In a recent individual-patient-based meta-analysis using propensity matching cerebral embolic protection reduced stroke rates (1.9% vs. 5.4%, $P = 0.0028$).[29] Future studies are needed to characterize the adoption of cerebral embolic protection during TAVI in clinical practice and its effect on clinical outcome. Cerebral embolic protection was not used on a routine basis in the current trial and use of these devices was not systematically assessed in case report forms.

Initial results of these new valve designs suggested that implantation of these new devices is associated with a much lower need for permanent pacemaker implantation. Pacemaker implantation in patients treated with Evolut R was at 16.4% in an early registry and 18.1% in the recent CENTER registry, whereas in the same registry Sapien 3 had a pacemaker rate of only 8.9%. Similar results have been observed in the recent intermediate and low-risk trials comparing TAVI vs. SAVR (Evolut R 17.4% and Sapien 3 8.5% and 6.6%, respectively).[2,3,30] In a recent systematic review, the SEV Evolut R and the BEV Sapien 3 required pacemaker implantation in a range of 14.7–26.7% and 4.0–24.0%, respectively.[4] Thus, the pacemaker implantation rate in SOLVE-TAVI is in the upper range of previously reported trials and registries. There were no differences in the indication for pacemaker implantation in both groups and it may be speculated that in some centres a more liberal indication has been applied for patients with long AV-block I.° and new left bundle branch block. Implantation depth and anatomical factors with more severe calcification may also have contributed to the relatively high pacemaker rate. Furthermore, implantation depth, need for additional balloon valvuloplasty, balloon and prosthesis size are well-known factors for pacemaker implantation which may be reduced with a further learning curve. In general, pacemaker implantation is associated with increased costs, longer hospital stay, and possibly patient morbidity. However, to date, it has not been associated with increased mortality.[4]



Take home figure Primary endpoint and components of the primary endpoint of the SOLVE-TAVI valve strategy comparison. PVL, paravalvular leakage.

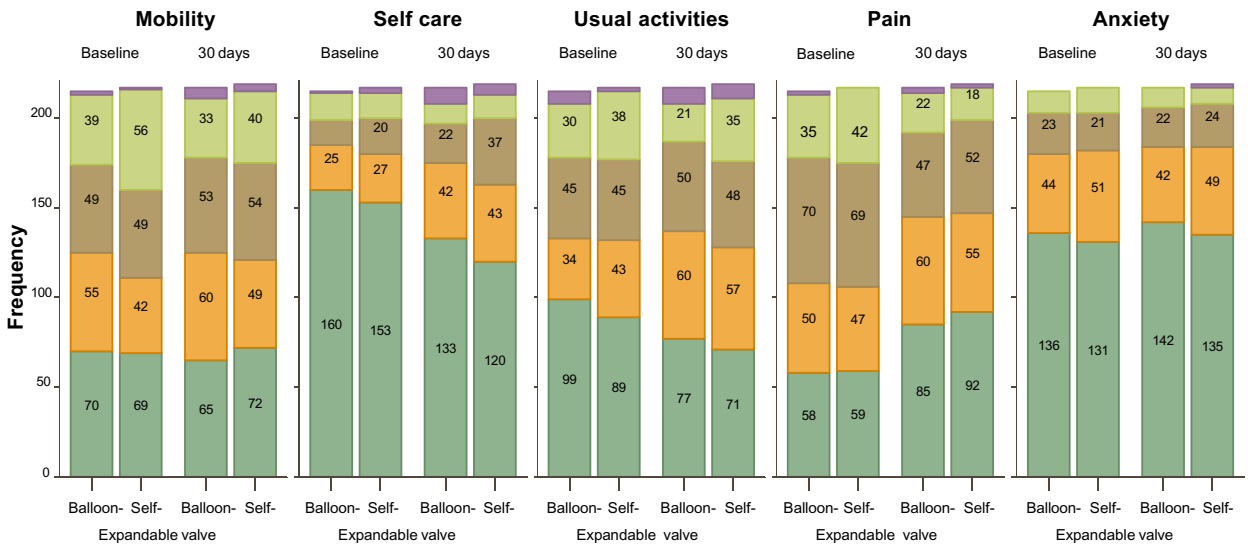


Figure 3 Quality of life for the five dimensions of the EuroQol 5D questionnaire at baseline and 30-day follow-up on 5-point Likert scales starting from no constraints (bottom bar) for self-expanding and balloon-expandable valve groups. Dark green, no constraints; Brown, slight constraints; Orange, moderate constraints; Light green, severe constraints; Purple, extreme constraints or unable to do.

Bleeding rates and access site complications were low and similar between both valve types. This is in contrast to the CENTER evaluation where patients treated with new generation BEV more often suffered from major or life-threatening bleedings than patients with new generation SEV.[8] The early generation Edwards SAPIEN valve and also the first-generation CoreValve required large sheath sizes (22 Fr/24 Fr) which has been reduced to 14 Fr/16 Fr with the newest generation as used in the current trial.

This trial like all trials has some limitations. First, blinding was not possible due to the different valves chosen. Second, the present study included mainly high-risk patients undergoing TAVI. Therefore, the impact of the two different valve types on outcome in lower-risk cohorts cannot be extrapolated. Third, cerebral protection devices have not been used on a routine basis and no additional information on cerebral protection has been collected in the case report forms. Fourth, this trial was powered to show equivalence between both treatment groups for the composite clinical endpoint only.[13] Thus, the individual endpoints are not powered to show equivalence. The chosen equivalence margin of 10% was considered clinically meaningful but is surely considered by others too large for claiming equivalence in particular for the individual components of the primary endpoint and all other secondary endpoints. Finally, although the vast majority of patients can be successfully treated by either valve type from the present study, valve choice should take into account individual factors in which a specific valve type might be favoured (e.g. severe calcification, bicuspid anatomy, horizontal aorta, or the requirement of uncomplicated coronary access).

Conclusions

Among high-risk patients with aortic stenosis, new generation SEV in comparison to BEV are equivalent with respect to the composite of all-cause mortality, stroke, permanent pacemaker implantation, and PVL. These findings support the safe application of these newer generation percutaneous valves which may be chosen on a general basis in the majority of patients with some specific preferences based on individual valve anatomy.

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