European Heart Journal (2016) **37**, 2252–2262
doi:10.1093/eurheartj/ehw112

Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis

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Received 25 January 2016; revised 17 February 2016; accepted 23 February 2016; online publish-ahead-of-print 31 March 2016

Aims Based on randomized trials using first-generation devices, transcatheter aortic valve replacement (TAVR) is well established in the treatment of high-risk (HR) patients with severe aortic stenosis (AS). To date, there is a paucity of adjudicated, prospective data evaluating outcomes with newer generation devices and in lower risk patients. We report early outcomes of a large, multicentre registry of inoperable, HR, and intermediate-risk (IR) patients undergoing treatment with the next-generation SAPIEN 3 transcatheter heart valve (THV).

Methods and results Patients with severe, symptomatic AS (583 high surgical risk or inoperable and 1078 IR) were enrolled in a multicentre, non-randomized registry at 57 sites in the USA and Canada. All patients received TAVR with the SAPIEN 3 system via transfemoral ($n = 1443$, 86.9%) and transapical or transaortic ($n = 218$, 13.1%) access routes. The rate of 30-day all-cause mortality was 2.2% in HR/inoperable patients [mean Society of Thoracic Surgeons (STS) score 8.7%] and 1.1% in IR patients (mean STS score 5.3%); cardiovascular mortality was 1.4 and 0.9%, respectively. In HR/inoperable patients, the 30-day rate of major/disabling stroke was 0.9%, major bleeding 14.0%, major vascular complications 5.1%, and requirement for permanent pacemaker 13.3%. In IR patients, the 30-day rate of major/disabling stroke was 1.0%, major bleeding 10.6%, major vascular complications 6.1%, and requirement for permanent pacemaker 10.1%. Mean overall Kansas City Cardiomyopathy Questionnaire score increased from 47.8 to 67.8 (HR/inoperable, $P < 0.0001$) and 54.7 to 74.0 (IR, $P < 0.0001$). Overall, paravalvular regurgitation at 30 days was none/trace in 55.9% of patients, mild in 40.7%, moderate in 3.4%, and severe in 0.0%. Mean gradients among patients with paired baseline and 30-day or discharge echocardiograms decreased from 45.8 mmHg at baseline to 11.4 mmHg at 30 days, while aortic valve area increased from 0.69 to 1.67 cm^2.

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Conclusions The SAPIEN 3 THV system was associated with low rates of 30-day mortality and major/disabling stroke as well as low rates of moderate or severe paravalvular regurgitation.

Trial Registration ClinicalTrials.gov #NCT01314313.

Keywords Transcatheter aortic valve replacement • TAVR • TAVI

Background

Based on randomized trials using the first-generation devices, transcatheter aortic valve replacement (TAVR) has been found superior to medical treatment in inoperable patients with aortic stenosis (AS) and at least equivalent to surgical aortic valve replacement (SAVR) in high-risk (HR) surgical candidates.[1–6] Although SAVR remains the current standard of care in patients not considered high surgical risk,[7] emerging evidence suggests that equivalent outcomes may be achievable with TAVR in appropriately selected lower risk patients.[8,9] Currently, there is a paucity of prospective data evaluating outcomes with TAVR in lower risk patients with the latest generation TAVR systems.

Reducing complications is imperative if TAVR is to be applied to intermediate–risk (IR) patients. Although operator experience, patient selection, and pre-procedural imaging are important in improving outcomes with TAVR,[10–12] many complications of TAVR may relate directly to device technology. Consequently, the development of the next-generation devices is critical, especially in evaluating the use of TAVR in lower risk populations, wherein excellent clinical outcomes after SAVR are expected.

We report early outcomes of a large, multicentre registry of inoperable, HR and IR patients undergoing TAVR with the new-generation SAPIEN 3 transcatheter heart valve (THV).

Methods

Study design and patient selection

The Placement of Aortic Transcatheter Valves (PARTNER) II SAPIEN 3 trial was a prospective, multicentre study which enrolled patients with symptomatic (New York Heart Association functional class II or greater), severe AS who were either inoperable/HR or at IR of operative mortality with SAVR. Severe AS was defined as an aortic valve area (AVA) $\leq$0.8 cm^2 or indexed AVA $<$0.5 cm^2/m^2 and a mean gradient $>$40 mmHg or peak velocity $>$4 m/s. While the study definition of severe AS differs somewhat from that published in the most recent AHA/ACC and ESC guidelines, both guidelines specifically note that an AVA of 0.8 cm^2 correlates better with a maximum velocity of 4 m/s and mean gradient of $>$40 mmHg, when compared with a cut-off of 1 cm^2. This has been well described in the work of Minners *et al.*,[13] and supports the use of 0.8 cm^2 as a more consistent and haemodynamically relevant definition. Furthermore, this stricter definition is consistent with previously published major randomized studies.[1,2,5] Operative risk was determined by Heart Team evaluation, including one cardiac surgeon and one interventional cardiologist. Patients were deemed HR or inoperable if the Society of Thoracic Surgeons (STS) risk score was $>$8% or the Heart Team considered the patient to be HR or inoperable for clinical reasons. Patients were deemed IR either based on the assessment of the Heart Team or if the STS score was between 4 and 8%. All patients received a comprehensive frailty assessment, which included 5 m walk, grip strength, Katz activities of daily living, and serum albumin. Patients were deemed frail if they met three of four criteria. Initially, three-dimensional (3D) imaging of the aortic annulus [either multi-detector computed tomography (MDCT) or 3D transoesophageal echocardiography (TEE)] was recommended prior to treatment. After enrolment of the HR/inoperable cohort, which was sized by site-determined methods, all IR patients had mandated MDCT analysis by the study core laboratory prior to treatment. All patients were presented on a conference call where a screening committee reviewed imaging and clinical data before enrolment in the registry. The Institutional Review Board of all participating sites approved the trial and all patients provided written informed consent.

Key exclusion criteria were a congenitally bicuspid aortic valve, severe aortic regurgitation, a prior prosthetic valve in any position, left ventricular ejection fraction $<$20%, stroke or transient ischaemic attack within 6 months, myocardial infarction within 1 month, upper gastrointestinal bleeding within 3 months, severe renal insufficiency (creatinine $>$3.0 mg/dL or dialysis dependent), and estimated life expectancy $<$2 years. Patients with left main or multivessel coronary disease with Syntax score $\geq$32 were excluded. Patients with less severe but untreated significant coronary disease could be enrolled if a treatment plan for the coronary disease was agreed upon prior to enrolment. The complete list of inclusion and exclusion criteria is shown in Supplementary material online, Appendix.

Procedure

The Edwards SAPIEN 3 balloon-expandable THV consists of bovine pericardial leaflets sutured to a cobalt chromium frame (*Figure 1*). An important component is a polyethylene terephthalate skirt that covers the lower portion of the frame, designed specifically to reduce paravalvular leak (PVL). The THV system is delivered through expandable 14- (20, 23, and 26 mm THV) or 16-Fr (29 mm THV) transfemoral (TF) delivery sheaths which expand to accommodate the device. The SAPIEN 3 THV can also be delivered via direct transaortic (TAo) or transapical (TA) routes. Procedures were performed via TF, TA, or TAo access, depending on pre-procedural vascular assessment. Patients were required to have an aortic annular area between 273 and 680 mm^2, appropriate for treatment with a 20, 23, 26, or 29 mm SAPIEN 3 THV. Pre-procedural sizing was performed on the basis of systolic measurements of annular area from MDCT or three-dimensional TEE. During the course of the study, recommendations for sizing and valve positioning were changed whereby less oversizing (5–10% by annular area) and a higher deployment position was recommended. Following the procedure, treatment with aspirin and clopidogrel was recommended for 6 months. In the case of pre-existing oral anticoagulation therapy, either aspirin or clopidogrel could be discontinued at the discretion of the treating physician.

Oversight and data management

The trial was designed collaboratively by the sponsor (Edward Lifesciences, Irvine, CA, USA) and members of the executive steering

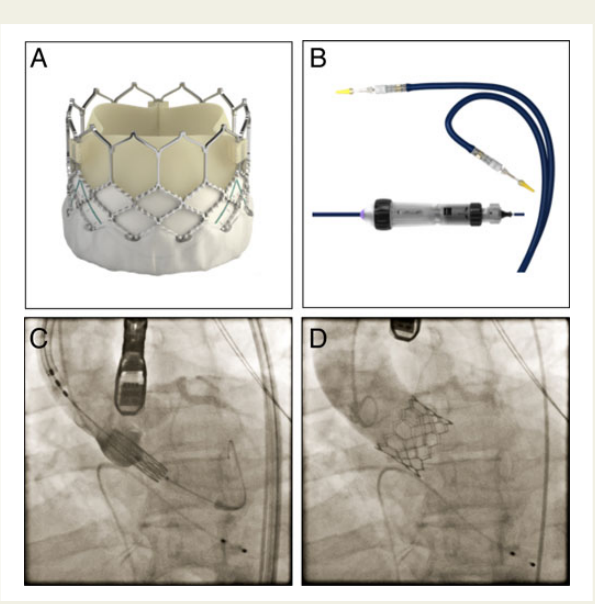

Figure 1 The SAPIEN 3 transcatheter heart valve. The SAPIEN 3 is a balloon-expandable transcatheter heart valve that consists of bovine pericardial leaflets sutured to a cobalt chromium frame with a polyethylene terephthalate skirt covering the inflow potion of the frame (*A*). The valve is available in 20, 23, 26, and 29 mm sizes and is compatible with a 14- or 16-Fr transfemoral delivery system (*B*). The valve is deployed in an intra-annular position via balloon inflation (*C* and *D*).

committee. The sponsor funded the study, participated in the selection and management of sites, and monitored the data. The first author and co-principal investigators had unrestricted access to the data after the database was locked, prepared all drafts of the manuscript, and made the final decision to submit the manuscript. Data analysis was performed by independent statisticians at the Cardiovascular Research Foundation. The sponsor had no role in data analysis, drafting of the manuscript, or in the decision to publish.

Clinical assessments were performed at baseline and at 30 days, and included formal examination by a neurologist. Serial echocardiographic follow-up was performed immediately following implant (intra-procedural), within 24 h of hospital discharge, and at 30 days. A consortium of echocardiography core laboratories analysed all echocardiography independently. Clinical events were independently adjudicated by a clinical events committee and a data and safety monitoring board reviewed all adverse events.

Clinical outcomes

Stroke is reported according to modified VARC-2 definitions utilizing either a 30- or 90-day modified Rankin score to allow comparability with the surgical arm of the PARTNER IIA study. All other relevant clinical outcomes are reported according to VARC-2 endpoint definitions. Pre-procedure echocardiography assessments were compared with 30-day studies, with particular attention to aortic valve haemodynamics and PVL. If the 30-day study was not available, the pre-discharge study was analysed.

Statistical analysis

An as-treated analysis was performed which included all patients entering the procedure room for the TAVR. Echocardiographic analyses utilize the valve implant population (i.e. those who actually received the valve). Categorical variables were summarized as percentages while continuous variables were reported as mean $\pm$ standard deviation. Time-to-event variables are presented as Kaplan–Meier estimates, using all available follow-up. Statistical comparisons between baseline and 30-day values were conducted with the use of paired *t*-tests or McNemar's test, as appropriate.

Results

Between October 2013 and February 2014, 583 inoperable/HR patients were enrolled at 29 implanting sites and between February 2014 and December 2014, 1078 IR patients were enrolled at 51 sites in the USA and Canada. One HR patient died before entering the procedure room.

Patient characteristics

The mean age of HR patients was 82.7 $\pm$ 8.1 years, 58.0% were male, and the mean STS score was 8.7 $\pm$ 3.7%. Frailty criteria were met by 30.9% of the HR patients. In this cohort, 64.7% were characterized as HR, the remainder as inoperable. The mean age of IR patients was 81.9 $\pm$ 6.6 years, 61.8% were male, and the mean STS score was 5.3 $\pm$ 1.3%. Of the IR patients, 8.9% had an STS score $<$4%. Other baseline characteristics of both cohorts are shown in *Table 1*.

Procedural factors

Transfemoral access was used in 84.2% of HR patients and 88.3% of IR patients. The distribution of THV sizes was 3.2% (20 mm), 32.9% (23 mm), 42.1% (26 mm), and 21.7% (29 mm). In the combined population ($n = 1661$), monitored anaesthesia care was used in 257 (15.5%) and percutaneous closure was used in 1329 (80.3%). Overall, post-dilatation was performed in 208 (12.5%), valve embolization occurred in 2 (0.1%), annular rupture in 2 (0.1%), and more than one THV was required in 9 (0.5%) patients. Six patients (one HR patient and five IR patients) required conversion to open surgery, for valve embolization (two patients), annular rupture (two patients), left atrial appendage thrombus (one patient), and a low-lying right coronary artery (one patient). Procedural mortality was 1.0% (six patients) in HR and 0.5% (five patients) in IR cohorts. The median length of hospital stay was 3 days (interquartile range, IQR 2–6 days) for HR patients and 3 days (IQR 2–4 days) for IR patients. Other procedural characteristics are shown in *Table 2*.

30-day clinical outcomes

Table 3 summarizes the 30-day clinical event rates by cohort. Two patients in the IR cohort were lost to follow-up. The rate [95% CI] of 30-day all-cause mortality was 2.2% [0.0, 3.4] in HR patients and 1.1% [0.0, 1.7] in IR patients. The rate of 30-day cardiovascular death was 1.4% (HR) [0.0, 2.3] and 0.9% (IR) [0.0, 1.5]. In HR patients, all-cause mortality was 1.6% [0.0, 2.7] for TF and 5.4% [0.0, 10.1] for non-TF patients. In the IR cohort, all-cause mortality was 1.1% [0.0, 1.7] for TF and 1.6% [0.6, 3.8] for non-TF patients.

Repeat hospitalization occurred by 30 days in 8.0% of HR patients and 4.6% of IR patients. The rate of all strokes at 30 days was 1.4% (HR) and 2.7% (IR). The rate of major/disabling stroke (modified Rankin score $\geq$2 at 30 days) was 0.9% (HR) and 1.0% (IR). At

Table 1 Baseline characteristics[a]

Characteristic	HR/inoperable (*N* = 583)	Intermediate risk (*N* = 1078)	*P*-value
Age (years)	82.7 ± 8.1	81.9 ± 6.6	0.07
Male sex, *n*/*N* (%)	338/583 (58.0)	666/1078 (61.8)	0.13
STS score[b]	8.7 ± 3.7	5.3 ± 1.3	<0.0001
Logistic EuroSCORE II[c]	8.6 ± 7.1	5.4 ± 4.5	<0.0001
NYHA class, *n*/*N* (%)			
II	58/583 (9.9)	294/1077 (27.5)	<0.0001
III or IV	525/583 (90.1)	781/1077 (72.5)	<0.0001
Coronary artery disease, *n*/*N* (%)	444/583 (76.2)	751/1078 (69.7)	0.005
Previous myocardial infarction, *n*/*N* (%)	117/583 (20.1)	172/1078 (16.0)	0.03
Previous cardiac intervention, *n*/*N* (%)			
CABG	193/583 (33.1)	301/1078 (27.9)	0.03
PCI	199/583 (34.1)	345/1078 (32.0)	0.38
Balloon aortic valvuloplasty	62/583 (10.6)	55/1078 (5.1)	<0.0001
Previous stroke, *n*/*N* (%)	64/583 (11.0)	97/1078 (9.0)	0.19
Peripheral vascular disease, *n*/*N* (%)	205/583 (35.2)	304/1078 (28.2)	0.003
Diabetes	201/583 (34.5)	367/1078 (34.0)	0.12
COPD, *n*/*N* (%)			
Any	259/581 (44.6)	322/1076 (29.9)	<0.0001
Oxygen dependent	68/581 (11.7)	54/1076 (5.0)	0.006
Creatinine >2 mg/dL (177 μmol/L), *n*/*N* (%)	70/583 (12.0)	82/1078 (7.6)	0.003
Atrial fibrillation, *n*/*N* (%)	255/583 (43.7)	389/1078 (36.1)	0.002
Permanent pacemaker, *n*/*N* (%)	95/583 (16.3)	143/1078 (13.3)	0.09
Severe pulmonary hypertension, *n*/*N* (%)	30/583 (5.1)	25/1078 (2.3)	0.002
Frailty, *n*/*N* (%)	180/583 (30.9)	92/1078 (8.5)	<0.0001
Porcelain aorta, *n*/*N* (%)	25/583 (4.3)	1/1078 (0.1)	<0.0001
Previous chest radiation, *n*/*N* (%)	9/583 (1.5)	8/1078 (0.7)	0.12
Chest wall deformity, *n*/*N* (%)	4/583 (0.7)	1/1076 (0.1)	0.054
Liver disease, *n*/*N* (%)	13/583 (2.2)	8/1078 (0.7)	0.002

[a]Plus–minus values are means ± standard deviation. CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.
[b]The STS score estimates the risk of 30-day mortality following cardiac surgery and ranges from 0 to 100%, with higher scores indicating higher predicted risk of mortality. An STS score of >8% indicates HR, 4–8% intermediate risk, and <4% low risk of 30-day mortality.
[c]The logistic EuroSCORE II (European System for Cardiac Operative Risk Evaluation) estimates the risk of operative mortality following cardiac surgery and ranges from 0 to 100%, with higher scores indicating higher predicted risk of mortality.

30 days, major bleeding had occurred in 14.0% (HR) and 10.6% (IR) and major vascular complications in 5.1% (HR) and 6.1% (IR). The rate of new permanent pacemaker was 13.3% in HR patients and 10.1% in IR patients. Outcomes based on access route for HR and IR cohorts are listed in *Tables 4* and *5*.

At baseline, the distribution of symptoms by NYHA functional class for the overall cohort was 0.0% (class I), 21.3% (II), 60.6% (III), and 18.1% (IV). At 30 days, functional class status was 52.5% (class I), 38.8% (II), 7.6% (III), and 1.1% (IV). Patient symptoms improved from baseline to 30 days in both cohorts (*Figure 2*). From baseline to 30 days, mean 6 min walk test (6MWT) increased from 138.2 to 176.7 feet in HR patients ($P < 0.0001$) and from 197.0 to 231.3 feet in IR patients ($P < 0.0001$). Paired quality-of-life assessments at the same time points showed increases in mean overall Kansas City Cardiomyopathy Questionnaire score from 47.8 to 67.8 in HR patients ($P < 0.0001$) and from 54.7 to 74.0 in IR patients ($P < 0.0001$).

30-day echocardiography outcomes

There were no significant differences in the baseline echocardiographic findings when HR and IR cohorts were compared. Thirty-day (or pre-discharge) echocardiographic evaluation was performed in 1597/1661 (96.1%) of patients. The pooled baseline and 30-day echocardiographic outcomes of both HR and IR cohorts are shown in *Table 6*. Overall, the mean AVA increased from 0.69 ± 0.17 to 1.67 ± 0.38 cm^2 ($P < 0.0001$) from baseline to 30 days. All THV sizes showed an increase in AVA from baseline to 30 days with the most significant proportional increase in AVA seen in larger valve sizes (*Figure 3A*, $P < 0.0001$ for trend). The overall mean gradient decreased from 45.8 ± 13.2 mmHg at baseline to

Table 2 Procedural characteristics and outcomes[a]

Characteristic	HR/inoperable (*N* = 583)	Intermediate risk (*N* = 1078)	Overall (*N* = 1661)
THV size			
20 mm	11/583 (1.9)	42/1073 (3.9)	53/1656 (3.2)
23 mm	200/583 (34.3)	345/1073 (32.2)	545/1656 (32.9)
26 mm	227/583 (38.9)	471/1073 (43.9)	698/1656 (42.1)
29 mm	145/583 (24.9)	215/1073 (20.0)	360/1656 (21.7)
Access			
Transfemoral	491/583 (84.2)	952/1078 (88.3)	1443/1661 (86.9)
Transapical	57/583 (9.8)	81/1078 (7.5)	138/1661 (8.3)
Transaortic	35/583 (6.0)	45/1078 (4.2)	80/1661 (4.8)
Monitored anaesthesia care	78/583 (13.4)	179/1076 (16.6)	257/1659 (15.5)
General anaesthesia	505/583 (86.6)	897/1076 (83.4)	1402/1659 (84.5)
Fluoroscopy time (min)	18.8 ± 10.1	19.3 ± 30.4	19.1 ± 25.2
Post-dilatation	86/583 (14.8)	122/1076 (11.3)	208/1659 (12.5)
Percutaneous closure	471/580 (81.2)	858/1075 (79.8)	1329/1655 (80.3)
Procedural death	4/583 (0.7)	2/1078 (0.2)	6/1661 (0.4)
Multiple valves implanted	5/583 (0.9)	4/1075 (0.4)	9/1658 (0.5)
Valve embolization	1/583 (0.2)	1/1078 (0.1)	2/1661 (0.1)
Coronary obstruction	1/583 (0.2)	4/1078 (0.4)	5/1661 (0.3)
Aortic rupture	0/583	2/1078 (0.2)	2/1661 (0.1)
Urgent cardiac surgery	1/583 (0.2)	5/1078 (0.5)	4/1661 (0.2)
IABP inserted	3/583 (0.5)	4/1076 (0.4)	7/1659 (0.4)
Cardiopulmonary bypass	13/583 (2.2)	10/1076 (0.9)	23/1659 (1.4)
Median hospital stay, days (IQR)	3 (2–6)	3 (2–4)	3 (2–5)

[a]Plus–minus values are means ± standard deviation. Duration of hospital stay is reported as median (interquartile range). All other values are reported as *n*/*N* (%). IABP, intra-aortic balloon pump; THV, transcatheter heart valve.

11.4 ± 4.8 mmHg at 30 days, with a similar proportional decrease in gradient seen when the overall cohort was stratified by THV size ($P < 0.0001$ for trend, *Figure 3B*). At 30 days, 55.9% of patients had no/trace PVL, 40.7% mild, 3.4% moderate, and no patients had severe PVL. No patients had more than mild transvalvular aortic regurgitation; 1.4% had mild, 98.6% had none/trace.

Discussion

Compared with previous SAPIEN THV clinical trials, the results of this study show that treatment of HR/inoperable and IR AS patients with the new SAPIEN 3 THV is associated with the following: (i) low rates of 30-day mortality, stroke, and repeat hospitalization; (ii) significant improvements in symptoms, quality of life, and functional status; (iii) low rates of procedural complications including aortic/annulus rupture, coronary occlusion, valve embolization, or valve-in-valve implants; (iv) low rates of significant aortic regurgitation; (v) higher than previously observed rate of new permanent pacemakers; (vi) shorter duration length of hospital stay.

The 30-day mortality reported in this study represents the lowest of any large TAVR registry and is a significant evolution in the field of TAVR.[14,15] Over the last 5 years, 30-day mortality has decreased significantly from 5.0% in early studies with the original SAPIEN THV to 1–2% in the current study with the new S3 THV.[1] Although the STS score for the HR cohort in this study was lower than that in the initial PARTNER I HR cohort, all patients were deemed to be HR due to the presence of factors not captured in the STS score, such as frailty. The apparent reductions in strokes, major vascular complications, life-threatening bleeding, and other acute procedural complications (e.g. annular rupture, coronary occlusion, and valve embolization), which contributed to early mortality in previous TAVR studies, are likely associated with the reduced mortality seen in this trial.

Several other factors are likely to have contributed to these excellent results, including but not limited to: operator experience, improved patient selection, and the systematic use of MDCT for vascular access and annulus sizing. In addition, iterative improvements in the THV, as well as the delivery catheter, have also played an important role. The very low bleeding and vascular complication rates are related to a large degree to the SAPIEN 3 THV expandable sheath with internal dimensions of 14- or 16-Fr. Furthermore, diminishing sheath size also expanded the population eligible for TF access. In this study, TF access was utilized in 87% of cases, the highest rate of TF access in a major valve trial to date. Transfemoral access allows faster recovery and shorter hospital stay than non-TF access; one recent analysis demonstrated the mortality benefit of TF access in a propensity-matched cohort.[16] Furthermore, TF access is associated with improved quality of life and functional status

Table 3 30-day clinical outcomes[a]

Outcome	HR/inoperable ($N = 583$)	Intermediate risk ($N = 1078$)
	No. of events (%) [95% CI]	
Death		
Any cause	13 (2.2) [1.0, 3.4]	12 (1.1) [0.5, 1.7]
Cardiovascular[b]	8 (1.4) [0.4, 2.3]	10 (0.9) [0.4, 1.5]
Repeat hospitalization	46 (8.0) [5.8, 10.2]	49 (4.6) [3.3, 5.8]
Stroke or TIA		
All	12 (2.1) [0.9, 3.2]	34 (3.2) [2.1, 4.2]
TIA	4 (0.7) [0.0, 1.4]	5 (0.5) [0.1, 0.9]
Stroke[c]	8 (1.4) [0.4, 2.3]	29 (2.7) [1.7, 3.7]
Major/disabling	5 (0.9) [0.1, 1.6]	11 (1.0) [0.4, 1.6]
Minor	3 (0.5) [0.0, 1.1]	18 (1.7) [0.9, 2.4]
Death or repeat hospitalization or major stroke	61 (10.5) [8.0, 12.9]	66 (6.1) [4.7, 7.6]
Myocardial infarction		
All	3 (0.5) [0.0, 1.1]	3 (0.3) [0.0, 0.6]
Periprocedural	1 (0.2) [0.0, 0.5]	3 (0.3) [0.0, 0.6]
Vascular complications		
All	75 (12.9) [10.1, 15.6]	131 (12.2) [10.2, 14.1]
Major	30 (5.1) [3.4, 6.9]	66 (6.1) [4.7, 7.6]
Acute kidney injury (VARC 2)		
Stage 1	40 (6.9) [4.8, 9.0]	41 (3.8) [2.7, 5.0]
Stage 2	4 (0.7) [0.0, 1.4]	10 (0.9) [0.4, 1.5]
Stage 3	6 (1.0) [0.2, 1.9]	5 (0.5) [0.1, 0.9]
Bleeding		
Life-threatening/ disabling	36 (10.2) [4.2, 8.1]	50 (4.6) [3.4, 5.9]
Major	81 (14.0) [11.1, 16.8]	114 (10.6) [8.8, 12.4]
New pacemaker	77 (13.3) [10.5, 16.1]	109 (10.1) [8.3, 12.0]

[a]All percentages are Kaplan–Meier estimates at 30 days and thus do not equal the number of events divided by the total number in the study group. TIA, transient ischaemic attack.
[b]Deaths from unknown cause were assumed to be from cardiovascular causes.
[c]Major/disabling stroke was defined as modified Rankin score ≥2.

Table 4 30-day clinical outcomes according to access approach: high risk/inoperable cohort ($N = 583$)[a]

Outcome	HR/inoperable transfemoral, $N = 491$	HR/inoperable transapical/TAo, $N = 92$
	No. of events (%) [95% CI]	
Death		
Any cause	8 (1.6) [0.5, 2.7]	5 (5.4) [0.8, 10.1]
Cardiovascular[b]	5 (1.0) [0.1, 1.9]	3 (3.3) [0.0, 6.9]
Repeat hospitalization	33 (6.8) [4.6, 9.0]	13 (14.3) [7.1, 21.5]
Stroke or TIA		
All	10 (2.0) [0.8, 3.3]	2 (2.2) [0.0, 5.2]
TIA	3 (0.6) [0.0, 1.3]	1 (1.1) [0.0, 3.2]
Stroke[c]	7 (1.4) [0.4, 2.5]	1 (1.1) [0.0, 3.2]
Major/disabling	4 (0.8) [0.0, 1.6]	1 (1.1) [0.0, 3.2]
Minor	3 (0.6) [0.0, 1.3]	0
Death or repeat hospitalization or major stroke	44 (9.0) [6.4, 11.5]	17 (18.5) [10.5, 26.4]
Myocardial infarction		
All	2 (0.4) [0.0, 1.0]	1 (1.1) [0.0, 3.2]
Periprocedural	0	1 (1.1) [0.0, 3.2]
Vascular complications		
All	68 (13.9) [10.8, 16.9]	7 (7.6) [2.2, 13.0]
Major	27 (5.5) [3.5, 7.5]	4 (4.4) [0.0, 6.9]
Acute kidney injury (VARC 2)		
Stage 1	28 (5.7) [3.7, 7.8]	12 (13.0) [6.2, 19.9]
Stage 2	2 (0.4) [0.0, 1.0]	2 (2.2) [0.0, 5.2]
Stage 3	4 (0.8) [0.0, 1.6]	2 (2.2) [0.0, 5.2]
Bleeding		
Life-threatening/ disabling	27 (5.5) [3.5, 7.5]	9 (9.8) [3.7, 15.9]
Major	60 (12.3) [9.4, 15.2]	21 (22.9) [14.3, 31.4]
New pacemaker	66 (13.5) [10.5, 16.6]	11 (12.0) [5.3, 18.6]

[a]All percentages are Kaplan–Meier estimates at 30 days and thus do not equal the number of patients divided by the total number in the study group. TIA, transient ischaemic attack.
[b]Deaths from unknown cause were assumed to be from cardiovascular causes.
[c]Major/disabling stroke was defined as modified Rankin score ≥2.

when compared with both SAVR and non-TF TAVR.[17] Interestingly, no difference in mortality was observed between non-TF and TF groups in the IR cohort despite greater co-morbidity in non-TF patients. Thus, in lower surgical risk patients with less co-morbidity, non-TF access may be better tolerated, with lower early mortality and complications.

The low rate of stroke in this study deserves special attention. In prior TAVR studies, strokes have been a concern; all strokes or TIA at 30 days in PARTNER I were 6.7% for the inoperable cohort[1] and 5.5% for HR patients.[5] The neurologic event rates in the current study are the lowest reported in a large study with clinical events committee-adjudication. At 30 days, the rate of all stroke or TIA was 2.1% in HR patients and 3.1% in IR patients while disabling stroke (which was not a metric reported in studies of previous generation SAPIEN valves) was observed in only 0.9% of the HR patients and 0.7% of the IR patients. These results are striking when one considers that all patients in the current trial underwent evaluation by a neurologist at baseline and at 30-day follow-up. Previous studies that did not mandate formal neurological examination have likely underestimated the incidence of stroke. A recent study showed that with careful neurologic assessment, stroke after SAVR was much higher (17%) than previously reported.[18] This very low stroke rate could reflect many patient- or procedure-related factors, but could

Table 5 30-day clinical outcomes according to access approach: intermediate-risk cohort (*N* = 1078)[a]

Outcome	Intermediate-risk transfemoral, *N* = 953	Intermediate risk transapical/TAo, *N* = 125
	No. of events (%) [95% CI]	
Death		
Any cause	10 (1.1) [0.4, 1.7]	2 (1.6) [0.0, 3.8]
Cardiovascular[b]	9 (0.9) [0.3, 1.6]	1 (0.8) [0.0, 2.3]
Repeat hospitalization	38 (4.0) [2.8, 5.3]	11 (8.8) [3.8, 13.8]
Stroke or TIA		
All	29 (3.1) [2.0, 4.2]	5 (4.0) [0.6, 7.4]
TIA	5 (0.5) [0.1, 1.0]	0 (0) [0.0, 0.0]
Stroke[c]	24 (2.5) [1.5, 3.5]	5 (4.0) [0.6, 7.4]
Major/disabling	7 (0.7) [0.2, 1.3]	4 (3.2) [0.1, 6.2]
Minor	17 (1.8) [0.9, 2.6]	1 (0.8) [0.0, 2.3]
Death or repeat hospitalization or major stroke	51 (5.4) [3.9, 6.8]	15 (11.9) [6.3, 17.6]
Myocardial infarction		
All	3 (0.3) [0.0, 0.7]	0 [0.0, 0.0]
Periprocedural	3 (0.3) [0.0, 0.7]	0 [0.0, 0.0]
Vascular complications		
All	124 (13.0) [10.9, 15.2]	7 (5.6) [1.6, 9.6]
Major	60 (6.3) [4.9, 8.0]	5 (4.0) [0.6, 7.4]
Acute kidney injury (VARC 2)		
Stage 1	32 (3.4) [2.2, 4.5]	9 (7.1) [2.6, 11.6]
Stage 2	5 (0.5) [0.1, 1.0]	5 (4.0) [0.6, 7.4]
Stage 3	3 (0.3) [0.0, 0.7]	2 (1.6) [0.0, 3.8]
Life-threatening/disabling bleeding	34 (3.6) [2.4, 4.8]	16 (12.7) [6.9, 18.6]
Major bleeding	83 (8.7) [6.9, 10.5]	31 (24.6) [17.1, 32.1]
New pacemaker	100 (10.5) [0.0, 4.8]	9 (7.2) [0.0, 18.6]

[a]All percentages are Kaplan–Meier estimates at 30 days and thus do not equal the number of patients divided by the total number in the study group. TIA, transient ischaemic attack.
[b]Deaths from unknown cause were assumed to be from cardiovascular causes.
[c]Major/disabling stroke was defined as modified Rankin score ≥ 2.

also relate to the lower crossing profile of the Sapien 3 system as well as greater active flexion by the delivery catheter resulting in less aortic arch injury. Moreover, previous studies of earlier SAPIEN generations have shown an association with post-dilatation and procedural strokes.[19] The effectiveness of the sealing cuff of the SAPIEN 3 THV in reducing PVL reduced the need for post-dilatation (performed in 12.5% of cases in this study), which, in turn could reduce the likelihood of stroke.

Paravalvular leak remains an important consideration when comparing TAVR with SAVR; moderate–severe PVL at 30 days were 12.2 and 10% in the PARTNER IA and US CoreValve Pivotal Study TAVR cohorts, respectively.[4,5] Even mild PVL was associated with increased mortality in earlier PARTNER analyses,[20] so modifications to prevent PVL have been a prominent focus in the development of the next-generation TAVR devices. The very low 30-day rate of moderate or severe PVL (3.4%) observed in this study is attributable partly to the systematic use of 3D imaging for correct THV size selection, but more likely reflects the effectiveness of the fabric skirt surrounding the inflow portion of the stent frame. These rates of PVL are in line with other next-generation devices that shown similarly low rates of moderate or greater PVL.[21,22] These other studies, however, have shown higher rates of none–trace PVL, the clinical significance of which remains unknown.

We also observed a slightly higher rate of new pacemakers in this study (13.0% for HR, 10.1% for IR), compared with the PARTNER I experience with the original SAPIEN THV (8.8%).[23] The reasons for a higher rate of new pacemakers are likely multifactorial. The SAPIEN 3 THV has a longer stent frame than previous generation devices and there is increased foreshortening of the frame. Depending on the exact implantation characteristics (including depth and degree of oversizing), the final position of the valve may be lower in the LV outflow tract, leading to an increased risk of injury to the conduction system. When this trial started, guidance regarding valve positioning as well as oversizing was limited, leading to a lower position of the inflow portion of the SAPIEN 3 valve. During the course of the study, both positioning recommendations and sizing algorithms changed (MDCT sizing was mandated and less oversizing was recommended) which resulted in a higher position and greater

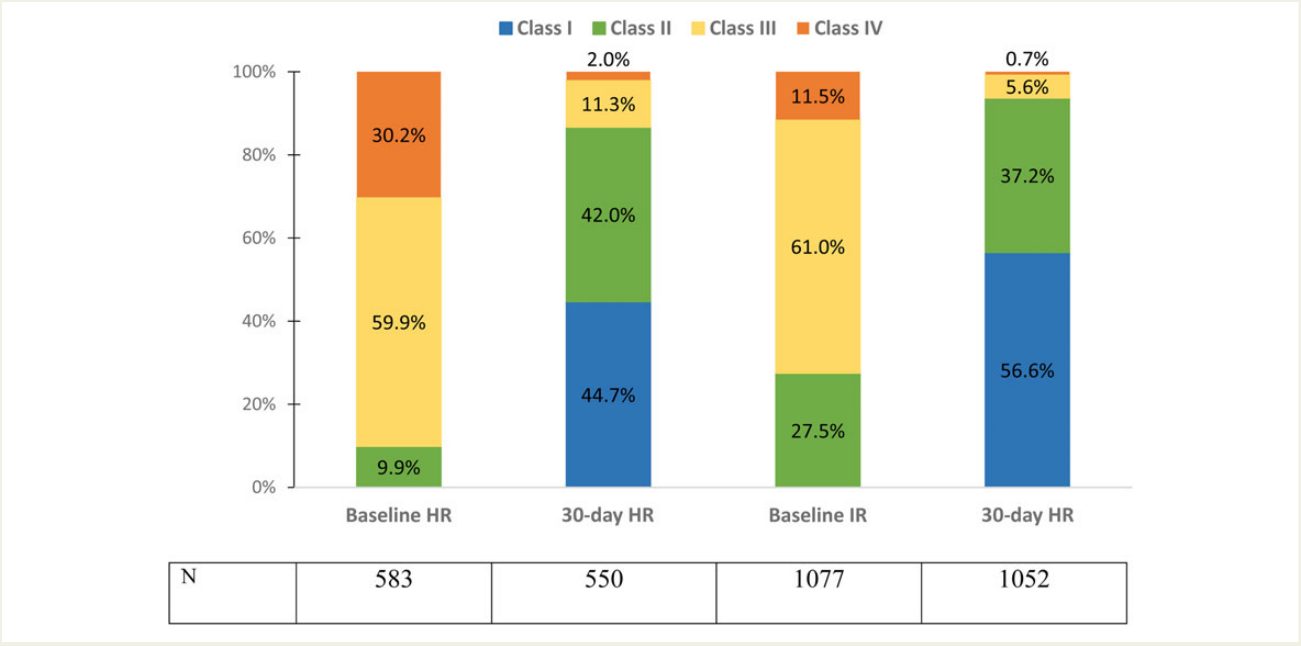

Figure 2 Symptom status by New York Heart Association functional class. Symptom status according to New York Heart Association class is shown at baseline and at 30 days among patients in both HR/inoperable and intermediate risk cohorts.

Table 6 Echocardiographic findings among patients with paired baseline and 30-day (or pre-discharge) assessments (combined high-risk/inoperable and intermediate cohorts)[a]

Parameter	Baseline	30 days	*P*-value
AVA (cm^2)	0.69 ± 0.17	1.67 ± 0.38	<0.0001
Mean gradient (mmHg)	45.8 ± 13.2	11.4 ± 4.8	<0.0001
LVEF (%)	57.6 ± 14.0	57.8 ± 12.9	0.3334
Paravalvular AR			
None	NA	466/1597 (29.2)	NA
Trace	NA	426/1597 (26.7)	NA
Mild	NA	650/1597 (40.7)	NA
Moderate	NA	55/1597 (3.4)	NA
Severe	NA	0/1597 (0.0)	NA
Total AR			
None	299/1582 (18.9)	430/1582 (27.2)	<0.0001
Trace	448/1582 (28.3)	456/1582 (28.8)	0.7492
Mild	732/1582 (46.3)	638/1582 (40.3)	0.0005
Moderate	101/1582 (6.4)	58/1582 (3.7)	0.0002
Severe	2/1582 (0.1)	0/1582 (0.0)	0.5637
LV mass (g)	224.3 ± 71.3	214.1 ± 65.7	<0.0001
MR			
Moderate	141/1557 (9.1)	105/1557 (6.7)	0.0031
Severe	15/1557 (1.0)	9/1557 (0.6)	0.1088

[a]Plus–minus values are means ± standard deviation. All other values are reported as *n*/*N* (%). LVEF, left ventricular ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; NA, not applicable. McNemar's test or paired *t*-test was performed for categorical or continuous variables, respectively.

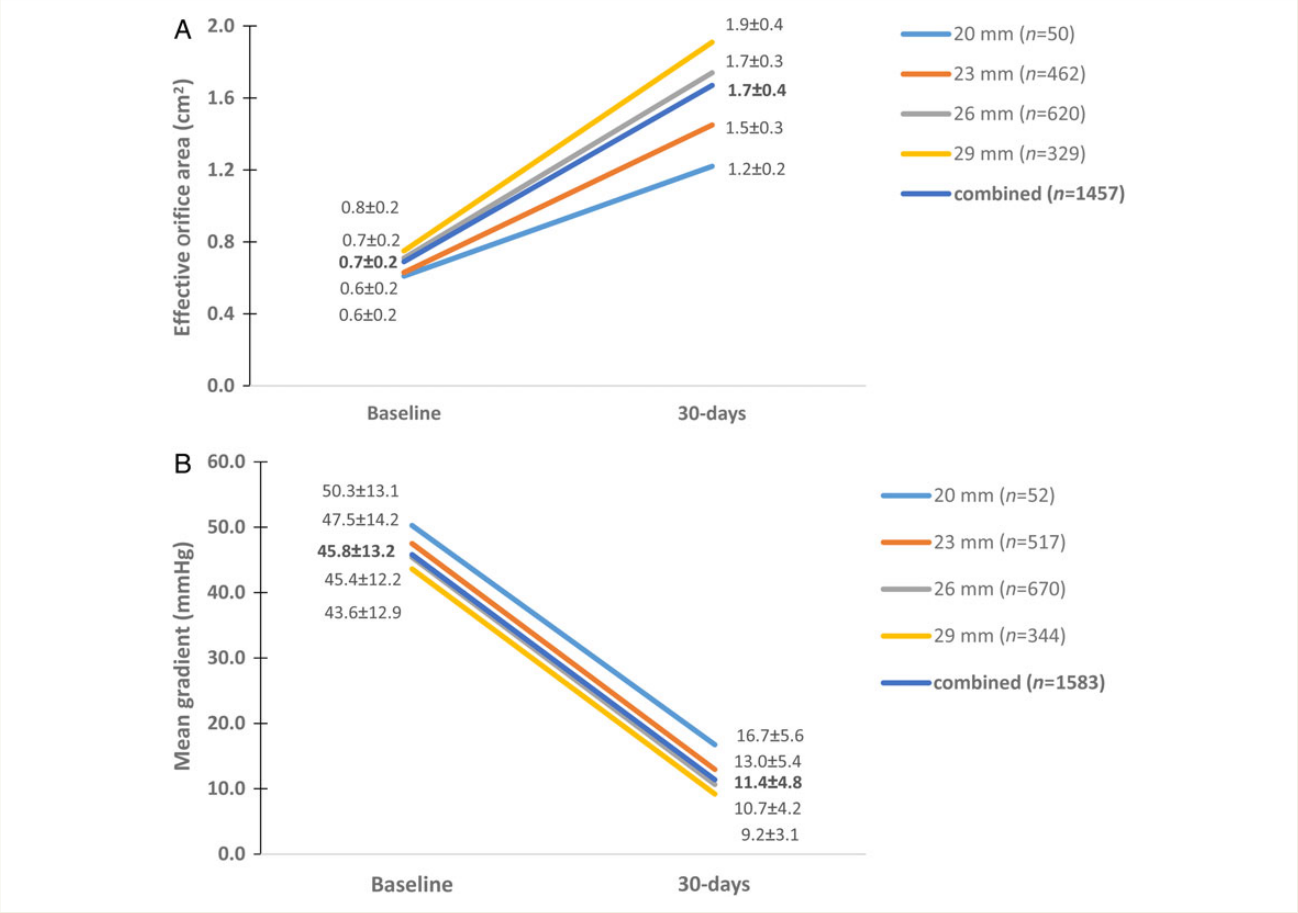

Figure 3 Change in effective orifice area and mean gradient stratified by transcatheter heart valve size. The effective orifice area (*A*) and mean aortic valve gradient (*B*) stratified by valve size are shown at baseline and 30-day follow-up.

foreshortening of the frame. This is potentially the reason for the lower incidence of pacemakers in the IR cohort, which enrolled after the HR cohort. A recent analysis of 101 IR patients from Europe demonstrated very low rates of new pacemakers (4%) after SAPIEN 3 implantation utilizing the recent procedural guidance.[24] Careful further analyses of the predictors of new pacemaker requirements after SAPIEN 3 will be important especially as TAVR moves into the IR cohort.

Finally, this is the largest series of IR TAVR patients reported thus far. As in the HR patients, the rates of major adverse events were remarkably low at 30 days (mortality 1.1%, disabling stroke 0.7%), although no direct comparisons with surgically treated patients are possible. In the future, after data from the PARTNER 2A randomized trial in IR patients are available, comparisons between this SAPIEN 3 registry and the randomized surgical arm would be appropriate and are planned. Nonetheless, the rates of mortality and stroke in the current study appear to be much lower than previously reported in large series of IR patients undergoing SAVR.[7] These results suggest that TAVR early mortality may be at least comparable with SAVR in IR patients and are consistent with the recently published NOTION trial, which randomized all-comers to TAVR or SAVR. Patients with a mean STS of 2.9% (TAVR) and 3.1% (SAVR) showed similar rates of adverse events at 1 year with TAVR vs. SAVR (13.1% vs. 16.3%, $P = 0.43$ for the composite endpoint of death, stroke, and myocardial infarction).[8] NOTION trial outcomes were consistent with a recent propensity-matched analyses in which TAVR and SAVR appeared to have similar results in IR patients.[9,25] The very low rates of significant PVL and the excellent haemodynamic results with SAPIEN 3 in the IR cohort are important if TAVR is to be applied to lower risk populations. Most assuredly, longer follow-up is required to assess valve durability, but if the low rates of adverse events are sustained, TAVR could be a viable alternative to SAVR in the management of IR patients with AS.

This study has a number of limitations. It is a registry with no randomized comparator arm. Also this study did not enrol HR patients consecutively and therefore may be confounded by selection bias. In particular, certain HR groups, such as patients on haemodialysis, were excluded. In addition, this study is confined to 30-day events, so further longer-term follow-up is required if these encouraging early results are to prove meaningful. Finally, this study was conducted during the earliest phases of introduction of the SAPIEN 3 THV, at which time optimal recommendations for valve sizing and THV positioning were in a state of evolution.

In summary, treatment of inoperable/HR AS patients with the SAPIEN 3 THV is associated with extremely low rates of mortality, major complications, and paravalvular leak at 30 days. Based upon

these data and other recent literature, TAVR should be considered a Class I indication in HR patients. In IR patients, these data are encouraging and with presentation of longer-term follow-up within the next year, TAVR with the SAPIEN 3 valve may become an alternative to surgery in many elderly IR patients as well. Longer-term follow-up and future studies in even lower risk patients will eventually determine the role of TAVR and SAVR in the treatment algorithm of all patients with severe AS.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

G.M.A. performed statistical analysis; M.L. handled funding and supervision; S.K., V.H.T., J.W., S.C.M., S.L., K.L.G., M.W., M.G., A.C.E., S.K., D.J.K., H.C.H., V.B., W.Y.S., R.T.H., P.P., N.J.W., J.L., P.B., B.K.W., R.M.S., R.R.M., L.G.S., J.G.W., M.J.M., C.R.S., and M.B.L. acquired the data; S.K., V.H.T., S.K., D.J.K., H.C.H., W.Y.S., B.K.W., L.G.S., J.G.W., M.J.M., C.R.S., M.B.L. conceived and designed the research; S.K., J.G.W., M.B.L. drafted the manuscript; S.K., V.H.T., J.W., S.C.M., S.L., K.L.G., M.W., M.G., A.C.E., S.K., D.J.K., H.C.H., V.B., W.Y.S., R.T.H., P.P., N.J.W., J.L., P.B., B.K.W., R.M.S., R.R.M., G.M.A., L.G.S., J.G.W., M.J.M., C.R.S., and M.B.L. made critical revision of the manuscript for key intellectual content.

Acknowledgements

The authors thank Rupa Parvataneni, MS (Cardiovascular Research Foundation) for statistical support and Maria Alu (Columbia University Medical Center) for editorial assistance in the preparation of this manuscript.

Funding

The PARTNER II Trial was funded by Edwards Lifesciences.

Conflict of interest: S.K. is a consultant for Edwards Lifesciences and a member of the Scientific Advisory Board of Thubrikar Aortic Valve. V.H.T. is a member of the PARTNER Trial Steering Committee and a consultant for Edwards Lifesciences, Sorin Medical, St Jude Medical, and DirectFlow. M.W. has received consulting fees/honoraria from Edwards Lifesciences. A.C.E. has received honoraria and proctoring fees from Edwards Lifesciences, Sorin Inc. and Medtronic, Inc. H.C.H. has received grants from Edwards Lifesciences, St Jude Medical, Medtronic, Boston Scientific, Abbott Vascular, Gore, Siemens, Cardiokinetix, and Mitraspan, is a consultant for Edwards Lifesciences and Siemens, and holds equity in Microinterventional Devices. W.Y.S. has received consulting fees/honoraria from Microinterventional Devices. R.T.H. has received research grant support from Philips Healthcare and consulting fees/honoraria from Edwards Lifesciences. P.P. holds the Canada research Chair in Valvular Heart Diseases, Canadian Institutes of Health research, Ottawa, Ontario, Canada and has received research grant support from Edwards Lifesciences. N.J.W. has received grants Edwards Lifescience, Abbott Vascular, Medtronic, Sorin, Direct Flow Medical, Boston Scientific, and JenaValve, R.R.M. has received grants from Edwards Lifesciences and St Jude Medical, is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical. L.G.S. holds equity in Cardiosolution and Valvexchange, and intellectual property with Postthorax. J.G.W. is a consultant for Edwards Lifesciences and a member of the PARTNER Trial Executive Committee. M.J.M., C.R.S., and M.B.L. are members of the PARTNER Executive Committee (no direct compensation).

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
2. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK, CoreValve United States Clinical I. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 2014;**63**:1972–1981.
3. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Smith CR, Akin JJ, Davidson MJ. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;**385**:2485–2491.
4. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, Investigators USCC. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–1798.
5. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
6. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Davidson MJ, Svensson LG, Akin J. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;**385**:2477–2484.
7. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, Szeto WY, Dewey TM, Guyton RA, Bavaria JE, Babaliaros V, Gammie JS, Svensson L, Williams M, Badhwar V, Mack MJ. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. *Ann Thorac Surg* 2015;**99**:55–61.
8. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Sondergaard L. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol* 2015;**65**:2184–2194.
9. Tamburino C, Barbanti M, D'Errigo P, Ranucci M, Onorati F, Covello RD, Santini F, Rosato S, Santoro G, Fusco D, Grossi C, Seccareccia F, Group OR. 1-year outcomes after transfemoral transcatheter or surgical aortic valve replacement: results from the Italian OBSERVANT study. *J Am Coll Cardiol* 2015;**66**:804–812.
10. Alli O, Rihal CS, Suri RM, Greason KL, Waksman R, Minha S, Torguson R, Pichard AD, Mack M, Svensson LG, Rajeswaran J, Lowry AM, Ehrlinger J, Tuzcu EM, Thourani VH, Makkar R, Blackstone EH, Leon MB, Holmes D. Learning curves for transfemoral transcatheter aortic valve replacement in the PARTNER-I trial: technical performance. *Catheter Cardiovasc Interv* 2015, doi: 10.1002/ccd.26120.
11. Binder RK, Webb JG, Willson AB, Urena M, Hansson NC, Norgaard BL, Pibarot P, Barbanti M, Larose E, Freeman M, Dumont E, Thompson C, Wheeler M, Moss RR, Yang TH, Pasian S, Hague CJ, Nguyen G, Raju R, Toggweiler S, Min JK, Wood DA, Rodes-Cabau J, Leipsic J. The impact of integration of a multidetector computed tomography annulus area sizing algorithm on outcomes of transcatheter aortic valve replacement: a prospective, multicenter, controlled trial. *J Am Coll Cardiol* 2013;**62**:431–438.
12. Green P, Arnold SV, Cohen DJ, Kirtane AJ, Kodali SK, Brown DL, Rihal CS, Xu K, Lei Y, Hawkey MC, Kim RJ, Alu MC, Leon MB, Mack MJ. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). *Am J Cardiol* 2015;**116**:264–269.

13. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J* 2008;**29**:1043–1048.
14. Walther T, Hamm CW, Schuler G, Berkowitsch A, Kotting J, Mangner N, Mudra H, Beckmann A, Cremer J, Welz A, Lange R, Kuck KH, Mohr FW, Mollmann H, Board GE. Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY registry. *J Am Coll Cardiol* 2015;**65**:2173–2180.
15. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes D, Registry SAT. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;**310**:2069–2077.
16. Blackstone EH, Suri RM, Rajeswaran J, Babaliaros V, Douglas PS, Fearon WF, Miller DC, Hahn RT, Kapadia S, Kirtane AJ, Kodali SK, Mack M, Szeto WY, Thourani VH, Tuzcu EM, Williams MR, Akin JJ, Leon MB, Svensson LG. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral transcatheter aortic valve replacement: a placement of aortic transcatheter valves (PARTNER)-I trial substudy. *Circulation* 2015;**131**:1989–2000.
17. Arnold SV, Reynolds MR, Wang K, Magnuson EA, Baron SJ, Chinnakondepalli KM, Reardon MJ, Tadros PN, Zorn GL, Maini B, Mumtaz MA, Brown JM, Kipperman RM, Adams DH, Popma JJ, Cohen DJ. Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk. *JACC Cardiovasc Interv* 2015;**8**:1207–1217.
18. Messe SR, Acker MA, Kasner SE, Fanning M, Giovannetti T, Ratcliffe SJ, Bilello M, Szeto WY, Bavaria JE, Hargrove WC III, Mohler ER III, Floyd TF, Determining Neurologic Outcomes from Valve Operations I. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation* 2014;**129**:2253–2261.
19. Hahn RT, Pibarot P, Webb J, Rodes-Cabau J, Herrmann HC, Williams M, Makkar R, Szeto WY, Main ML, Thourani VH, Tuzcu EM, Kapadia S, Akin J, McAndrew T, Xu K, Leon MB, Kodali SK. Outcomes with post-dilation following transcatheter aortic valve replacement: the PARTNER I trial (placement of aortic transcatheter valve). *JACC Cardiovasc Interv* 2014;**7**:781–789.
20. Kodali S, Pibarot P, Douglas PS, Williams M, Xu K, Thourani V, Rihal CS, Zajarias A, Doshi D, Davidson M, Tuzcu EM, Stewart W, Weissman NJ, Svensson L, Greason K, Maniar H, Mack M, Anwaruddin S, Leon MB, Hahn RT. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. *Eur Heart J* 2015;**36**:449–456.
21. Meredith IT, Worthley SG, Whitbourn RJ, Antonis P, Montarello JK, Newcomb AE, Lockwood S, Haratani N, Allocco DJ, Dawkins KD. Transfemoral aortic valve replacement with the repositionable Lotus Valve System in high surgical risk patients: the REPRISE I study. *EuroIntervention* 2014;**9**:1264–1270.
22. Lefevre T, Colombo A, Tchetche D, Latib A, Klugmann S, Fajadet J, De Marco F, Maisano F, Bruschi G, Bijuklic K, Nava S, Weissman N, Low R, Thomas M, Young C, Redwood S, Mullen M, Yap J, Grube E, Nickenig G, Sinning JM, Hauptmann KE, Friedrich I, Lauterbach M, Schmoeckel M, Davidson C, Schofer J. Prospective multicenter evaluation of the direct flow medical transcatheter aortic valve system: 12-month outcomes of the evaluation of the direct flow medical percutaneous aortic valve 18F system for the treatment of patients with severe aortic stenosis (DISCOVER) study. *JACC Cardiovasc Interv* 2016;**9**:68–75.
23. Nazif TM, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, El-Chami MF, Herrmann HC, Mack M, Makkar RR, Miller DC, Pichard A, Tuzcu EM, Szeto WY, Webb JG, Moses JW, Smith CR, Williams MR, Leon MB, Kodali SK, Office PP. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc Interv* 2015;**8**(1 Pt A):60–69.
24. Vahanian A. 30-day outcomes of intermediate-risk patients with the new-generation balloon-expandable transcatheter heart valve via the transfemoral approach. In: EuroPCR. Paris, France, 2015.
25. Piazza N, Kalesan B, van Mieghem N, Head S, Wenaweser P, Carrel TP, Bleiziffer S, de Jaegere PP, Gahl B, Anderson RH, Kappetein AP, Lange R, Serruys PW, Windecker S, Juni P. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. *JACC Cardiovasc Interv* 2013;**6**:443–451.