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FASTTRACK

One year follow-up of the multi-centre European PARTNER transcatheter heart valve study

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Background Transcatheter aortic valve implantation (TAVI) has emerged as a new therapeutic option in high-risk patients with severe aortic stenosis.

Aims PARTNER EU is the first study to evaluate prospectively the procedural and mid-term outcomes of transfemoral (TF) or transapical (TA) implantation of the Edwards SAPIEN® valve involving a multi-disciplinary approach.

Methods and results Primary safety endpoints were 30 days and 6 months mortality. Primary efficacy endpoints were haemodynamic and functional improvement at 12 months. One hundred and thirty patients (61 TF, 69 TA), aged 82.1 $\pm$ 5.5 years were included. TA patients had higher logistic EuroSCORE (33.8 vs. 25.7%, $P = 0.0005$) and more peripheral disease (49.3 vs. 16.4%, $P < 0.0001$). Procedures were aborted in four TA (5.8%) and six TF cases (9.8%). Valve implantation was successful in the remaining patients in 95.4 and 96.4%, respectively. Thirty days and 6 months survival were 81.2 and 58.0% (TA) and 91.8 and 90.2% (TF). In both groups, mean aortic gradient decreased from 46.9 $\pm$ 18.1 to 10.9 $\pm$ 5.4 mmHg 6 months post-TAVI. In total, 78.1 and 84.8% of patients experienced significant improvement in New York Heart Association (NYHA) class, whereas 73.9 and 72.7% had improved Kansas City Cardiomyopathy Questionnaire (KCCQ) scores in TA and TF cohorts, respectively.

Conclusion This first team-based multi-centre European TAVI registry shows promising results in high-risk patients treated by TF or TA delivery. Survival rates differ significantly between TF and TA groups and probably reflect the higher risk profile of the TA cohort. Optimal patient screening, approach selection, and device refinement may improve outcomes.

Keywords Aortic valve stenosis • Transcatheter heart valve • Transfemoral • Transapical

Introduction

Degenerative aortic stenosis is the most commonly acquired valvular heart disease in adults. Its prevalence is ~4% in patients over 80 years of age and due to population ageing, the absolute number of patients should continue to increase. In symptomatic patients, surgical aortic valve replacement (AVR) has been the treatment of choice for >40 years.[1] However, among the elderly, up to 30–60%[2–4] of cases are considered too high risk for open-heart surgery. Transcatheter aortic valve implantation (TAVI) initially described by Andersen[5] was introduced for non-operable patients by Cribier in 2002.[6] The transeptal approach used was technically demanding and in 2005 Webb[7] introduced an arterial retrograde transfemoral (TF) delivery system. A transapical (TA) off-pump

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delivery system was also developed in 2004.[8] The Edwards SAPIEN® transcatheter heart valve (THV) used in this study (Edwards Lifesciences Irvine, CA, USA) is a second generation bovine pericardial balloon-expandable prosthesis available in 23 and 26 mm sizes for native aortic annuli diameters between 18 and 25 mm. The TF delivery system is suitable for ileo-femoral vessels with a diameter ≥7 mm for the 22 Fr and ≥8 mm for the 24 Fr sheath. The TA approach incorporates a shorter and larger diameter (33 Fr) delivery system compatible with the 23 or 26 mm Edwards SAPIEN™ valve.

The aim of the PARTNER EU trial was to prospectively establish the role of both TF and TA in this high-risk population. This paper reports the 30 day, 6 month, and 1 year results of this study.

Methods

Patients with severe aortic stenosis underwent joint interdisciplinary screening by a dedicated local team to determine study eligibility. They were prospectively enrolled between April 2007 and January 2008 in a non-randomized, multi-centre European prospective study.

Because this study was intended as a landmark report, the majority of centres were in the learning phase and 4 of 9 centres (44.4%) carried out their first TAVI cases on the occasion of the study. The implant approach (TA or TF) was selected following review of the patients' screening data according to the local TAVI team's experience. There were no guidelines given to the team recommending one type of procedure or another, as the decision to utilize the TF or the TA approach involves myriad factors, including assessment of access vessel size and the tortuosity of those vessels, the amount of disease in the peripheral vasculature and its specific characteristics, as well as other factors, such as respiratory status, that may predispose to a TF or TA approach.

In adjudicating events, the members of the Clinical Events Committee were not blinded to the implant approach. This study complies with the declaration of Helsinki. Ethics committee approval was obtained in all participating centres prior to commencement of the study. All subjects provided written informed consent to participate in the study.

Inclusion/exclusion criteria

Main inclusion criteria were severe, symptomatic, degenerative aortic stenosis, with an effective orifice area (EOA) <0.8 cm^2 (or indexed <0.6 cm^2) or mean gradient >40 mmHg (or jet velocity >4.0 m/s), New York Heart Association (NYHA) Functional Class ≥II, logistic EuroSCORE ≥20, or Society of Thoracic Surgeons Score (STS Score) ≥10 or surgical contra indications such as porcelain aorta, prior thoracic radiation therapy, or severe chest deformities.

Main exclusion criteria were native aortic annulus size <18 or >25 mm by transoesophageal echo (TEE), acute myocardial infarction <14 days, unprotected left main disease >70%, any therapeutic invasive cardiac procedure other than balloon valvuloplasty within 30 days, active infection, life expectancy <12 months, primary hypertrophic obstructive cardiomyopathy, haemodynamic instability, severe neurological disease, renal failure, preexisting prosthetic heart valve, or thoracic aneurysm.

Study endpoints

The primary safety endpoints were freedom from death at 30 days and 6 months. The primary efficacy endpoints were haemodynamic, NYHA class and quality of life (QoL) improvement at 12 months. Clinical and echocardiographic data were obtained at baseline, before discharge, and at 30 days, 6 months, and 1 year.

Quality of life questionnaires using the EuroQol with EQ-5D UK-TTO rating scale[9] and Kansas City Cardiomyopathy Questionnaire (KCCQ)[10] were assessed at baseline and at all follow-up intervals to 1 year. Outcomes were described according to the guidelines for reporting mortality and morbidity after cardiac valve intervention.[11] All events related to primary and secondary endpoints were adjudicated by an independent clinical events committee.

Study definitions

Cardiac death was defined as death resulting from any cardiac causes or any sudden unexplained deaths.

Device Success was defined as successful delivery and deployment of the device and retrieval of the delivery catheter resulting in an aortic valve area greater than 0.9 cm^2 with 2+ (moderate) or less aortic regurgitation (AR) in the earliest evaluable echocardiogram and only one valve implanted in the correct anatomical position.

A stroke was defined as follows: focal neurological deficit lasting ≥24 h or focal neurological deficit lasting <24 h with imaging findings of acute infarction or haemorrhage.

Stroke was further classified as ischaemic, haemorrhagic, or ischaemic with haemorrhagic conversion.

Vascular complications were defined as a haematoma >5 cm at the access site, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischaemia, nerve injury, transfusion except for indications clearly other than catheterization complications, unplanned vascular surgical repair, annular dissection, aortic dissection or thoracic wound complication. Any event which was not a major complication was considered a minor event. Major vascular complications were defined as any access-related vascular injury leading to either death, need for significant blood transfusions (>3 units), unplanned percutaneous or surgical intervention, ischaemia, neurological impairment or irreversible end-organ damage, and left ventricular perforation.

Bleeding events were defined according to the TIMI definition as major or minor. They included surgical bleeding, haemorrhage, cardiac tamponade, or need for transfusion.

Valve deployment time was defined as the time from balloon valvuloplasty to deployment of the valve.

Procedure

Transfemoral procedures were performed under conscious sedation or general anaesthesia and TEE at the discretion of the team. After retrograde pre-dilation of the native valve, THV was advanced by the RetroFlex™ catheter, positioned within the native aortic valve, and then delivered by balloon inflation under rapid ventricular pacing (RVP). For the TA procedure a left anterolateral mini-thoracotomy and pericardiotomy were performed, and a double pledgeted purse-string suture or U stitches were placed at the left ventricular apex. After puncture of the apex, antegrade crossing, and pre-dilatation, THV was deployed under RVP. Transoesophagal echo was used at the discretion of the team.

Statistical analysis

Patient data were analysed according to the intention-to-treat (ITT) principle. Comparison of baseline factors between TF and TA patients used Wilcoxon signed rank tests for continuous variables or Pearson's Chi-square tests for categorical variables. Early (≤30 days) events were summarized as percentages. Survival was estimated at 30 days, 6 months, and 1 year using the method of Kaplan and Meier. The procedure day was considered 'day 0.' A logistic regression model was fit with 1 year survival and Logistic Euroscore as the dependent and

independent variables, respectively. Logistic Euroscore was modelled with a 4-knot natural spline in this model to allow a flexible association between the risk score and 1 year mortality. The statistical significance of this effect was investigated via a likelihood ratio statistic. A similar logistic regression analysis was performed for the STS score. In order to declare device success for a given patient, a discharge or 30 day value for both EOA and AI was required. The percentage of subjects experiencing NYHA improvement at 1 year relative to baseline was based on all subjects that had a recorded NYHA value at both baseline and 1 year follow-up. For the KCCQ score, a patient was classified as improved if he experienced an increase $\geq$5 points over baseline.[12] Percentage of patients improved was calculated for patients

Table 1 Number of patients enrolled per centre (does not include one screening failure)

	Transapical	Transfemoral	Total
AKH, Wien	10	9	19
Hopital Bichat, Paris	9	9	18
Kings College Hospital, London	10	7	17
West-German Heart Center University Hospital, Essen	10	6	16
Institut Hospitalier Jacques Cartier, Massy	5	10	15
Onze Lieve Vrouwziekenhuis (OLVZ), Aalst	5	8	13
Hopital Charles Nicolle, Rouen	5	7	12
J.W. Goethe University, Frankfurt	10	2	12
Erasmus MC, Rotterdam	5	3	8
Total	69	61	130

Table 2 Baseline characteristics by delivery approach

Characteristics	Overall (*n* = 130)	Transapical (*n* = 69)	Transfemoral (*n* = 61)	*P*-value
Age, years	82.1 ± 5.5 (67.7–93.3)	81.9 ± 5.7 (67.7–93.3)	82.3 ± 5.2 (69.1–92.5)	0.7194
Female gender (%)	72 (55.4)	35 (50.7)	37 (60.7)	0.2556
NYHA (%)				0.9920
Class I	2 (1.5)	1 (1.4)	1 (1.6)	
Class II	18 (13.8)	9 (13.0)	9 (14.8)	—
Class III	88 (67.7)	47 (68.1)	41 (67.2)	—
Class IV	22 (16.9)	12 (17.4)	10 (16.4)	—
Diabetes (%)	41 (31.5)	20 (29.0)	21 (34.4)	0.5053
Coronary artery disease (%)	78 (60.0)	45 (65.2)	33 (54.1)	0.1965
Myocardial infarction (%)	27 (20.8)	14 (20.3)	13 (21.3)	0.8861
Mitral valve disease (%)	68 (52.3)	43 (62.3)	25 (41.0)	0.0151
Carotid disease	31 (23.8)	23 (33.3)	8 (13.1)	0.0069
High blood pressure (%)	96 (73.8)	53 (76.8)	43 (70.5)	0.4132
Previous PCI (%)	32 (24.6)	18 (26.1)	14 (23.0)	0.6787
Previous CABG (%)	41 (31.5)	29 (42.0)	12 (19.7)	0.0062
Peripheral disease (non-carotid) (%)	44 (33.8)	34 (49.3)	10 (16.4)	<0.0001
Atrial fibrillation (%)	32 (24.6)	17 (24.6)	15 (24.6)	0.9950
Previous pace-maker (%)	17 (13.1)	11 (15.9)	6 (9.8)	0.3028
AV Block (%)	21 (16.2)	10 (14.5)	11 (18.0)	0.5842
Renal failure (%)	54 (41.5)	32 (46.4)	22 (36.1)	0.2338
Pulmonary disease (%)	54 (41.5)	24 (34.8)	30 (49.2)	0.0964
Cancer (%)	19 (14.6)	9 (13.0)	10 (16.4)	0.5895
EOA (cm^2)	0.6 ± 0.2 (0.3–1.2)	0.6 ± 0.2 (0.3–1.2)	0.6 ± 0.2 (0.3–1.1)	0.4732
Mean gradient (mmHg)	47.3 ± 18.9 (18.0–120.0)	46.6 ± 18.6 (18.0–87.0)	48.0 ± 19.4 (18.0–120.0)	0.6744
LVEF (%)	52.8 ± 16.1 (15.0–86.1)	52.8 ± 14.6 (17.3–77.0)	52.9 ± 17.8 (15.0–86.1)	0.7712
Logistic EuroSCORE (%)	30.0 ± 13.7 (5.1–72.1)	33.8 ± 14.4 (5.1–72.1)	25.7 ± 11.5 (6.4–65.5)	0.0005
STS-score (%)	11.6 ± 6.5 (2.0–41.0)	11.8 ± 6.8 (2.0–41.0)	11.3 ± 6.1 (3.7–32.7)	0.7994

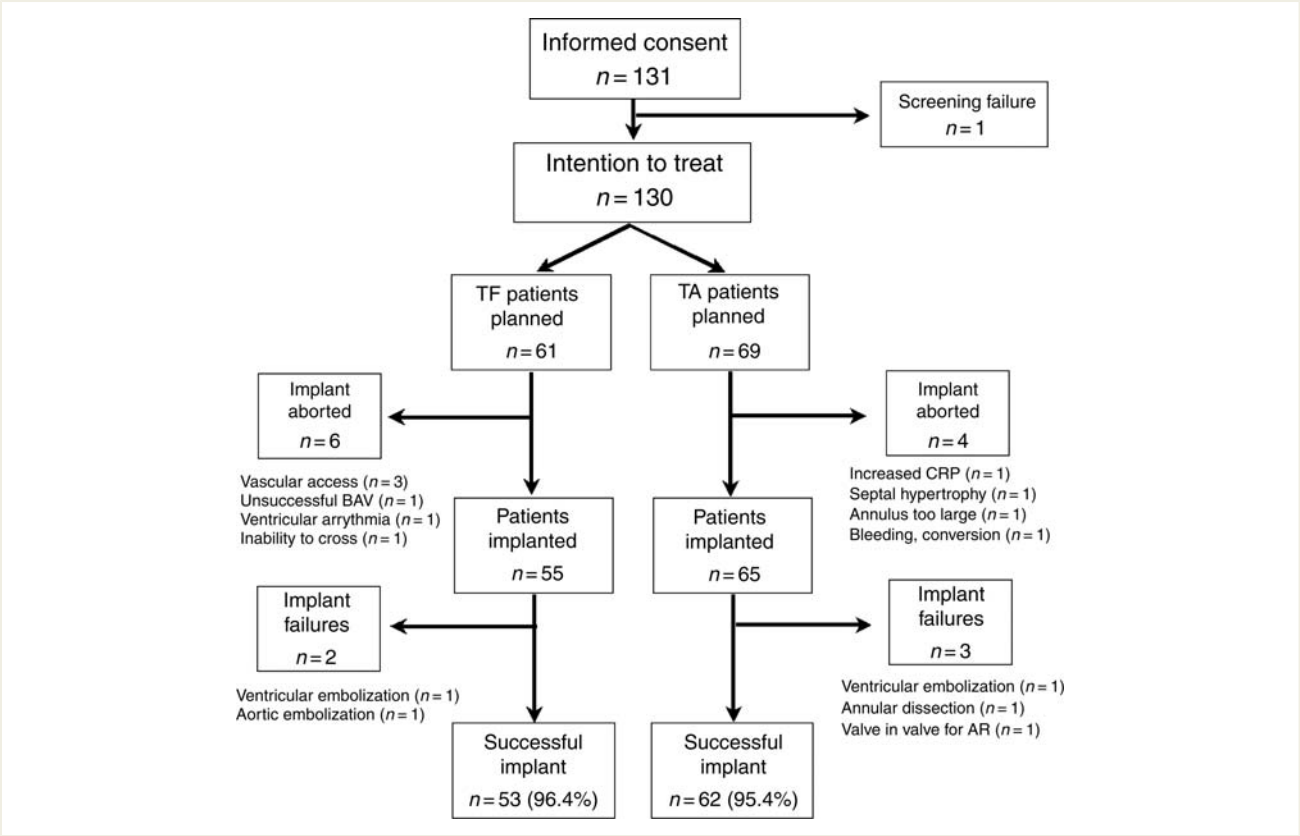

Figure 1 Procedural outcome.

Table 3 Procedural characteristics by delivery approach

	Transfemoral	Transapical
Deployment time (min)	30.7 ± 18.0 (range: 7–120)	11.4 ± 5.1 (range: 2–26)
Contrast volume (mL)	212.5 ± 121.8 (range: 50–620)	153.8 ± 76.7 (range: 50–370)
Total procedure time (min)	145.3 ± 61.3 (range: 26–361)	131.6 ± 59.3 (range: 35–475)
Procedure to discharge (median days)	8 (range: 0–77)	11 (range: 0–59)
Total ICU (median days)	1 (range: 0–77)	1 (range: 0–56)

with both baseline and 1 year KCCQ score and EQ-5D data, using 0.05 as the minimum clinically important difference.[9] A Wilcoxon test was performed on paired differences between 1 year and baseline KCCQ and EQ-5D in patients with baseline and 1 year data using 0.05 as the minimum clinically important difference.[9] For EOA, mean gradient, and LVEF the mean and standard deviation were calculated at baseline, 6 months, and 1 year. For each of these parameters, a Wilcoxon test was performed on the paired differences between 6 months and baseline for patients with data available at both time points. All analyses were carried out using the SAS version 9.1.2 and Splus version 8.

Medication regimens

It was recommended that all patients receive aspirin and thienopyridine prior to procedure and continue thienopyridine for 6 months post-procedure and aspirin indefinitely. A bolus of 5000 units of heparin was injected when starting the procedure and monitoring was performed to keep the patient's ACT >250 s. Post-discharge antibiotic prophylaxis for endocarditis was recommended according to the most recent guidelines of the American Heart Association.[13]

Results

Patients were included from April 2007 to January 2008. Informed consents were signed by 131 patients. In one patient, TAVI was not attempted due to active endocarditis which was diagnosed after inclusion in the study.

Demographics and baseline characteristics

Of the remaining 130 patients, 61 were scheduled to receive a TF and 69 a TA intervention. Distribution of TF and TA approach according to centre is shown in *Table 1*. Patient clinical and echocardiographic characteristics are summarized in *Table 2*. After Bonferroni adjustment, the only significant differences between TA and TF patients were logistic EuroSCORE (33.8 ± 14.4 vs. 25.7 ± 11.5%, $P = 0.0109$) and peripheral disease (49.3 vs. 16.4%, $P = 0.0018$).

Table 4 Kaplan–Meier safety estimates (non-hierachical ranking)—transapical patients[a]

	30 Days	6 Months	1 Year
Death	81.2% (13)	58.0% (29)	49.3% (35)
Stroke	98.5% (1)	92.4% (4)	89.7% (5)
Myocardial infarction	94.0% (4)	92.2% (5)	92.2% (5)
Coronary obstruction	98.6% (1)	98.6% (1)	98.6% (1)
Emergent aortic valve replacement	97.1% (2)	97.1% (2)	94.5% (3)
Valve embolization	98.6% (1)	98.6% (1)	98.6% (1)
Structural valve deterioration	100.0% (0)	100.0% (0)	100.0% (0)
New pacemaker	96.2% (2)	94.0% (3)	94.0% (3)
Vascular complications	95.3% (3)	91.2% (5)	91.2% (5)
Incidence at 30 days[b] overall	5.8% (4)		
Major	5.8% (4)		
Minor	0		
Bleeding event	78.3% (14)	70.4% (18)	70.4% (18)
Incidence at 30 days[c] overall	20.3% (19)		
Major	11.6% (8)		
Minor	10.1% (7)		
Undetermined	5.7% (4)		
Renal failure (new onset)[c]	93.8% (2)	93.8% (2)	93.8% (2)

[a]Unless otherwise stated, numbers in parentheses refer to the number of patients experiencing an event.
[b]Here incidence refers to the number of events (as opposed to number of patients experiencing an event) divided by the number of patients.
[c]Patients with pre-existing renal failure are excluded from these estimates.

Table 5 Kaplan–Meier safety estimates (non-hierachical ranking)—transfemoral patients[a]

	30 Days	6 Months	1 Year
Death	91.8% (5)	90.2% (6)	78.7% (13)
Stroke	96.7% (2)	94.9% (3)	93.0% (4)
Myocardial infarction	96.7% (2)	95.0% (3)	93.2% (4)
Coronary obstruction	100.0% (0)	100.0% (0)	100.0% (0)
Emergent aortic valve replacement	98.4% (1)	98.4% (1)	98.4% (1)
Valve embolization	96.7% (2)	96.7% (2)	96.7% (2)
Structural valve deterioration	100.0% (0)	100.0% (0)	100.0% (0)
New pacemaker	98.2% (1)	98.2% (1)	98.2% (1)
Vascular complications	71.6% (17)	71.6% (17)	71.6% (17)
Incidence at 30 days[b] overall	27.9% (17)		
Major	16.4% (10)		
Minor	11.5% (7)		
Bleeding event	76.5% (14)	76.5% (14)	76.5% (14)
Incidence at 30 days[b] overall	23.0% (15)		
Major	4.9% (3)		
Minor	14.8% (9)		
Undetermined	4.9% (3)		
Renal failure (new onset)[c]	100.0% (0)	97.1% (1)	97.1% (1)

[a]Unless otherwise stated, numbers in parentheses refer to the number of patients experiencing an event.
[b]Here incidence refers to the number of events (as opposed to number of patients experiencing an event) divided by the number of patients.
[c]Patients with pre-existing renal failure are excluded from these estimates.

Procedural outcomes

Procedural outcome and characteristics are summarized in *Figure 1* and *Table 3*. Implantation of the Edwards SAPIEN™ THV was attempted in 61 TF and 69 TA patients. Transfemoral procedures were aborted in six patients (9.8%), due to access failure in three cases. One of these patients was treated by the TA approach 49 days later and remains alive and well. The two other patients have had no reported adverse events. A fourth procedure was aborted due to unsuccessful balloon dilatation. The patient was successfully converted to surgical AVR with no further reported adverse events. There was one case of inability to cross the valve. The procedure was stopped and the patient has had no further reported adverse events. Finally, one patient who suffered refractory arrhythmia after balloon pre-dilatation went into cardiac arrest as a result and died on the day of implant. In the remaining 55 patients, valve implantation (26, 23 mm and 29, 26 mm) was successful in 53 (96.4%). Implant failure was related to ventricular embolization in one case and aortic embolization in one. There were no cases of coronary occlusion in the TF group.

Transapical procedures were aborted in four patients (5.8%). There was one case of ventricular injury where the patient was successfully converted to surgical AVR and remains well. In a second case, the procedure was aborted due to severe septal hypertrophy. The patient died 725 days later of respiratory failure. The third patient had elevated C-reactive protein and died 320 days post-procedure of cancer. The last patient in whom it was discovered that the annulus was too large for the TH, had surgical AVR 15 days after the THV procedure and survived 534 days. The death was reported as sudden. The valve was successfully implanted (21, 23 mm and 44, 26 mm) in 62 (95.4%) of the remaining 65 TA patients. Implant failure was related to ventricular embolization in one case, annulus dissection in one, and severe AR requiring valve-in-valve deployment in one. There was one case of peri-procedural coronary occlusion that occurred in the TA group (1.4%), which was treated by a drug-eluting stent.

Thirty-day outcome

Thirty-day outcome as well as 6- and 12-month outcomes are summarized in *Table 4* for the TA group and *Table 5* for the TF group. Mortality was lower than predicted by the logistic EuroSCORE (8.2% in the TF and 18.8% in the TA group). The rate of stroke and atrioventricular block requiring pace-maker implantation was low in both groups. Major bleeding events were more frequent in the TA arm, whereas major access site complications were more frequent in the TF arm. In the TF arm, 5 of 10 (50%) major access site complications were dissection or damage to the vessel, followed by iliac perforation (2), femoral perforation (1) and iliac artery stent

thrombosis (1). Minor vascular groin complications were scarpa wound (2), haematoma (1), false aneurysm (1), iliac stenosis (1), lymphatic fistula (1), and minor dissection (1). No death related to vascular complications occurred in the TF group. In the TA arm, there was one annular dissection resulting in death, one thoracic wound complication due to gauze being left in at the end of the procedure, one case of femoral artery suture rupture, and one case of leg ischaemia secondary to surgical canulation.

Six- and twelve-month outcome

Study compliance is summarized in *Table 6*. One-year Kaplan–Meier survival curves in the TF and TA arms are shown in *Figure 2A* and *B*, respectively. The causes of death from implant to 1-year follow-up are summarized in *Table 7*.

An improvement in NYHA class was observed in 78.1% of patients at 1 year in the TA group (*Table 8*) and 84.8% in the TF group (*Table 9*).

Of the TF patients, KCCQ score improved in 72.7% (*Table 10*) and EQ-5D in 51.6%. Among TA patients, KCCQ score improved in 73.9% and EQ-5D in 60.0%.

Table 6 Study compliance at baseline, 30 days, 6 months, and 1 year

	Baseline (%)	30 Days (%)	6 Months (%)	1 Year (%)
Follow-up	100.0[a]	93.8	93.7	100.0
NYHA	100.0	77.7	79.4	95.2
Echo[b]	100.0	87.6	83.0	82.7
KCCQ	89.2	59.8	64.2	78.0
EQ-5D	87.7	61.6	61.1	78.0

[a]For baseline, 'follow-up' implies collection of baseline risk forms.
[b]Patients that did not receive the valve were not eligible for echo follow-up. It should also be noted that in certain instances, some parameters are not evaluable from the echocardiogram.

There was one case of valve thrombosis in the TA group requiring explant at Day 257.[14]

Valve performance

Echocardiographic parameters are summarized in *Table 11*. In both groups, there was a significant reduction in the mean aortic gradient and increase in EOA. Post-implantation AR was similar in both groups and improved at follow-up. At discharge, 53.0% of patients had ≤1+ AR, 42.0% 2+, and 5% had ≥3+. At 1 year, 75.0% of patients with available data had ≤1+ AR and 25.0% had 2+.

Discussion

As life expectancy continues to increase in industrialized countries, so the incidence of degenerative aortic stenosis is expected to increase in parallel.[15] However, many of these patients are ineligible or poor surgical candidates[16–18] and TAVI may provide an alternative therapeutic approach. The PARTNER EU Trial is intended as a landmark study, which concurrently evaluates for the first time both TF and TA implantation of the Edwards SAPIEN™ THV with the selection of the delivery approach determined in each centre by the heart team. A drawback inherent in all studies of this nature is that the majority of centres commenced their TAVI experience in PARTNER EU. Consequently, this study describes all aspects of the learning phase, including patient selection and imaging as well as procedural tips and tricks. It is interesting to note that the overall proportion of patients treated by the TF approach was 46.9%, but this rate varied from 16.7 to 66.7% according to the experience and preferences of the heart team in each centre. Importantly, the findings from this study influenced the nature and design of subsequent studies, including the randomized PARTNER US Study.

Implant success

The study shows that despite limited experience, TAVI either via the TF or TA approach can be performed with a high rate of implant success (96.4 and 95.4% per protocol, and 87 and 90%

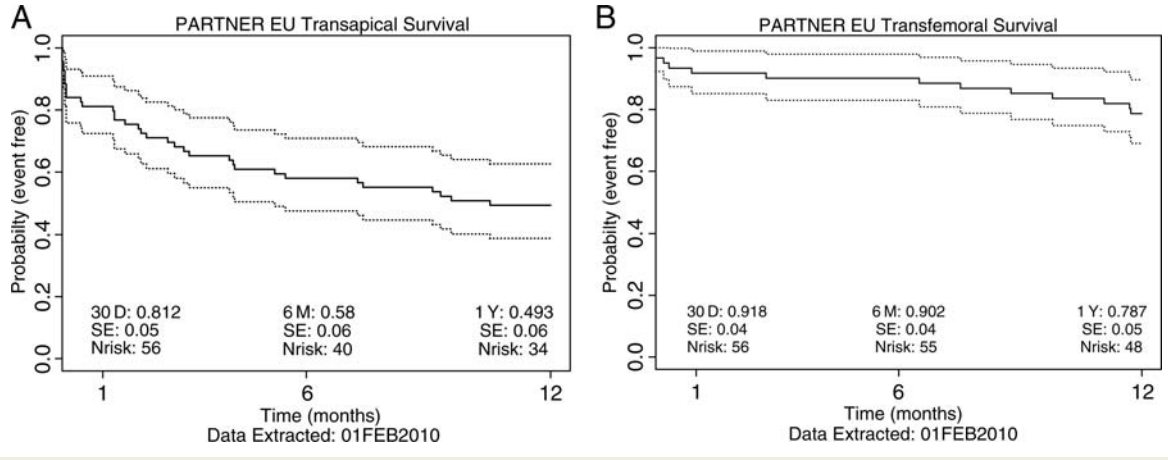

Figure 2 (*A*) Overall survival for transapical patients. (*B*) Overall survival for transfemoral patients.

Table 7 Causes of death within the first-year post-implant (early: ≤30 days; late: 31–365 days)

	Transapical			Transfemoral		
	Early	Late	Total	Early	Late	Total
Annulus dissection	1	0	1	0	0	0
Ventricular arrythmia	0	0	0	1	0	1
Cardiac failure	1	6	7	1	1	2
Bleeding	2	0	2	0	0	0
Multiple organ failure	1	3	4	2	0	2
Myocardial infarction	3	0	3	0	2	2
Severe paravalvular leak	1	0	1	0	0	0
Sepsis	0	3	3	1	0	1
Infection/Inflamation	0	2	2	0	1	1
Stroke	0	1	1	0	0	0
Sudden death	2	3	5	0	1	1
Cancer	0	1	1	0	0	0
Other	1	3	4	0	3	3
Unknown	1	0	1	0	0	0

Table 8 New York Heart Association over time (transapical patients)

Value	Baseline (%)	30 Days (%)	6 Months (%)	1 Year (%)
I	1 (1.4)	17 (30.4)	17 (42.5)	16 (47.1)
II	9 (13.0)	16 (28.6)	11 (27.5)	11 (32.4)
III	47 (68.1)	6 (10.7)	4 (10.0)	4 (11.8)
IV	12 (17.4)	3 (5.4)	0 (0.0)	1 (2.9)
Unknown	0 (0.0)	14 (25.0)	8 (20.0)	2 (5.9)
Total	69	56	40	34

Table 9 New York Heart Association over time (transfemoral patients)

Value	Baseline (%)	30 Days (%)	6 Months (%)	1 Year (%)
I	1 (1.6)	20 (35.7)	24 (43.6)	19 (39.6)
II	9 (14.8)	20 (35.7)	15 (27.3)	22 (45.8)
III	41 (67.2)	5 (8.9)	6 (10.9)	4 (8.3)
IV	10 (16.4)	0 (0.0)	0 (0.0)	1 (2.1)
Unknown	0 (0.0)	11 (19.6)	10 (18.2)	2 (4.2)
Total	61	56	55	48

on an ITT basis for TF and TA, respectively), in this very high-risk population. The procedure was aborted before valve implantation in 7.7% of cases mainly due to technical problems or non-optimal screening (difficult femoral or apical access, annulus too large, failure to cross the native valve, C-reactive protein elevation, etc.). Overall, device success was 79% (TA) and 75% (TF). Ongoing training for optimal screening and progressive experience with the device and procedure, in addition to device and delivery system downsizing should further increase the success rate.

Mortality prediction

The observed 30-day mortality of 8.2% in the TF group and 18.8% in the TA group is lower than the predicted mortality rates calculated by the logistic EuroSCORE (25.7 and 33.8%, respectively). These promising results are consistent with previous TAVI series.[19–22] This suggests that even though the EuroSCORE probably overestimates the procedural mortality risk after TAVI,[23] it also reflects the relative safety of the procedure either by the TF or the TA approach in these high-risk patients. Logistic regression analysis revealed a significant association between 1 year mortality and logistic Euroscore ($P = 0.0161$) as shown in *Figure 3*. It may not be appropriate to extrapolate EuroSCORE algorithms based on operated patients to this TAVI population, the majority of which was deemed inoperable, and other clinical and morphological variables which are not captured by this score may play an important role in risk assessment. Despite being more precise, the STS score was not associated with the 1 year mortality rate in this study ($P = 0.8515$).

Differences in survival outcomes between the transfemoral and transapical approach

As shown in *Figure 2*, the survival rate was lower after TA than TF TAVI. The difference in mortality occurred in the first 6 months. After 6 months of follow-up, the two survival curves began to run parallel. Interestingly, the mortality rate in the TA cohort is not consistent with a number of published series[22,24] which deserves careful examination in order to identify the reasons for this discrepancy. First, there was a substantial selection bias resulting from the inclusion of patients with a higher co-morbidity rate

Table 10 Summary statistics for EQ-5D overall score (UK-TTO) and Kansas City Cardiomyopathy Questionnaire overall summary scores

Type	Delivery	Visit	*n*	Overall score	*P*-value
EQ-5D	Transapical	Baseline	20	0.59 ± 0.30	0.1294
		1 year	20	0.66 ± 0.43	
	Transfemoral	Baseline	31	0.57 ± 0.32	0.3319
		1 year	31	0.62 ± 0.31	
KCCQ	Transapical	Baseline	23	49.6 ± 22.7	0.0004
		1 year	23	77.1 ± 23.4	
	Transfemoral	Baseline	33	49.9 ± 21.7	0.0002
		1 year	33	67.9 ± 23.7	

Table 11 Summary statistics for valve performance

Type	Delivery	Visit	*n*	Value
EOA (cm^2)	Transapical	Baseline	47	0.6 ± 0.2
		6 months	25	1.4 ± 0.4
		1 year	18	1.6 ± 0.5
	Transfemoral	Baseline	38	0.7 ± 0.2
		6 months	26	1.5 ± 0.4
		1 year	21	1.5 ± 0.5
Mean gradient (mmHg)	Transapical	Baseline	58	47.2 ± 18.9
		6 months	31	10.6 ± 6.9
		1 year	23	11.5 ± 3.9
	Transfemoral	Baseline	50	46.6 ± 17.3
		6 months	34	11.1 ± 3.7
		1 year	34	12.7 ± 4.8
LVEF (%)	Transapical	Baseline	51	54 ± 13.8
		6 months	30	56.1 ± 14.8
		1 year	23	55.2 ± 8.2
	Transfemoral	Baseline	46	53.2 ± 18.4
		6 months	29	56.2 ± 16.1
		1 year	29	56.3 ± 13.0

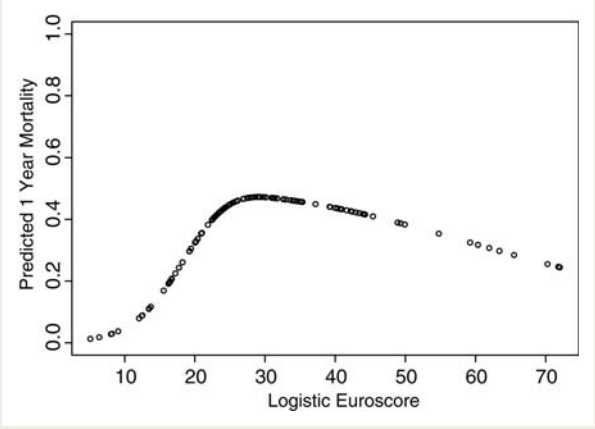

Figure 3 Predicted 1 year mortality vs. Logistic Euroscore.

(mainly peripheral disease) in the TA group. Furthermore, although several complications of TAVI are common to both approaches, TA TAVI requires thoracotomy, puncture of the apex and introduction of a large sheath into the left ventricle, which may lead to specific post-operative complications. Importantly, as the current results represent early experiences with these devices, better outcomes in the TA group are to be expected in the future. Careful patient selection by avoiding, for example, patients with severe respiratory failure, in addition to optimal training and collaboration between the cardiac surgeon and the interventional cardiologist, and optimal image quality in the operating room are all required for successful TAVI outcomes using the TA approach.

Atrioventricular block

The incidence of complete atrioventricular block requiring pacemaker implantation at ≤30 days was low (1.8% for the TF and 3.8% for TA approach), and is consistent with other reports on the Edwards SAPIEN™ valve prosthesis.[18–21,23] This incidence is lower than that observed with the CoreValve™ device.[25,26] One of the major differences between the two devices is the depth of placement of the valve at the left ventricular outflow track level. The CoreValve™ device is designed to be seated lower than the SAPIEN™ valve and may compress the underlying conduction system.

Valve positioning

There was one ostial coronary obstruction secondary to valve implantation which required stent implantation in the TA group. This is a rare complication which may occur in ~1% of cases.[27,28] When the distance between the annulus and the coronary ostia is short, the native valve may be pushed against the coronary ostium by the THV. Positioning the valve too high or not coaxial with the outflow track may increase this risk. In all cases, excellent image quality when carrying out the TA and also TF approach is crucial for identifying potential problems. No device-induced mitral valve dysfunction was observed.

Valve embolization occurred in two TF and in one TA cases. This is another infrequent complication which occurs in ~1% of cases.[28] Careful pre-procedure annulus measurements, stable lead positioning for rapid pacing, optimal valve positioning, full balloon inflation at the time of valve deployment, and complete balloon deflation before stopping rapid pacing are of utmost importance to prevent this complication.

Risk of stroke

The incidence of stroke at ≤30 days was relatively low, 1.5% in the TA group and 3.3% in the TF group. This compares favourably with the risk of peri-operative stroke following surgical AVR in elderly patients ranging from 3 to 7%.[15,29,30] Careful patient selection, device preparation, optimal device progression, and positioning, as well as adequate antiplatelet pre-medication and anticoagulation regimen are likely to reduce this risk.

Valve performance

Echocardiographic data have shown an immediate reduction in the transvalvular gradient after valve implantation and, in the majority of cases, no significant AR. Furthermore, the initial increase in EOA remained stable at 6- and 12-month follow-up. Finally, there was no evidence of THV deterioration up to 1 year. The SAPIEN™ valve was explanted in one patient on Day +252 due to valve thrombosis. Although the cause of thrombosis is unknown, the fact that the patient discontinued aspirin and clopidogrel 6 weeks post-procedure may have played a role.

Quality of life

Improvement in QoL and activities of daily living may well be the most important benefit of TAVI in this elderly population of patients who prefer to add life to their years rather than years to their life; 82.1% had an improvement in their NYHA class, 87.2% being in Class I or II. EQ-5D demonstrated marginal improvement at 1 year post-intervention. However, this score is not specific to this patient population and may not be an adequate gauge. On the other hand, the KCCQ overall summary score, which is specific for cardiac patients, demonstrated an important treatment effect with 73.2% of patients experiencing a significant improvement from baseline to 1 year.

Study limitations

PARTNER EU embedded the 'learning curve' for most European TAVI operators, compounded by the use of an earlier generation delivery system which was more prone to complications. Unfortunately, the number of patients included in the study is too small to provide information about the role of the learning phase and predictors of complications. This study is not a randomized comparison of TA vs. TF approach, but a complementary approach. Assessment of bioprosthetic valve durability will require longer-term follow-up in PARTNER EU and other TAVI clinical trials. Finally, when adjudicating events, the Clinical Events Committee was not blinded to the procedure performed.

Conclusion

The results of this first registry, PARTNER EU, confirm the safety and efficacy of the Edwards SAPIEN™ valve implanted in very high-risk patients with severe aortic stenosis via either the TF or the TA route, depending on the decision of the heart team. The higher mortality rate observed in the TA group seems to be mainly related to a selection bias. The use of this device and similar devices mandates multi-specialty collaboration. Future registries and randomized trials should provide a better definition of the safety and durability aspects of both techniques.

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Conflict of interest: D.H. is a proctor for Edwards Lifesciences. T.L. is a proctor for Edwards Lifesciences. M.R. is a proctor for Edwards Lifesciences. M.T. is a proctor and advisory board member for Edwards Lifesciences. M.T. is a proctor for Edwards Lifesciences. The remaining authors report no conflict.

Appendix

Participating investigators/centres/patient numbers

Site name	# of patients
Vienna—*Medical University (AKH)* H. Baumgartner, D. Glogar, M.T. Kasimir, P. Simon, W. Wisser, E. Wolner	19
Paris—*Hôpital Bichat* N. Al-Attar, D. Himbert, P. Nataf, A. Vahanian	18
London—*Kings College Hospital* A. El-Gamel, P. MacCarthy, M. Thomas, O. Wendler	17
Essen—*West-German Heart Center, Essen, University Hospital* H. Eggebrecht, R. Erbel, H. Jakob, P. Kahlert, S. Sack, M. Thielmann, D. Wendt	16
Massy—*Institut Hospitalier Jacques Cartier* P. Donzeau-Gouge, A. Farge, T. Lefevre, M.-C. Morice, M. Romano	15
Aalst, Onze Lieve Vrouwziekenhuis (*OLVZ*) F. Casselman, B. De Bruyne, I. Degrieck, Marc Vanderheyden, H. Vanermen	13
Rouen—*Charles Nicole Hôpital* J.-P. Bessou, A. Cribier, H. Eltchaninoff, Y.-P. Litzler	12
Frankfurt—*J.W. Goethe University* M. Doss, S. Fichtlscherer, V. Schächinger, G. Wimmer-Greinecker	12
Rotterdam—*Erasmus Medical Center* P. DeJaegere, A.P. Kappetein, P. Serruys	8

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