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The JUPITER registry: 1-year results of transapical aortic valve implantation using a second-generation transcatheter heart valve in patients with aortic stenosis

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Abstract

OBJECTIVES: Transcatheter aortic valve replacement (TAVR) is an established therapy for patients with aortic stenosis (AS) at high surgical risk. The JenaValve™ is a second-generation, self-expanding transcatheter heart valve (THV), implanted through transapical access (TA). During stent deployment, a specific 'clipping-mechanism' engages native aortic valve cusps for fixation. We present 1-year outcomes of the JUPITER registry, a post-market registry of the JenaValve for TA-TAVR.

METHODS: The JUPITER registry is a prospective, multicentre, uncontrolled and observational European study to evaluate the long-term safety and effectiveness of the Conformité Européenne-marked JenaValve THV. A total of 180 patients with AS were enrolled between 2012 and 2014. End-points were adjudicated in accordance with the valve academic research consortium document no. 1 definitions.

RESULTS: The mean age was 80.4 ± 5.9 years and the mean logistic European system for cardiac operative risk evaluation I 21.2 ± 14.7%. The procedure was successful in 95.0% (171/180), implantation of a second THV (valve-in-valve) was performed in 2.2% (4/180) and conversion to surgical aortic valve replacement (SAVR) was necessary in 2.8% (5/180). No annular rupture or coronary ostia obstruction occurred. Two patients required SAVR after the day of index procedure (1.1%). All-cause mortality at 30 days was 11.1% (20/180), being cardiovascular in 7.2% (13/180). A major stroke occurred in 1.1% (2/180) at 30 days, no additional major strokes were observed during 1 year. All-cause mortality after 30 days was 13.1% (21/160) and combined efficacy at 1 year was 80.8% (122/151). At 1-year follow-up, no patient presented with more than moderate paravalvular leakage, while 2 patients (3.2%) showed moderate, 12 (19.0%) mild and 49 (82.4%) trace/none paravalvular regurgitation.

CONCLUSIONS: In a high-risk cohort of patients undergoing TA-TAVR for AS, the use of the JenaValve THV is safe and effective. In patients at higher risk for coronary ostia obstruction, annular rupture or with limited aortic valve calcification, the JenaValve might be preferable for implantation due to its clipping-mechanism engaging native aortic valve cusps for fixation with reduced radial forces of the self-expanding stent.

Keywords: TAVI • TAVR • Transcatheter heart valves • Aortic stenosis

INTRODUCTION

During the last decade, transcatheter aortic valve replacement (TAVR) has emerged as the preferred treatment for aortic stenosis (AS) in patients at high risk or not suitable for surgery. Since then, TAVR has entered international guideline recommendations and more than 250 000 patients have undergone TAVR worldwide [1, 2]. The generally desired access route is through the transfemoral artery (TF-TAVR) and the miniaturization of transcatheter heart valve (THV) delivery systems has made TF-TAVR feasible in >80% of patients [3, 4]. However, retrograde TF-TAVR and also trans-sub-clavian TAVR are limited by size, anatomy and the degree of calcification found in the access vessels and the aorta. Hence, TAVR is still performed through transapical access (TA-TAVR) in 10–20% of patients [3, 4]. Apart from the evolvement of delivery techniques, second-generation THV became available and received Conformité Européenne (CE)-mark approval. The main focus of the next-generation THV was to overcome remaining technical challenges, such as malpositioning, paravalvular regurgitation and conduction disturbances, known complications from the first-generation THV experience [5].

The JenaValve™ (JenaValve Technology GmbH, Munich, Germany) is a second-generation THV, designed to ease correct positioning and to reduce the incidence of paravalvular regurgitation and complete heart block. It enables calcium-independent annular fixation by engaging the native aortic cusps through an active 'clipping mechanism' for fixation with tactile feedback during implantation. Allowing for anatomically aligned positioning without the need for rapid-ventricular pacing during implantation, it is also fully repositionable during the first step of implantation [6]. The feasibility and efficacy have been reported previously [6–8]. We report 1-year safety and efficacy outcomes of a multicentre, post-market registry in patients undergoing TA-TAVR for AS using the JenaValve THV, conducted at 15 centres across Europe.

MATERIALS AND METHODS

Registry

The JenaValve evalUation of long-term Performance and safety In paTients with sEvere aortic stenosis oR aortic insufficiency (JUPITER) registry is a prospective, multicentre, uncontrolled and observational European post-market registry to evaluate the long-term safety and effectiveness of the CE-marked JenaValve system. Enrolment was initiated in May 2012 and completed in 2014 with 210 patients enrolled ($n = 180$ for AS, $n = 30$ for aortic regurgitation). A total of 15 centres participated (see Fig. 1 for study population).

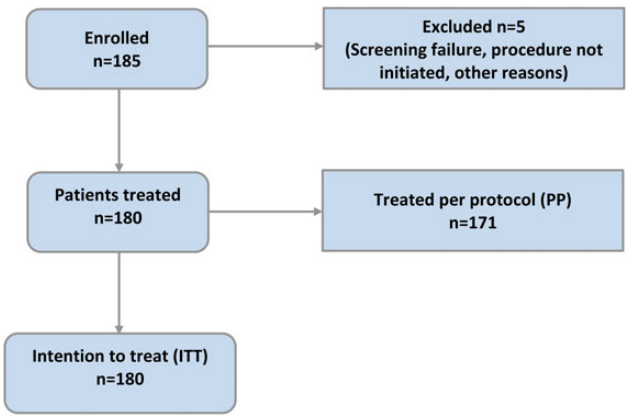

Figure 1: Study population. Intention-to-treat patients were included for further analyses.

Patients

Patients with severe symptomatic AS or aortic regurgitation eligible for TAVR as per existing contraindications for surgery or per definition of high surgical risk were eligible candidates for the study. This manuscript refers to data on AS patients only. Surgical risk was assessed using the logistic European system for cardiac operative risk evaluation (EuroSCORE I), whereas patients were identified to be at increased risk on the basis of a logistic EuroSCORE I ≥20% or the consensus of the heart team. In addition, patients with anatomical unsuitability for TAVR using the JenaValve THV [i.e. unsuitable aortic annulus diameter, bicuspid aortic valve, previous surgical aortic valve replacement (SAVR), ascending aortic aneurysm, low origin of the left-main stem, evidence of thrombus] were not eligible for JenaValve treatment. Patients with a history of recent myocardial infarction and patients with concomitant coronary artery disease and the need for simultaneous revascularization were also not included in this registry.

All participating centres followed a 'TF first' strategy, but were also experienced in performing TA-TAVR. The study protocol was approved by the local ethics committees of the participating centres and all patients provided written informed consent in accordance with the declaration of Helsinki.

The study is registered under the ClinicalTrials.gov identifier NCT01598844.

Procedure and device

The JenaValve THV is a biological prosthesis made of porcine leaflets mounted into a self-expandable, low profile, Nitinol stent. Three positioning feelers ensure implantation into the respective native aortic valve sinuses through flexible stent posts with a 'clipping' mechanism, leading to commissural and anatomical alignment of the trileaflet THV. This special feature of the JenaValve ensures, in combination with the radial forces applied by the self-expanding stent, fixation of the THV inside the native aortic valve [6]. The procedural steps of implantation have been described elsewhere [6, 9]. The JenaValve gained market access in Europe with CE-mark approval for use in AS in September 2011 and in September 2013 for the treatment of pure aortic regurgitation in patients at high surgical risk. The prosthesis is available in sizes 23, 25 and 27 mm, suitable for implantation in annuli with a diameter ranging from 21 to 27 mm, and is delivered through a 32-French flexible catheter in an antegrade fashion via TA access [9].

During the study period, adjustments on the Cathlete delivery system were made and since October 2013, the Cathlete Plus delivery system has been used in 47 patients. The Cathlete Plus mainly features a newly designed handle, which allows the operator to activate all steps of valve deployment by rotating the proximal portion of the handle. In contrast to its predecessor, it allows for a more controlled and intuitive positioning and deployment of the JenaValve as attention to the fluoroscopy screen during implantation is maintained. A safety button is integrated in the handle and prevents unintentional activation of each deployment step. The sequence of valve deployment remained unchanged.

As per the study protocol, each implantation was performed through a left-sided anterolateral mini-thoracotomy under general anaesthesia. Intraprocedural transoesophageal echocardiography and fluoroscopy were applied to monitor valve function and the procedure itself. In each patient with AS, balloon valvuloplasty was performed under rapid-ventricular pacing prior to implantation of the THV using a balloon of annular size. During implantation, no rapid-ventricular pacing was necessary. Post-procedural anticoagulation and platelet antiaggregation therapy was performed as per institutional standard; however, most centres followed recommendations of dual antiplatelet therapy for 4–24 weeks followed by permanent treatment with acetylsalicylic acid [10]. A number of patients were discharged on additional medication with coumadin as they presented with atrial fibrillation.

Outcomes measures

The primary end-point of the study was all-cause mortality at 30 days after implantation.

The secondary end-points were adjudicated in accordance with the first valve academic research consortium document no. 1 (VARC-I) standardized end-point definitions, the composite end-points being: device success; combined safety at 30 days and combined efficacy at 1-year [11]. In addition, quality of life was assessed as the secondary end-point using the Short-Form health survey (SF-12) [12].

Definition and data collection

Participating centres completed standardized electronic case report forms for each patient enrolled in the study. An independent monitor ensured compliance in following the protocol, complete, timely and accurate data submission and overall data integrity. Prespecified serious adverse events were adjudicated by an independent medical reviewer.

Statistical analysis

All patients of the study cohort were analysed, irrespective of conversions. Categorical variables are expressed as absolute numbers and percentages throughout the manuscript, continuous variables as mean and standard deviation unless stated otherwise. Percentages are calculated relative to the total study population, except for rates of new events during follow-up, which were calculated on the basis of the actual numbers at risk. Overall rates of events during the total follow-up period were calculated on the basis of the total study population. For the primary and secondary categorical end-points, estimates of relative frequencies were calculated. For changes in pre–post differences of follow-up data, McNemar–Bowker test was used for categorical variables, the paired Wilcoxon-test for ordinal variables and a paired *t*-test for continuous variables. Significance level was set to a *P*-value of 0.05. Missing values of follow-up data were not replaced, only data of patients under observation were analysed. Kaplan–Meier analyses were used for survival estimates at 1 year. Sub-group analysis was performed, stratified by EuroSCORE I/II, gender and degree of paravalvular regurgitation. All computation was carried out using the SAS software, Version 9.1.3. Copyright © 2004 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

The mean patient age was 80.4 ± 5.9 years and the mean logistic EuroSCORE I was 21.2 ± 14.7%. Most patients were in New York Heart Association Class (NYHA) class III or IV prior to the procedure and presented with a considerable number of comorbidities (see Table 1). The majority of patients had concomitant coronary artery disease and concomitant mitral regurgitation.

Acute procedural outcomes

Procedural success, defined as implantation of one THV in the intended position, was achieved in 95.0% (171/180). In 5.0% (9/180), conversion to another procedure was necessary. Of these patients, 6 (66.7%), showed residual severe paravalvular regurgitation after post-deployment balloon dilatation and therefore underwent open SAVR (4/6) or valve-in-valve (ViV, 2/6) implantation of a second THV. In one of these cases, not only paravalvular regurgitation but also a concomitant apical rupture made conversion to SAVR necessary, in which the THV was

Table 1: Baseline characteristics of the cohort

Baseline characteristics	*n* = 180
Age, mean (SD)	80.4 ± 5.9
Men, no. (%)	105 (58.3)
Logistic EuroSCORE I, mean (SD), %	21.2 ± 14.7
Logistic EuroSCORE II, mean (SD), %	7.5 ± 8.0
STS-PROM, mean (SD), %	7.3 ± 6.8
Functional NYHA class	
II, no. (%)	30 (16.7)
III, no. (%)	139 (77.2)
IV, no. (%)	11 (6.1)
Concomitant coronary artery disease, no. (%)	103 (57.2)
Previous MI, no. (%)	24 (13.3)
Previous PTCA/PCI, no. (%)	65 (36.1)
Previous CABG, no. (%)	46 (25.6)
Concomitant mitral regurgitation, no. (%)	146 (81.1)
Mild, no. (%)	107 (73.3)
Moderate, no. (%)	37 (25.3)
Severe, no. (%)	2 (1.4)
Chronic atrial fibrillation, no. (%)	58 (32.2)
Previous pacemaker implantation, no. (%)	27 (15.0)
Peripheral vascular disease, no. (%)	43 (23.9)
Carotid artery stenosis >50%, no. (%)	30 (16.7)
Previous transient ischaemic attack, no. (%)	14 (7.8)
Previous stroke, no. (%)	23 (12.8)
COPD, no. (%)	33 (18.3)
Pulmonary hypertension, no. (%)	43 (23.9)
Chronic renal disease, no. (%)	69 (38.3)
Haemodialysis, no. (%)	5 (7.2)
Cardiovascular risk factors	
Diabetes mellitus, no. (%)	62 (34.4)
Arterial hypertension, no. (%)	157 (87.2)
Hyperlipidaemia/hypercholesterolaemia, no. (%)	94 (52.2)

PTCA: percutaneous transluminal coronary angioplasty; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; SD: standard deviation; EuroSCORE: European system for cardiac operative risk evaluation; NYHA: New York Heart Association Class; MI: myocardial infarction.

replaced with a simultaneous repair of the ventricle. Other reasons for conversion were elevated transvalvular pressure gradients after repeat balloon dilatation in 1 patient, incomplete expansion of the JenaValve with subsequent ViV implantation of a second THV in 1 patient and supracoronary migration of the JenaValve with implantation of a second THV in annular position in another patient (see Tables 2 and 3). Post-deployment balloon dilatation was performed in 43.9% (79/180) of patients, either due to significant paravalvular regurgitation in 64.6% (51/79), or elevated transvalvular pressure gradients in 20.3% (16/79). Of note, no patient experienced annular rupture or mechanical obstruction of the coronary ostia. The overall rate of device success, defined as implantation of one THV in the proper position without need for conversion to SAVR and intended valve performance in echocardiography, was 79.1% (136/172). The median stay on intensive care unit was 2 days (lower, upper quartile: 1, 3) and the total mean postoperative length of stay was 10.6 ± 5.6 days.

Table 2: Procedural outcomes, at 30 days and 1 year

Procedural outcomes	
Duration (skin-to-skin), mean (SD), min	95.9 ± 57.7
Duration of valve deployment[a], mean (SD), min	8.3 ± 5.9
Volume of contrast agent, mean (SD), ml	122.7 ± 79.9
Fluroscopy time, mean (SD), min	9.2 ± 4.3
THV size used	
23 mm, no. (%)	40 (22.2)
25 mm, no. (%)	78 (43.3)
27 mm, no. (%)	62 (34.5)
Outcomes at 30 days	
All-cause mortality at 30 days, no. (%)	20 (11.1)
Logistic EuroSCORE I <20%, no. (%)	9 (8.8)
Logistic EuroSCORE I 20–30%, no. (%)	7 (16.7)
Logistic EuroSCOREI >30%, no. (%)	4 (11.1)
Paravalvular regurgitation[b]	
None, no. (%)	89 (60.1)
Trace, no. (%)	33 (22.3)
Mild, no. (%)	25 (16.9)
Moderate, no. (%)	1 (0.7)
Permanent pacemaker implantation, no. (%)	26 (14.4)
Acute kidney injury	
Stage I, no. (%)	16 (8.9)
Stage II, no. (%)	5 (2.8)
Stage III, no. (%)	11 (6.1)
Minor bleeding, no. (%)	16 (8.9)
Major bleeding, no. (%)	27 (15.0)
Life-threatening or disabling bleeding, no. (%)	19 (10.6)
Myocardial infarction, no. (%)	2 (1.1)
Periprocedural, no. (%)	1 (0.56)
Spontaneous, no. (%)	1 (0.56)
New onset	
Transient ischaemic attack, no.	0
Minor stroke, no. (%)	1 (0.56)
Major stroke, no. (%)	2 (1.1)
Outcomes at 1 year	
All-cause mortality[c], no. (%)	41 (23.3)
Logistic EuroSCORE I <20%, no. (%)	20 (19.6)
Logistic EuroSCORE I 20–30%, no. (%)	13 (30.9)
Logistic EuroSCORE I >30%, no. (%)	8 (22.2)
Paravalvular regurgitation	
None, no. (%)	34 (54.0)
Trace, no. (%)	15 (23.8)
Mild, no. (%)	12 (19.0)
Moderate, no. (%)	2 (3.2)
Permanent pacemaker implantation, no. (%)	35 (19.4)
Acute kidney injury	
Stage I, no. (%)	16 (8.9)
Stage II, no. (%)	5 (2.8)
Stage III, no. (%)	11 (6.1)
Minor bleeding, no. (%)	17 (9.4)
Major bleeding, no. (%)	34 (18.9)
Life-threatening or disabling bleeding, no. (%)	21 (11.7)
Myocardial infarction, no. (%)	3 (1.7)
New onset	
Transient ischaemic attack, no. (%)	2 (1.1)
Minor stroke, no. (%)	1 (0.56)
Major stroke, no. (%)	2 (1.1)

SD: standard deviation; THV: transcatheter heart valve; EuroSCORE: European system for cardiac operative risk evaluation.
[a]Time from initial insertion until full removal of delivery system.
[b]Paravalvular regurgitation was measured at discharge visit.
[c]According to Kaplan–Meier survival estimates.

Haemodynamic outcomes

Implantation of the THV led to immediate reduction in mean transvalvular pressure gradients from 39.3 ± 13.9 to 14.1 ± 5.6 mmHg at discharge ($P < 0.01$). Correspondingly, effective orifice area (EOA) increased from 0.8 ± 0.3 to 1.7 ± 0.4 cm^2 ($P < 0.01$). The rate of paravalvular regurgitation was low, as 82.4% had no or only

Table 3: Outcomes according to VARC-I composite end-points

Composite end-point	*n* = 180
Device success, no. (%)	136 (79.1)[a]
Need for valve-in-valve of a second THV, no. (%)	4 (2.2)
Conversion to open SAVR, no. (%)	5 (2.8)
Function of THV not as intended assessed by echo[a], no. (%)	27 (15.7)
Combined safety end-point at 30 days, no. (%)	45 (25.0)
All-cause mortality, no. (%)	20 (11.1)
Cardiovascular mortality, no. (%)	13 (7.2)
Major stroke, no. (%)	2 (1.1)
Life-threatening or disabling bleeding, no. (%)	19 (10.6)
Acute kidney injury stage 3, no. (%)	11 (6.1)
Periprocedural MI, no. (%)	1 (0.6)
Coronary ostia occlusion, no. (%)	0
Major vascular complication, no. (%)	15 (8.3)
Annular rupture, no. (%)	0
Repeat procedure for valve-related dysfunction, no. (%)	10 (5.6)
Valve migration, no. (%)	1 (0.6)
Combined efficacy at 1 year, no. (%)	122/151[b] (80.8)
All-cause mortality after 30 days, no. (%)	21 (13.1)
Cardiovascular mortality, no. (%)	12 (7.5)
Rehospitalization for valve-related symptoms, no. (%)	9 (5.0)
Prosthetic valve endocarditis, no. (%)	1 (0.6)
Repeat procedure for valve-related dysfunction, no. (%)	11 (6.1)
SAVR, no. (%)	7 (3.9)
Valve-in-valve, no. (%)	4 (2.2)

VARC-I: valve academic research consortium document no. 1; THV: transcatheter heart valve; SAVR: surgical aortic valve replacement; MI: myocardial infarction; EOA: effective orifice area.
[a]Percentage related to a total number of 172 patients where all information was available. In 51 patients, no data on EOA were available and only transvalvular gradient/peak velocity/regurgitation was taken into account for the assessment of valve performance.
[b]Nine of the 160 patients alive at 30 days withdrew informed consent during 1-year follow-up.

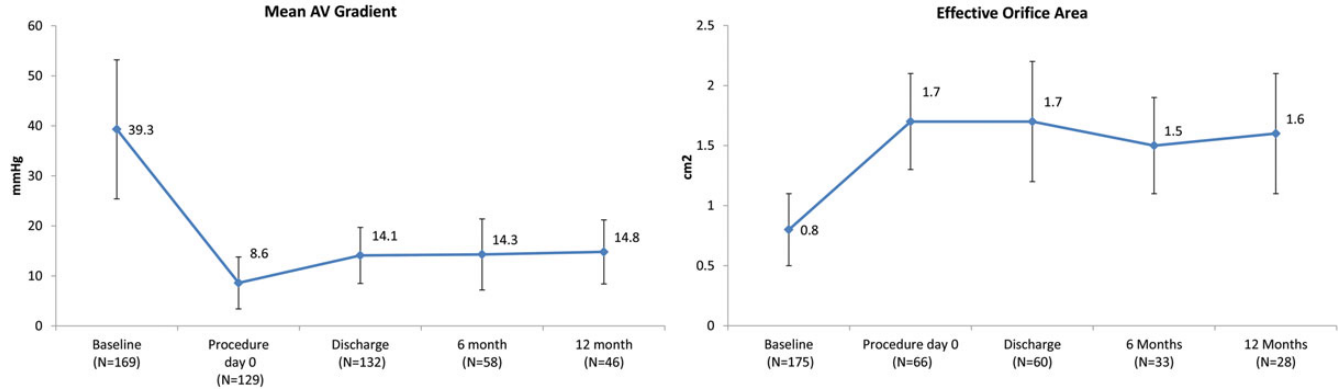

Figure 2: Mean transvalvular aortic gradient and effective orifice area at baseline and during follow-up ($P < 0.01$). The error bars in the figure illustrate standard deviation.

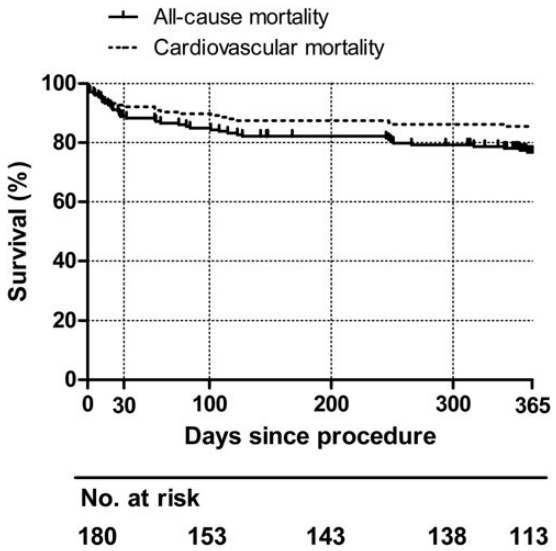

Figure 3: Survival of the study cohort. Separate survival curves are reported for all-cause and cardiovascular mortality.

trace paravalvular regurgitation. Significant paravalvular regurgitation was found in 1 patient at discharge (0.7%, 1/148) and was moderate.

At 1 year, paravalvular regurgitation was moderate in 3.2% (2/63), mild in 19.0% (12/63) and trace or not present in 82.4% (49/63). For echocardiographic follow-up, see Fig. 2.

Mortality at 30-day and 1-year follow-up

All-cause mortality at 30 days was 11.1% (20/180), being cardiovascular in 7.2% (13/180). Neither all-cause nor cardiovascular mortality showed an association with the logistic EuroSCORE I/II, gender or the degree of paravalvular regurgitation (see Tables 2 and 3). Of the patients with conversion to another procedure, mortality at 30 days was 22.2% (2/9).

At 1-year follow-up, all-cause mortality according to Kaplan–Meier survival estimates was 23.3% (41/180) with a cardiovascular mortality of 14.2%. Consequently, mortality between 30 days and 1 year was 13.1% (21/160), being cardiovascular in 7.5% (12/160) (see Fig. 3). No association was seen between mortality and gender or rate of paravalvular regurgitation.

Secondary end-points according to valve academic research consortium document no. 1 at 30-day and 1-year follow-up

The combined safety end-point at 30 days was met in 25% of patients (45/180), thus 75% of the patients did not suffer any such event. Major strokes occurred in 1.1% (2/180); no additional major strokes occurred up to 1-year follow-up. After 30 days, 1.1% of patients (2/180) had a transient ischaemic attack. The most frequent complication was major or life-threatening bleeding, being 25.6% (46/180), while only life-threatening bleeding event accounts for the combined safety end-point. From major/life-threatening bleeding events, 54.3% (25/46) were due to post-operative anaemia/transfusion requirements, as per VARC-I definition. In addition, 10.9% of major/life-threatening bleeding events (5/46) were caused by ventricular rupture with the need for surgical repair and 17.4% of bleeding events (8/46) were due to the need for re-exploration for bleeding. An additional 5% (9/180) had either major or life-threatening bleeding events between 30 days and 1 year. Of note, 12.8% (23/180) of patients were discharged on single antiplatelet plus coumadin medication. In addition, 3.3% (6/180) received classic 'triple' therapy at discharge (dual antiplatelet medication plus Coumadin) and another 8.9% (16/180) were on three different antithrombotic/antiplatelet drugs at discharge. The rate of permanent pacemaker implantation at 30 days was 14.4% (26/180), and was performed in 12.2% (22/180) of patients due to total atrioventricular block. Between 30 days and 1 year, pacemaker implantation was necessary in 5.8% (9/154), with the indication having been reported as total atrioventricular block in 2.6% (4/154). The overall rate of reoperation for valve-related dysfunction was 6.1% (11/180), in 5.0% (9/180) necessary on the day of index procedure as mentioned above. Thereafter, reoperations were necessary in 1.11% (2/180) due to paravalvular regurgitation and were treated with SAVR. All cases of acute kidney injury according to VARC-I criteria observed in our cohort were observed directly after the procedure, and no additional patient developed acute kidney injury thereafter. Combined efficacy at 1 year was achieved in 80.8% (122/151) (see Tables 2 and 3).

Quality of life at 1-year follow-up

NYHA class improved from 83.3% (150/180) of patients being in NYHA III/IV at baseline to 75.0% of patients (93/124) being in

NYHA class I/II at 1-year follow-up ($P < 0.001$). Correspondingly, the physical health component scale of the SF-12 health survey improved from 35.7 ± 9.1 to 39.9 ± 9.2 ($P = 0.022$, $n = 106$), while the mental component scale remained stable being 48.5 ± 10.3 at baseline and 51.0 ± 9.7 at 1 year ($P = 0.112$, $n = 106$).

DISCUSSION

We report the results of a multicentre post-market registry of the JenaValve for TA-TAVR in patients with AS. This second-generation THV is characterized by a special fixation mechanism of the THV by clipping the native cusps. It also provides tactile feedback during deployment and is repositionable after the first step of implantation. Since market access in Europe in 2011, the JUPITER registry has ensured prospective data collection of real-world patients treated with the JenaValve system. The unique fixing mechanism, which allows for safe anchoring of the prosthesis regardless of the degree of calcification, as well as good early outcomes in patients with aortic regurgitation has also resulted in CE mark approval of the JenaValve for the treatment of isolated, non-calcified aortic regurgitation in September 2013.

Acute procedural outcomes

The rate of procedural success of 95.0% in our high-risk clinical cohort was higher compared with the success rate reported (89.6%) for the initial JenaValve experience in the CE-mark study, which may reflect a learning curve of the participating centres and refinements of the delivery system [6]. The rate of procedural success was also comparable with that of previously published experiences of other THV as it was 92.4% in the SOURCE registry and 96.5% in a real-world experience of self-expanding, next-generation THV for TA-TAVR [5, 13]. After implantation of the THV, post-deployment balloon dilatation was necessary in a substantial proportion of patients (43.9%), which may be due to the lower radial forces of this Nitinol-based stent compared with those of other self-expandable prostheses (post-deployment balloon dilatation: 21.2%) and balloon-expandable stents (21.0%), but also limits the hypothetical advantage of an implantation without rapid-ventricular pacing [14, 15]. However, this may explain why no annulus rupture, with its usual catastrophic consequences, has been observed in this registry. The fixation mechanism of the JenaValve enables active engagement of the native aortic leaflets within the THV stent, leading to anatomically aligned positioning and a low profile of the stent in the native sinuses. This most likely is the main reason that coronary ostia obstruction did not occur throughout the study period. Yet, the risk of such event in overall TAVR for native AS is low, as the incidence is <0.1% [16]. The number of patients in our study cohort is not sufficient to prove this hypothesis. THV migration or malpositioning, however, one of the complications most frequently causing conversion to SAVR or bailout ViV [33% of causes for emergent cardiac surgeries, was rare in our cohort (0.56%)] [16]. This seems reasonable when considering that due to the engagement of the native aortic valve leaflets, the implantation height of the JenaValve is predetermined by the native valve level, so that axial THV malpositioning is unlikely. In our study, reasons most frequently leading to surgical conversion of the procedure were paravalvular regurgitation in 2.8% (5/180).

As a result of the above, the JenaValve could be particularly advantageous in patients at high risk for annular rupture [e.g. excessive calcification of the left ventricular outlow tract (LVOT)], or patients with low coronary ostia. Moreover, in patients with a short aorto-mitral continuity (e.g. due to prior mitral valve replacement), the JenaValve could be beneficial as it has little interaction with structures of the LVOT. Given its anatomical alignment with preserved ostial access after implantation, this THV could also be advantageous in patients with a high probability of future percutaneous coronary intervention due to underlying coronary artery disease.

Haemodynamic outcomes

From previous experience with the JenaValve, a significant reduction in transvalvular pressure gradients with an increase in EOA could be anticipated [6]. We also observed a very low incidence of significant paravalvular regurgitation, as only 1 patient had moderate regurgitation at 30 days (0.56%), which is lower compared with experience from the CE-mark study (13.6%) and previous experience with other self-expandable THV (9.9%) [6, 17]. However, out of the cases with conversion to SAVR or ViV, 5 were due to the paravalvular regurgitation and must be taken into account when looking at outcome data of our cohort. This would add another 2.8%, leading to a total of 3.5% of significant paravalvular regurgitation after implantation, which is still significantly lower than reported previously for self-expanding THV—naturally at higher risk for paravalvular regurgitation [18]. Data on other self-expanding THV of the second generation (ACURATE TA™, Symetis SA Ecublens, Switzerland) showed moderate paravalvular regurgitation in 3.4% plus 2 patients being converted to SAVR/ViV due to paravalvular regurgitation (7.5%). We therefore conclude that the very low incidence of paravalvular regurgitation achieved with the JenaValve in conjunction with the high rate of procedural success may yield excellent long-term outcomes.

At 1 year, limited echo data were available, but showed a sustained THV performance with no increase in gradients or apparent THV thromboses. There was only one additional patient with moderate paravalvular regurgitation. Clinically significant valve deterioration was not observed in any case. As the JenaValve is folded into the 32-French catheter for delivery and not crimped, there is the possibility of more favourable long-term durability. However, the observational period of our study was certainly too short to assess valve durability and further studies are needed to investigate this issue.

Mortality

The mortality rates of TA-TAVR procedures have continuously improved during the last years, but remain higher than the mortality seen after TF-TAVR. One reason certainly is the higher risk profile of TA-TAVR patients, but the additional surgical trauma has also been accused to account for some of the mortality difference. The 30-day mortality rate of 11.1% observed in our cohort corresponds to real-world data on TA-TAVR, as a recently published outcome analysis of the UK TAVR registry showed a 30-day mortality of 11.0% in a cohort of 761 TA-TAVR patients with similar age and baseline comorbidities; a report on outcomes of 567 patients in the FRANCE 2 registry showed a 30-day mortality of 13.9% for TA-TAVR [3, 4]. The German aortic valve registry demonstrated a lower 30-day mortality of 9.0% in TA-TAVR patients; however, baseline characteristics and risk profile of patients were not specified in detail [19]. All-cause mortality at 1 year was 23.3% in our

cohort, which again corresponds to the average mortality rate of patients undergoing TA-TAVR when looking at data from the UK TAVR registry (27.0%) [4]. The mortality of TA-TAVR at 1 year was higher in the FRANCE-2 registry (32.3%) [3]. On the one hand, this might be a reflection of a learning curve of TAVR procedures *per se*, as in these registries all procedures performed since the introduction of TAVR were included. Patients also had a higher mean logistic EuroSCORE I (24%) compared with that of our cohort (21.2%), while age was comparable. Likely, a higher degree of comorbidities resulted in a higher mortality at 1 year. In this context, it is important to keep in mind that the annual mortality rate of European citizens at 81 years of age was 5.5% in 2013 [20]. Thus, a mortality rate of 13.1% between 30 days and 1 year is indeed higher compared with that of the healthy population, but does not seem excessive in view of the severe comorbidities present in these patients and has to be weighed against the potential mortality of medical therapy alone.

Secondary end-points according to valve academic research consortium document no. 1

The actual stroke risk of patients undergoing TA-TAVR has been hypothesized to be lower as in TF-TAVR and was 2.7% for TA-TAVR in a large meta-analysis of over 10 000 patients [21]. On the other hand, post-deployment balloon dilatation has been reported to be a major risk factor for perioperative strokes after TAVR and was performed in 43.9% of the patients in our cohort. The resulting stroke rate in our patients was very low, being approximately one-third of the rate in the conventional TA-TAVR experience (1.1 vs 3.0%) [4]. The low incidence of stroke observed directly after the procedure was sustained at 1-year follow-up as no additional major strokes were observed between 30 days and 1 year. This is in contrast to the data from the German aortic valve registry, where the actual stroke rate doubled during 1 year, being 3.6% at 365 days for TA-TAVR patients [19]. We can only speculate on why the stroke rate of our study cohort was lower than anticipated; nevertheless, we think that the fixation mechanism of the JenaValve engaging the native leaflets may produce less radial pressure on the annulus than other THV, which may lead to less mobilization of calcium. Together with the access route used, this may have led to a stroke rate below average. Of note, there was no standard use of cerebral protection devices in our study cohort.

We observed a relatively high rate of bleeding events, with 25% of study patients having experienced major- or life-threatening bleeding events at 30 days, increasing to 30.6% at 1 year. A substantial incidence of bleeding complications might on the one hand lie in the nature of TA-TAVR and a 32F delivery system. On the other hand, a relatively vigorous antithrombotic and anticoagulant medication might cause a higher risk of bleeding in TAVR. Latest recommendations advise the use of dual platelet antiaggregation therapy during the first 4–24 weeks after implantation, complemented by oral anticoagulation in case of concomitant atrial fibrillation [10]. While one-third of our cohort had chronic atrial fibrillation at baseline, one-fourth were discharged on a combination of anticoagulant and antiplatelet medication; therefore, an increased risk of bleeding caused by oral anticoagulation could be anticipated. Of note, a recent randomized controlled trial suggests that there might be no difference between the use of either single platelet or dual platelet antiaggregation therapy after TAVR [22], further weakening evidence of the simultaneous medication of antiplatelet agents with oral anticoagulants in these elderly and comorbid patients. These results call for more evidence in medical therapy after TAVR.

The rate of permanent pacemaker implantation of 14.4% during the first 30 days was complemented by another 5.0% during follow-up. This is lower when compared with previous reports on self-expanding THV. In the German aortic valve registry, the incidence of permanent pacemaker implantation was 33.7% after TAVR—mainly observed in patients receiving a CoreValve™ (Medtronic, Minneapolis, MN, USA) [23]. In a single-centre experience on next-generation self-expanding THV for TA-TAVR, the actual rate of permanent pacemaker implantation was 20.5%—still higher compared with that of our cohort [5]. Of note, Seiffert's sub-group of patients receiving a JenaValve consisted of 88 patients with a pacemaker rate of 14.8%, identical to our observation. On the one hand, the reduced radial forces inherent in the fixation of the JenaValve and also little interaction of the JenaValve with structures of the LVOT may have contributed to a lower rate of permanent pacemaker implantation. On the other hand, one could argue that 15.0% of our patients already had a permanent pacemaker at baseline, but this is also consistent with the published experience, as 14.8% had a pacemaker at baseline in the German aortic valve registry [23]. Certainly, in comparison with routinely used balloon-expandable THV, the rate of pacemaker implantation of the JenaValve is higher [4]. We therefore conclude that the JenaValve carries a low risk of permanent pacemaker implantation compared with other self-expanding THV.

Limitations

Post-market registries are important to ensure monitoring of the device in early use after CE-mark approval and to conclude from a 'real-world' experience in a less targeted population. While these observational data reflect current practice, further analyses on reasons for selection of the JenaValve over other available devices could not be identified and the data may be associated with a selection bias in these patients. This could not be further explored or excluded. Additionally, the dataset design was set at the beginning of the registry, only allowing analysis according to VARC-I criteria. Therefore, data could not be reported according to the updated VARC-II end-point definitions in the manuscript. Another limitation may be an increased inaccuracy due to coding, not allowing for deeper analysis when reporting on outcomes. In 51 patients with procedural success, EOA was not assessed after implantation of the JenaValve. In these patients, calculation of the composite end-point 'device success' was based on the mean transvalvular pressure gradient (<20 mmHg) and peak velocity (<3 m/s) only. A relatively high rate of missing variables in follow-up echocardiography at 1 year (data for gradient complete in 34.6% of patients) was another apparent limitation of our study. Therefore, conclusions regarding performance of the device at 1 year can only be drawn very carefully.

CONCLUSION

In a high-risk cohort of patients undergoing TA-TAVR for AS, the use of JenaValve was safe and effective. Moreover, in patients at risk for coronary ostia obstruction or annular rupture who cannot undergo TF-TAVR, implantation of a JenaValve might be a preferable option due to the special clipping-mechanism engaging the native valve leaflets for fixation with reduced radial forces of the self-expanding stent. Different factors, such as calcification

pattern, root anatomy and mode of native valve failure, should determine the choice of the adequate THV for each individual patient. A next-generation platform of the JenaValve for TF-TAVR will soon be evaluated in a multinational trial.

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