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ABSTRACT

OBJECTIVES The purpose of this study is to report the 1-year results of the CENTERA-EU trial.

BACKGROUND The CENTERA transcatheter heart valve (THV) (Edwards Lifesciences, Irvine, California) is a low-profile (14-F eSheath compatible), self-expanding nitinol valve, with a motorized delivery system allowing for repositionability. The 30-day results of the CENTERA-EU trial demonstrated the short-term safety and effectiveness of the valve.

METHODS Implantations were completed in 23 centers in Europe, Australia, and New Zealand. Transfemoral access was used in all patients. Echocardiographic outcomes were adjudicated by a core laboratory at baseline, discharge, 30 days, 6 months, and 1 year. Major adverse clinical events were adjudicated by an independent clinical events committee.

RESULTS Between March 2015 and July 2016, 203 high-risk patients (age 82.7 ± 5.5 years, 67.5% women, 68.0% New York Heart Association functional class III or IV, Society of Thoracic Surgeons score 6.1 ± 4.2%) with severe, symptomatic aortic stenosis underwent transcatheter aortic valve replacement with the CENTERA THV. The primary endpoint of the study was 30-day mortality (1.0%). At 1 year, overall mortality was 9.1%, cardiovascular mortality was 4.6%, disabling stroke was 4.1%, new permanent pacemakers were implanted in 6.5% of patients at risk, and cardiac-related rehospitalization was 6.8%. Hemodynamic parameters were stable at 1 year, with a mean aortic valve gradient of 8.1 ± 4.7 mm Hg, a mean effective orifice area of 1.7 ± 0.42 cm^2, and no incidences of severe or moderate aortic regurgitation.

CONCLUSIONS The CENTERA-EU trial demonstrated mid-term safety and effectiveness of the CENTERA THV, with low mortality, sustained improvements in hemodynamic performances, and low incidence of permanent pacemaker implantations in high-risk patients with symptomatic aortic stenosis. (Safety and Performance of the Edwards CENTERA-EU Self-Expanding Transcatheter Heart Valve [CENTERA-2]; NCT02458560) (J Am Coll Cardiol Intv 2019;12:673–80)

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ABBREVIATIONS AND ACRONYMS

CEC = Clinical Events Committee

DVI = Doppler velocity index

EOA = effective orifice area

NYHA = New York Heart Association

PPM = permanent pacemaker

PVL = paravalvular leak

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

VI = valve implant

Transcatheter aortic valve replacement (TAVR) is established for use in patients with severe, aortic stenosis at increased risk for surgery (1). The vast adoption of TAVR in high-risk patients has led to an increased interest in the option of TAVR for lower-risk patients; certain valves have already received indication for use in intermediate-risk patients, and trials evaluating TAVR in low-risk patient populations are ongoing (2–4). As indication for risk level in TAVR is broadening and patients at lower risk are receiving valves, the need for improved outcomes is higher, as lower-risk patients tend to be younger, have fewer comorbidities, and have a longer life expectancy.

SEE PAGE 681

Apart from operator experience, one factor critical to improving outcomes in TAVR is the refinement of valve technology. The Edwards CENTERA transcatheter heart valve (THV) (Edwards Lifesciences, Irvine, California) is a new self-expanding nitinol valve with bovine pericardial leaflets and a low profile (14-F eSheath compatible). The CENTERA delivery system is steerable and motorized, allowing for repositionability, coaxial alignment with the aortic annulus, and stable deployment. The CENTERA valve obtained Conformité Européenne mark in February 2018, based on the 30-day results of the CENTERA-EU study that have been previously published (5). At 30 days post-implantation, the primary endpoint of mortality was 1.0%, disabling stroke occurred in 2.5% of patients, and a new permanent pacemaker (PPM) was implanted in 4.9% of patients at risk. In addition, the treatment demonstrated significant improvement in hemodynamics, not only for mean gradient and effective orifice area (EOA) but also with low rate of moderate or severe paravalvular aortic regurgitation (0.6%) at 30 days.

The objective of this publication is to present the mid-term (1 year) safety and effectiveness of this novel THV based on the CENTERA-EU trial.

METHODS

VALVE AND DELIVERY SYSTEM. The Edwards CENTERA THV (sizes 23 mm, 26 mm, and 29 mm) features a contour-shaped, self-expanding nitinol valve frame with bovine pericardial tissue leaflets (5) (**Figure 1A**). The bovine pericardium preparation incorporates a proprietary tissue treatment (RESILIA) that allows dry tissue storage and a <5-min valve preparation using heparinized saline. The CENTERA THV is pre-attached to the delivery system and advanced to the native aortic valve via transfemoral access using an expandable 14-F inner-diameter introducer sheath for all valve sizes (**Figure 1B**). The delivery system is steerable and motorized, allowing coaxial alignment within the annulus and stable deployment. The CENTERA THV is repositionable up to 80% of its deployment (6).

STUDY DESIGN. Between March 2015 and July 2016, the CENTERA-EU prospective, multicenter trial enrolled 203 patients with aortic stenosis at high surgical risk from 23 centers in Europe, Australia, and New Zealand. The study was approved by the local ethics committees, the respective health authorities in participating countries, and all patients provided a written informed consent. The study was registered with ClinicalTrials.gov (NCT02458560).

As per protocol, patients who met eligibility criteria and for whom TAVR was deemed the best treatment option by the clinical consensus of the Heart Team (a multidisciplinary team of cardiac surgeons, interventional cardiologists, anesthesiologists, and cardiac imaging specialists) (5) were enrolled in this study. Key inclusion and exclusion criteria have been previously published (5).

An independent Clinical Events Committee (CEC) reviewed and adjudicated all key clinical events according to Valve Academic Research Consortium-2 criteria (7). All echocardiographic data were reviewed by an independent Echo Core Laboratory up to 1 year (Neil J. Weissman, MD, MedStar Health Research Institute, Washington, DC).

has served as a proctor for Boston Scientific; has received institutional research grants from St. Jude Medical and Biotronik; and has received speaker honoraria from Edwards Lifesciences and Medtronic. Dr. Le Breton has served as a board member for Abbott and received lecture fees from Edwards Lifesciences. Dr. Søndergaard has served as a proctor for and received institutional grants from Edwards Lifesciences. Dr. Spence has received research funding, travel support, and speaker honoraria from Edwards Lifesciences; has served as a consultant for Abbott; and has served as a proctor for Edwards Lifesciences, Medtronic, and Boston Scientific. Dr. Petronio has served as a consultant for Abbott, Medtronic, and Boston Scientific. Dr. Baumgartner has received speaker honoraria and congress travel support from Edwards Lifesciences and Actelion. Dr. Hovorka is an employee of Edwards Lifesciences. Dr. Blanke has served as a consultant to Edwards Lifesciences, Circle Imaging, Neovasc, and Tendyne. Dr. Reichenspurner has received speaker support and travel honoraria from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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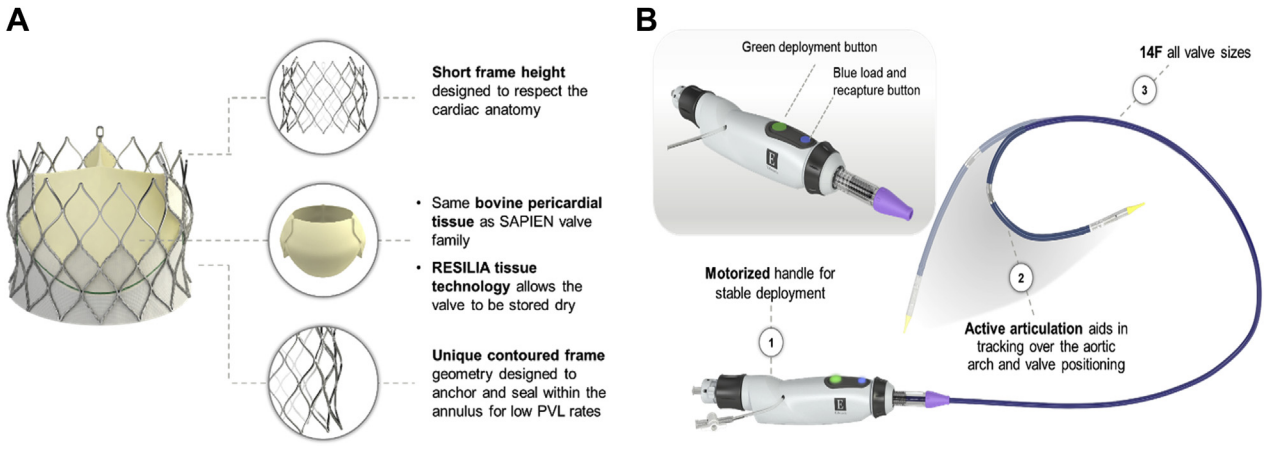
FIGURE 1 CENTERA Transcatheter Aortic Valve and Delivery System



(A) Structure of the CENTERA self-expanding transcatheter heart valve. **(B)** Characteristics of the CENTERA delivery system. PVL = paravalvular leak.

A patient was considered to have prosthetic valve dysfunction if the mean gradient was ≥20 mm Hg, the EOA was ≤0.9 cm^2 to 1.1 cm^2 or the Doppler velocity index (DVI) was <0.35, or paravalvular leak (PVL) was greater than or equal to moderate.

Detailed description of the methods is available in the published 30-day results (5).

Patients filled in a quality-of-life Euro-Qol-5D (Q-5D) questionnaire at baseline and 1 year.

DATA COLLECTION AND STATISTICAL ANALYSIS. Data collection for this study has been described previously in the 30-day paper (5). The as-treated patient population was defined as the patients for whom the study valve implant (VI) procedure was begun, and the VI population consisted of all patients who received an implant and retained the valve upon leaving the procedure room. Continuous variables are presented as mean ± SD. Categorical variables are presented as percentage of patients. Freedom from events was calculated using the Kaplan-Meier method.

Fisher exact test was used to compare categorical variables, such as New York Heart Association (NYHA) functional class and paravalvular regurgitation at 30 days, 6 months, and 1 year to values at baseline. Mean gradients, EOA, and EQ-5D were analyzed with a paired *t*-test. An alpha level of 0.05 was used for all hypothesis testing. Univariate analysis was performed to assess associations between patient's baseline characteristics (NYHA functional class, logistic EuroSCORE [European System for Cardiac Operative Risk Evaluation], renal insufficiency, atrial fibrillation, gradient, body mass index), procedural (post-dilatation, days in intensive care unit), and post-procedural complications (acute kidney injury, new conduction abnormality, major vascular complications, and disabling stroke) with 1-year mortality.

TABLE 1 Baseline Characteristics (N = 203)

	As Treated
Age, yrs	82.7 ± 5.5
Female	137 (67.5)
EuroSCORE II (n = 202)	5.1 ± 3.95
STS score	6.1 ± 4.2
NYHA functional class III/IV	138 (68.0)
NYHA functional class IV	12 (5.9)
Previous stroke	19 (9.4)
Coronary artery disease	80 (39.4)
Peripheral vascular disease	30 (14.8)
Renal insufficiency	68 (33.5)
Prior pacemaker	16 (7.9)
Incomplete RBBB	17 (8.4)
Atrial fibrillation	40 (19.7)
Porcelain aorta	13 (6.4)
Mean gradient, mm Hg	40.8 ± 13.2
Effective orifice area, cm^2	0.7 ± 0.2
LVEF, %	54.6 ± 9.9

Values are mean ± SD or n (%).

EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RBBB = right bundle branch block; STS = Society of Thoracic Surgeons.

TABLE 2 Clinical Outcomes at 30 Days and 1 Year in the As-Treated Population (CEC Adjudicated)

Safety Endpoints	Kaplan-Meier (n = 203) 30 Days	1 Year
All-cause mortality	1.0 (2)	9.1 (18)
Cardiovascular mortality	1.0 (2)	4.6 (9)
Stroke	4.0 (8)	7.6 (15)
Disabling stroke	2.5 (5)	4.1 (8)
Nondisabling stroke	1.5 (3)	4.1 (8)
Myocardial infarction	1.5 (3)	2.0 (4)
New onset atrial fibrillation	8.0 (16)	11.6 (23)
Cardiac-related rehospitalization	0.5 (1)	6.8 (13)
New conduction abnormalities	24.7 (50)	29.4 (59)
Overall PPMI (as treated)	4.9 (10)	6.0 (12)
Naive PPMI (n = 187)	5.4 (10)	6.5 (12)
Life-threatening or disabling bleedings	4.9 (10)	NA*
Major bleedings	14.4 (29)	NA*
Valve prosthesis endocarditis	0 (0)	0.5 (1)
Structural valve deterioration requiring reintervention	0 (0)	0 (0)

Values are % (n). *Bleedings were adjudicated up to 30 days only.
CEC = Clinical Events Committee; NA = not applicable; PPMI = permanent pacemaker implantation.

Variables with p value < 0.2 in the univariate model were selected for multivariate stepwise Cox proportional hazards model for all-cause mortality. Proportional hazards were checked in the subset and highly correlated variables were further removed. Thereafter, a multivariable stepwise Cox proportional hazards model was computed for all-cause mortality.

All statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

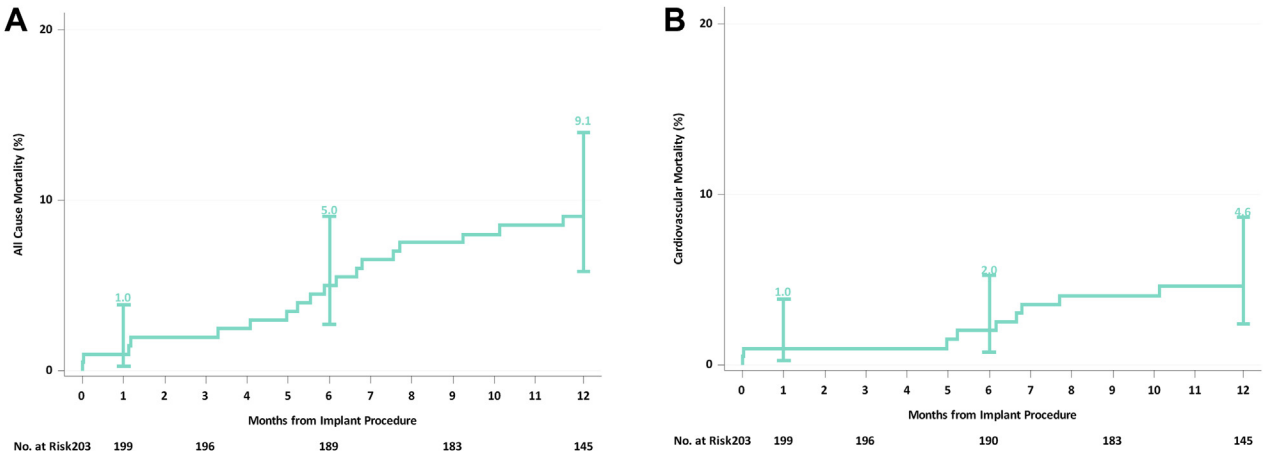
RESULTS

PATIENT DISPOSITION. The analysis presented was performed on the as-treated population (n = 203) and the VI population (n = 198). For this mid-term analysis, the database of the CENTERA-EU trial was frozen on January 2018.

Baseline and procedural characteristics are displayed in Table 1. Approximately, two-thirds of the population were female, the mean ± SD (minimum to maximum) Society for Thoracic Surgeons score was 6.1 ± 4.2% (1.4% to 28.0%) and the mean EuroSCORE II was 5.1 ± 4.0% (0.8% to 27.2%) at baseline. The mean left ventricular ejection fraction was 54.6% and 7.9% of patients had a PPM at baseline. Device success, defined as alive at 3 days and device in proper anatomic location, was 97.5% (n = 198 of 203).

Between the implantation and 30 days, 3 patients discontinued the study (1 patient expired due to cardiac arrest following post-operative bleeding and vascular complications, 1 patient had cardiac tamponade that led to death, 1 patient had valve embolization resulting in a conversion to surgery and valve explantation). Of the 200 patients eligible for the 30-day visit, 199 completed the visit within the time window. Between 30 days and 1 year, a total of 21 patients exited the study (including 3 withdrawals, 16 deaths, and 2 explantations). The 2

FIGURE 2 Kaplan-Meier Curves to 1 Year



Kaplan-Meier curves for **(A)** all-cause and **(B)** cardiovascular mortality in the CENTERA-EU trial.

explantations were followed until patients' discontinuation at day 46 and day 285. At 1 year, 179 patients were eligible for follow-up, and all completed their 1-year visit.

CLINICAL OUTCOMES TO 1 YEAR. One-year clinical outcomes are shown in Table 2.

The primary endpoint of all-cause mortality was 1.0% at 30 days and 9.1% at 1 year (Figure 2A). Cardiovascular mortality was 1.0% at 30 days and 4.6% at 1 year (Figure 2B). The median follow-up for survival was 391 (interquartile range: 362 to 732) days. Reasons for cardiovascular death to 1 year (n = 9) were stroke (n = 3), decompensated heart failure (n = 1), cardiogenic shock (n = 1), worsening of heart failure (n = 1), post-operative bleeding (n = 1), vascular complications leading to cardiac arrest (n = 1), and guidewire-related cardiac tamponade (n = 1). Two of these cardiovascular deaths were adjudicated as device-related by the CEC: the post-operative bleeding and an ischemic stroke occurring on day 304 after the implantation. Reasons for noncardiovascular death to 1 year (n = 9) were sepsis (n = 2), renal failure (n = 2), head trauma, gastric cancer, pneumonia, chronic lymphocyte leukemia, and metastatic cancer.

At 1 year, 10.6% of patients experienced new onset atrial fibrillation. A new PPM was implanted in 6.0% of patients (Figure 3) and 6.5% of patients at risk (Table 2), mainly for third-grade atrioventricular block (9 of 12 cases). The cardiac-related rehospitalization rate was 6.8%; 2 of the 13 cases were valve related.

Two of the 8 patients with disabling stroke at 1 year had a prior stroke, 2 had post-dilatation, only 1 had repositioning, 2 had major vascular complications on the day of implant, and 2 had new onset atrial fibrillation 2 days post-procedure. One of the disabling strokes was hemorrhagic; the other 7 were ischemic (Table 3). Three of the patients with disabling stroke expired from cardiovascular causes; 2 disabling strokes were device related (Table 3).

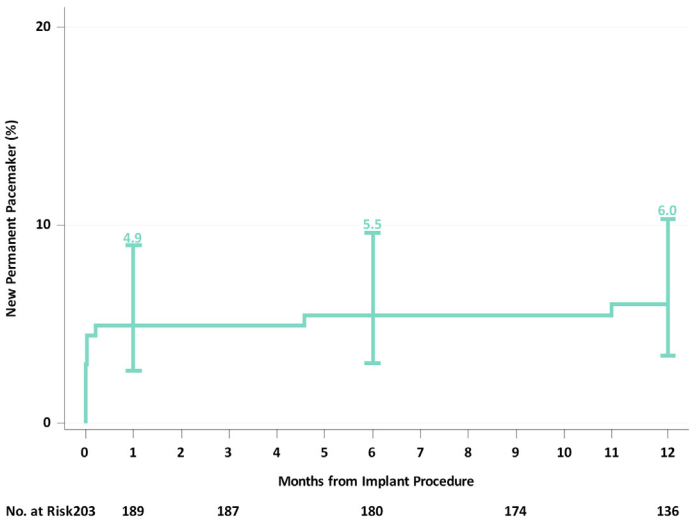
Only 32.5% of patients were NYHA functional class I or II at baseline, whereas 91.2% were in NYHA functional class I or II at 1 year. The functional status remained fairly stable from 30 days to 1 year, with 93.0% and 91.3% patients in functional class I or II, respectively (p = 0.83). Significant improvements in quality of life were observed: the EQ-5D visual analog score at 1 year was 67.3 ± 17.94 (n = 146), which was an improvement from the baseline results of 62.0 ± 16.4 (n = 192) (p = 0.002, paired *t*-test).

ECHOCARDIOGRAPHIC RESULTS. Echocardiographic core laboratory evaluation documented a significant decrease in mean transaortic gradients from 40.6 ± 13.3 mm Hg (n = 185) at baseline to 8.1 ± 4.7 mm Hg (n = 147) at 1 year (p < 0.001, paired *t*-test). EOA significantly increased from 0.7 ± 0.2 cm^2 (n = 146) at baseline to 1.7 ± 0.4 cm^2 (n = 129) at 1 year (p < 0.001, paired *t*-test) (Central Illustration). At 1 year, no central regurgitation was observed, and PVL was mild or less in all patients. The majority of PVL was classified as none or trace (71.4%) (Central Illustration). The Central Illustration shows a summary of all subjects, and the p values are from paired *t*-tests. At 30 days, only 1 patient was reported with moderate PVL, but he did not have an echocardiogram evaluation at 6 months and 1 year.

There were 2 cases of prosthetic valve dysfunction reported from 30 days to 1 year. One patient had a mean gradient of 9.6 mm Hg, EOA of 1.1 cm^2, and DVI of 0.34 at 30 days; nevertheless, the patient presented with normal hemodynamic values at 6 months with a mean gradient of 7.8 mm Hg, EOA of 1.7 cm^2, and DVI of 0.43. The other patient, with a mean gradient of 25.8 mm Hg, EOA of 1.0 cm^2, and DVI of 0.31 at 1 year, had a seemingly unrelated adverse event of peritonitis during the second year in the study.

PREDICTORS OF ALL-CAUSE 1-YEAR MORTALITY. The predictors of mortality at 1 year were NYHA functional status at baseline, acute kidney injury at 7 days, and major vascular complications at 30 days. Baseline atrial fibrillation was found to be predictive in the univariate analysis only (Table 4).

FIGURE 3 Kaplan-Meier Curve for Permanent Pacemaker Implantation



Permanent pacemaker implantation in the CENTERA-EU trial.

TABLE 3 Patients Who Experienced Disabling Strokes

Patient #	Type of Disabling Stroke	Days From Implant	Outcome	Antithrombotic Therapy	Relationship to Device
1	Ischemic	0	Ongoing	Aspirin and clopidogrel	No
2	Ischemic	2	Ongoing with hemiparesis right side (consent withdrawn)	Not documented	No
3	Ischemic	3	Resolved with sequelae (decreased visual acuity, persistent mild left lower limb weakness, and moderate left upper limb weakness)	Antiplatelets and warfarin	Yes
4	Ischemic	4	Death for cause unknown	None	No
5	Ischemic	13	Resolved with sequelae (right arm paralysis and light ataxia of the leg)	Platelet aggregation inhibition therapy (phenprocoumon) for 1 year then aspirin	No
6	Ischemic	123	Death due to stroke	Not documented	No
7	Hemorrhagic	203	Death due to stroke	None	No
8	Ischemic	300	Death due to stroke	Aspirin and clopidogrel	Yes

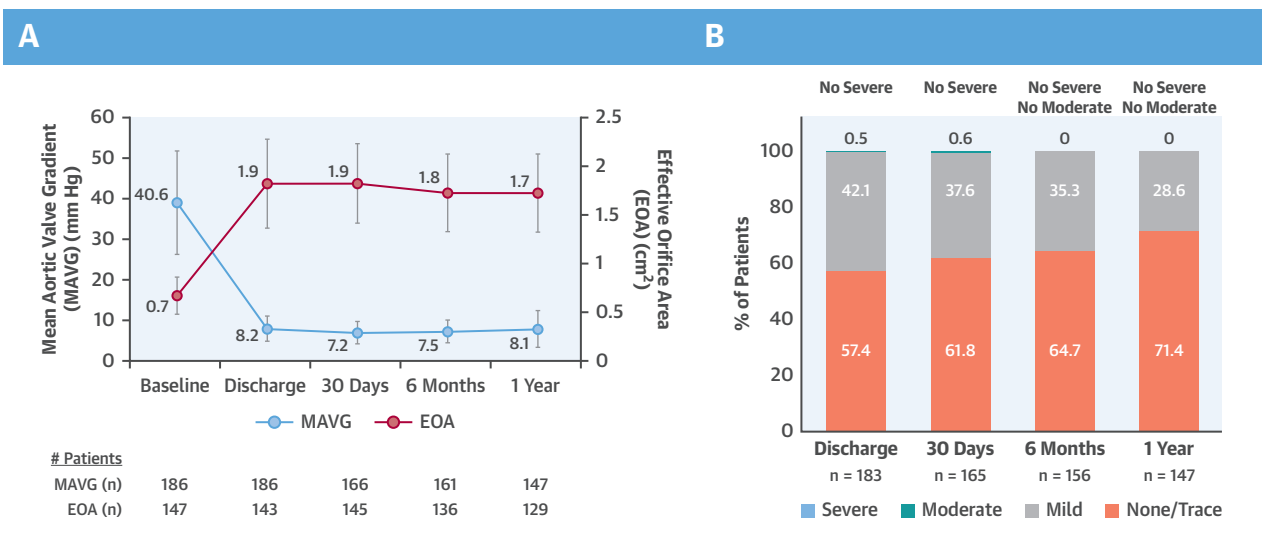
DISCUSSION

The 1-year follow-up to the 30-day, prospective, multicenter trial evaluating the CENTERA self-expanding THV demonstrates a continued safety and effectiveness profile of this new TAVR system for the treatment of severe aortic stenosis in high-risk patients. The data support that the CENTERA self-expanding THV maintains hemodynamic stability up to 1 year and displays low rates of cardiovascular mortality and PPM implantation and similar rates of disabling stroke and cardiac-related rehospitalization.

The low incidence of disabling stroke at 1 year aligns with results from similar TAVR studies in high-risk patient populations (8,9). The small number of disabling stroke (4.1%), and small overall study size did not provide power for an analysis of predictors for stroke. In this study, we did not observe any trends related to potential predictors of stroke, including prior stroke, post-dilatation (10), valve repositioning, vascular complications, and new onset atrial fibrillation (11–14).

The rate of new PPM implantation post-TAVR was low for patients at risk at 1 year in this study. The 6.5% rate is relatively low when compared with similar patient populations receiving a TAVR device (8). There were no cases of sudden cardiac death, which supports that PPM implantation was not underused in the study. A potential explanation for the low PPM rate may be a novel aspect of the valve design, which keeps the valve high above the left ventricular outflow tract during deployment and

CENTRAL ILLUSTRATION Echocardiographic Parameters



Tchétché, D. et al. J Am Coll Cardiol Intv. 2019;12(7):673-80.

(A) Changes in mean aortic valve gradient (MAVG) and effective orifice area (EOA). The line graph shows changes in the MAVG **(blue)** and EOA **(red)** of patients at baseline, discharge, and 1 year. Error bars represent SD. **(B)** Aortic regurgitation at discharge and to 1 year. For MAVG and EOA, the p value is <0.001 for all visits compared with baseline, based on a 2-sided paired *t*-test with the null hypothesis that there is no change from baseline (paired analysis).

maintains a high final implant position minimizing overall contact with the conduction system. The motorized handle of the valve may also be a contributing factor as it allows for stable delivery and may provide better control, limiting interactions that may cause conduction disturbances. Most of the new pacemakers were implanted within the first 7 days post-procedure, 6 of which were implanted during the procedure. The remaining 2 were implanted at days 137 and 330. The timing of new pacemaker implant is of interest when considering a minimalist approach to TAVR. Indeed, there is growing interest in the medical community toward simplification of TAVR procedures to promote better clinical outcomes and early discharge (15). Our study demonstrates that in the majority of cases, the need for a new PPM was identified within 2 to 3 days post-implant with the CENTERA THV, which provides confidence for safely discharging patients from the hospital early. Further investigation is required to confirm this finding, but the initial results are promising.

In addition to a low PPM implantation rate in this study, the CENTERA valve also demonstrated low rates of total aortic regurgitation to 1 year (with three-quarters of patients having none or trace amounts and none having moderate to severe amounts). There were no cases of central regurgitation, indicating that leaflet coaptation is good to 1 year, and all total aortic regurgitation is paravalvular. No moderate or greater PVL is notable and may be attributed to the contoured valve frame geometry designed for leak prevention. It should also be noted that one-third of patients in this study received post-dilation for PVL mitigation with no associated adverse events. Also, as demonstrated in the Kim et al. (16) computed tomography substudy, oversizing for PVL prevention (while performed infrequently in this study) did not increase the PPM rate. These findings provide an indication that, although not always necessary, post-dilatation and oversizing with the CENTERA valve for PVL reduction may be performed without trade-offs in clinical outcomes, particularly PPM or stroke.

The valve performances were good as assessed by hemodynamic parameters and were remarkably stable up to 1 year.

STUDY LIMITATIONS. The primary limitation of this study was the small sample size and lack of randomization. In addition, the delivery system for the CENTERA THV evaluated herein is the original design; future studies will evaluate a next-generation delivery system, which will feature a shorter stiff distal section for enhanced tracking.

TABLE 4 Multivariate Model for 1-Year Mortality

	Univariate*		Multivariate	
	HR†	p Value	HR†	p Value
Baseline parameters				
NYHA functional class IV vs. other NYHA functional classes	–	0.002	–	0.002
IV vs. I	6.81	0.120		
IV vs. II	0.34	0.210		
IV vs. III	0.48	0.334		
Log EuroSCORE	0.97	0.30		
Renal insufficiency	1.25	0.64		
Atrial fibrillation	3.47	0.01		
Mean aortic valve gradient	1.01	0.55		
Body mass index, kg/m^2	1.01	0.92		
Post-procedural parameters				
Post-dilatation	0.74	0.57		
Days in ICU	1.02	0.75		
Acute kidney injury (≤7 days)	5.61	0.02	6.48	0.017
New conduction abnormality (≤30 days)	1.19	0.74		
Major vascular complications (≤30 days)	5.67	0.002	4.60	0.023
Stroke (≤30 days)	0	0.99		

*All univariates with p value <0.20 were included in the multivariable analyses. †Hazard ratio (HR) is calculated only for continuous and dichotomous variables.

ICU = intensive care unit; NYHA = New York Heart Association.

CONCLUSIONS

At 1 year, the CENTERA self-expanding THV maintained significant hemodynamic improvements from baseline, and there was no moderate or severe total aortic regurgitation. In addition, the valve demonstrated low rates of cardiovascular mortality, unprecedentedly low rates of PPM implantation, and rates of disabling stroke and cardiac-related rehospitalization similar to other TAVR devices, supporting sustained clinical safety and efficacy with this valve in a high surgical risk patient cohort. Further studies in larger patient populations are required to confirm these findings, but initial results are favorable.

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PERSPECTIVES

WHAT IS KNOWN? The 30-day results of the CENTERA-EU trial demonstrated the safety and effectiveness of this novel self-expanding THV in high-risk patients undergoing TAVR.

WHAT IS NEW? Low rates of cardiovascular mortality, stroke, and pacemaker are confirmed at 1 year.

WHAT IS NEXT? These sustained clinical outcomes could further support the use of this novel THV as a device of choice in lower risk patients.

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