1-Year Outcomes of the CENTERA-EU Trial Assessing a Novel Self-Expanding Transcatheter Heart Valve

By: Exemplary Student

I. Introduction

According to CDC, heart disease is the leading cause of death for the majority of racial and ethnic groups in the US. Indeed, there were 697,000 reported deceased cases due to heart diseases in the US in 2020. In terms of financial damage, heart diseases cost the US about $229 billion each year. Because of those reasons, many medical devices companies have constantly come up with new technologies to help restore the original functions of the hearts of patients battling against heart diseases.

II. Background

Aortic stenosis, a heart valve disease, is a condition in which buildup calcium constricts the valve between the lower left heart chamber and the body's main artery. This leads to the reduction or blockage of bloodflow from the heart to the rest of the body. Edward Lifesciences, based in Irvine, California, is one of a few companies that manufactures artificial heart valves as well as catheter to assist patients with this disease. The research article *1-Year Outcomes of the CENTERA-EU Trial Assessing a Novel Self-Expanding Transcatheter Heart Valve*, published in the Cardiovascular Interventions in 2019, reported the mid-term (1 year) safety and effectiveness of the novel transcatheter heart valves(THV) based on the CENTERA-EU trial.

III. Methodology

From March 2015 to July 2016, 203 patients with aortic stenosis at high surgical risk from 23 centers in Europe, Australia, and New Zealand were enrolled by the CENTERA-EU multicenter trial. This clinical trial received the approvals from local ethics committees as well as the respective health authorities in participating countries. The study was also registered with ClinicalTrials.gov. In addition, all subjects were provided with writtent informed consent. Patients' eligibilities were determined by the clinical consensus of the Heart Team(a multidisciplinary team of cardiac surgeons, interventional cardiologists, anesthesiologists, and cardiac imaging specialists). Moreover, all key clinical events were reviewed and adjudicated by an independent Clinical Events Committee (CEC) in accordance with Valve Academic Research Consortium-2 criteria. All echocardiographic data were reviewed by an independent Echo Core Laboratory up to 1 year. Subjects also filled in a quality-of-life Euro-Qol-5D (EQ-5D) questionnaire at baseline and 1 year.

The primary endpoint of this clinical trial is all-cause mortality at 30 days post-procedure and at 1 year. The secondary endpoints are device success, safety endpoints, clinical functional efficacy, and echocardiographic outcomes.

Data were collected electronically by participating centers, monitored by sponsors. Continuous variables were presented as mean plus or minus standard deviation while categorical variables were presented as percentage of patients. Freedom from events was calculated using the Kaplan-Meier method. Since the sample size was small, Fisher exact test was used to compare NYHA functional class and paravalvular leak at 30 days, 6 months, and 1 year with values at baseline. Mean gradients, effective orifice area, and EQ-5D were analyzed with a paired t-test. Univariate analysis was performed to assess associations between patients' baseline characteristics and post-procedural complications with 1-year mortality. Finally, variables with p-value < 0.2 in the univariate model will be retained to use in the multivariate stepwise Cox Proportional Hazards model so as to calculate all-cause mortality.

IV. Results

According to the publication, the transcatheter managed to deploy the artificial heart valves to proper anatomic locations with the success rate of 97.5%(198/203). Between the implantation and 30 days, 3 subjects dropped out of the study (1 with cardiac arrest following post-operative bleeding and vascular complications, 1 with cardiac tamponade that led to death, and 1 with 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 subjects discontinued the trial(3 withdrawals, 16 deaths, and 2 explantations). At 1 year, 179 patients were eligible for follow-up, and all completed their 1-year visit.

As a result, the primary endpoint of all-cause mortality was 1.0% at 30 days and 9.1% at 1 year. For the secondary endpoints, cardiovascular mortality was 1.0% at 30 days and 4.6% at 1 year. The event of stroke was 4.0 % at 30 days and 7.6% at 1 year. Meanwhile, the events of disabling and nondisabling strokes were 2.5% and 1.5% at 30 days respectively as well as 4.1% for both at 1 year. Other life-threatening events, such as myocardial infarction or disabling bleedings were also reportedly low(1.5% and 4.9% respectively at 30 days).

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).

For the results of univariate and multivariate Cox Proportional Hazard models, the following table was provided:

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.

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 model only.

V. Conclusion

At 1 year, the CENTERA self-expanding THV maintained significant hemodynamic improvements from baseline as well as caused NO moderate or severe total aortic regurgitation. This delivery system also demonstrated low rates of cardiovascular mortality, permanent pacemaker implantation, disabling stroke and cardiac-related rehospitalization. Indeed, based on these statistical reports, the initial results were deemed favorable. However, larger sample size would be required to confirm with these findings.

VI. Key Tables

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.

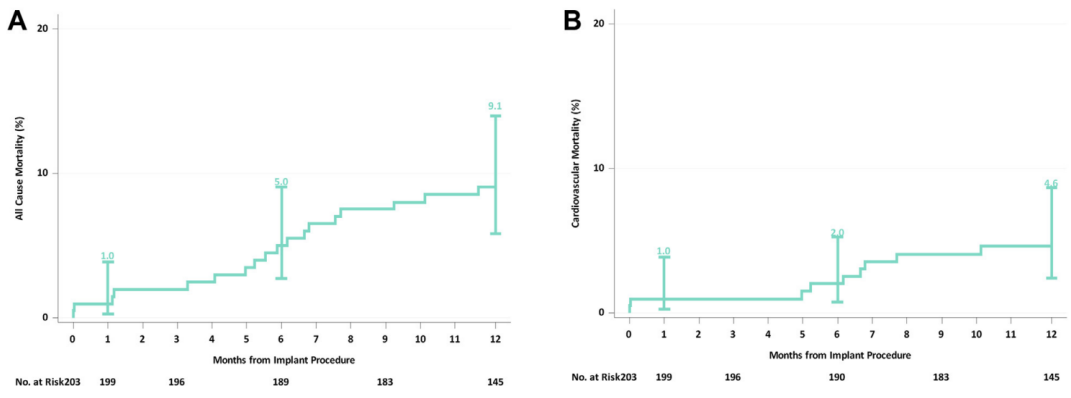
TABLE 2 Clinical Outcomes at 30 Days and 1 Year in the As-Treated Population (CEC Adjudicated)

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.

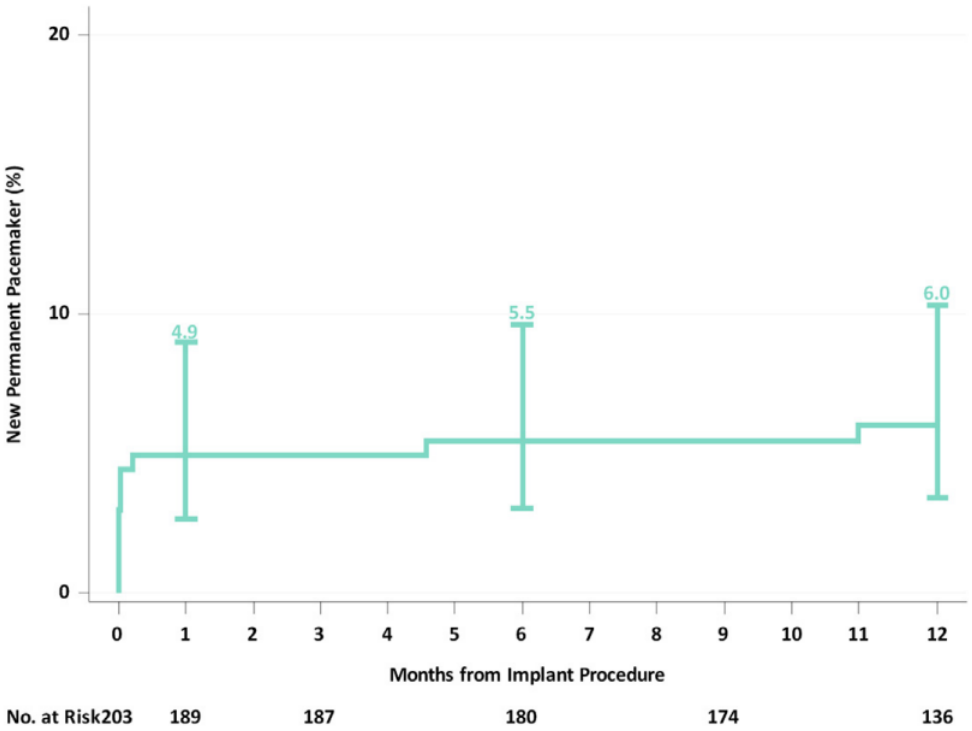
CEC = Clinical Events Committee; NA = not applicable; PPMI = permanent pacemaker implantation.

FIGURE 2 Kaplan-Meier Curves to 1 Year



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

FIGURE 3 Kaplan-Meier Curve for Permanent Pacemaker Implantation



Permanent pacemaker implantation in the CENTERA-EU trial.

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VII. Reference

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