JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 5, 2018

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Prognostic Impact of Low-Flow Severe Aortic Stenosis in Small-Body Patients Undergoing TAVR

The OCEAN-TAVI Registry

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ABSTRACT

OBJECTIVES This study aimed to analyze the prognostic impact of low-flow (LF) severe aortic stenosis in small-body patients undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND Western literature demonstrates a poor prognosis with paradoxical LF and low-flow low-gradient (LF-LG) severe aortic stenosis (AS), as defined by stroke volume index (SVi) <35 ml/m^2 and mean pressure gradient <40 mm Hg with preserved left ventricular ejection fraction (LVEF). However, this poor prognosis is contested in Japan owing to the smaller body size of Japanese patients relative to that of Western patients. Additionally, there are no reports of the prognostic implication of paradoxical LF or LF-LG severe AS in small-body patients undergoing TAVR.

METHODS This was a retrospective analysis of 723 consecutive Japanese patients (median age 85 years; 32.6% male; median body surface area 1.4 m^2) who underwent TAVR for severe AS at 9 sites in Japan. The primary and secondary endpoints were cumulative all-cause and cardiovascular mortality after TAVR, respectively.

RESULTS Ninety-seven (13.4%) patients had paradoxical LF severe AS whereas 38 (5.3%) had paradoxical LF-LG with severe AS. PLF was associated with a significant increase in all-cause (hazard ratio [HR]: 3.00; 95% confidence interval [CI]: 1.34 to 6.72; $p < 0.001$) and cardiovascular mortality (HR: 5.58; 95% CI: 1.19 to 26.2; $p < 0.01$), as compared with patients' normal flow and preserved LVEF. PLF-LG was associated with a significant increase in all-cause mortality (HR: 3.76; 95% CI: 1.09 to 13.73; $p < 0.01$), as compared with normal flow high gradient with preserved LVEF. SVi was an independent predictor of cardiovascular mortality on multivariate analysis after adjustments for age, sex, clinically relevant variables, and other echocardiographic parameters (HR: 1.96; 95% CI: 1.19 to 3.23; $p < 0.01$).

CONCLUSIONS Among Japanese small-body patients with severe AS, both paradoxical LF and LF-LG severe AS were associated with poor outcomes following TAVR. SVi was an independent predictor of cardiovascular mortality after TAVR. (Optimised Transcatheter Valvular Intervention registry [OCEAN-TAVI]; UMIN000020423) (J Am Coll Cardiol Img 2018;11:659–69)

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Manuscript received August 22, 2016; revised manuscript received December 1, 2016, accepted December 22, 2016.

ISSN 1936-878X/$36.00 http://dx.doi.org/10.1016/j.jcmg.2016.12.028

JACC: CARDIOVASCULAR IMAGING, VOL. 11, NO. 5, 2018
MAY 2018:659–69

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

HG = high-gradient

HR = hazard ratio

LF = low-flow

LF-LG = low-flow low-gradient

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

NF = normal-flow

PEF = preserved left ventricular ejection fraction

REF = reduced left ventricular ejection fraction

SVi = stroke volume index

TAVR = transcatheter aortic valve replacement

Paradoxical low-flow (LF) low-gradient (LG) severe aortic stenosis (AS) was reported to be associated with an increased risk of mortality by several Western studies, including a meta-analysis (1-5). The outcomes in these patients improved following aortic valve replacement (1-6). The guidelines of the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association for Cardio-Thoracic Surgery list the recommendations for aortic valve replacement in these patients as Class IIa (7,8). Paradoxical LF-LG severe AS also had a poorer prognosis among patients undergoing transcatheter aortic valve replacement (TAVR), and LF has been identified as an independent predictor of early, as well as late, mortality (4,9).

However, the evidence presented by some Japanese studies is contradictory to the Western experience owing to the small body size of Japanese patients (10,11). A recent retrospective study from Japan reported that small-body-sized Japanese patients with severe AS had a smaller left ventricular (LV) chamber size, which may cause a LF status, and in those patients, paradoxical LF-LG severe AS had a better natural prognosis than high-gradient (HG) severe AS. According to their study, the risk with LF-LG severe AS was similar to that of moderate AS. Studies also suggest that the criterion of stroke volume index (SVi) of <35 ml/m^2, as per the guidelines' definition of LF, was inappropriate for Japanese patients, whose body sizes are smaller than their Western counterparts (7,8,12). In addition, there are no published Japanese data regarding the prognosis of paradoxical LF or LF-LG severe AS following TAVR.

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Therefore, the aim of this study was to evaluate the prognosis of Japanese patients, who generally have a smaller body size than Western patients, with LF severe AS undergoing TAVR, and to verify the adequacy of the existing definition of LF in Japanese patients. We hypothesized that paradoxical LF or LF-LG severe AS is associated with increased mortality in the Japanese population.

METHODS

STUDY POPULATION. The OCEAN (Optimized CathEter vAlvular iNtervention)-TAVI registry is a prospective, multicenter, observational registry of symptomatic (New York Heart Association functional class II or greater) and high-risk or inoperable patients with degenerative severe AS, as defined according to guidelines, undergoing TAVR using the Edwards Sapien XT prosthesis (Edwards Lifesciences, Irvine, California) (7,8,13-15). Nine high-volume institutions in Japan contributed to this registry. Data were collected from October 10, 2013, to August 7, 2015. All participating centers had an established training and certifying program for the use of the Edwards Sapien XT. More than 749 patients are included in this OCEAN-TAVI registry. Of these, 26 patients were excluded due to incomplete echocardiographic data (n = 16), valve-in-valve procedure (n = 4), and the conversion to surgical aortic valve replacement (n = 6). Therefore, a total of 723 patients (median age 84 years [interquartile range: 82 to 88 years], 32.6% male, and median body surface area 1.4 m^2 [interquartile range: 1.30 to 1.53 m^2]) were included for final analysis in the study. The institutional review boards of all participating centers approved the study protocol that was developed in accordance with the Declaration of Helsinki, and all patients gave informed written consent for participating in the study. This trial was registered with the University Hospital Medical Information Network as number UMIN000020423.

ECHOCARDIOGRAPHIC MEASUREMENT. All participants underwent standard 2-dimensional B mode and Doppler transthoracic echocardiography before the procedure and the conventional parameters were measured according to the American Society of Echocardiography guidelines (16,17). Patients were divided into 4 groups based on their left ventricular ejection fraction (LVEF) and flow status by SVi as measured on Doppler echocardiography at the LV outflow tract as follows: 1) NF-PEF: normal flow (NF) (SVi $\geq$35 ml/m^2) with preserved LVEF (LVEF $\geq$50%); 2) LF-PEF: LF (SVi $<$35 ml/m^2) with preserved LVEF; 3) NF-REF: NF with reduced LVEF (LVEF $<$50%); and 4) LF-REF: LF with reduced LVEF (9,18). Subsequently, the preserved LVEF groups were divided into 4 subgroups based on mean gradient, defined as HG (mean gradient $\geq$40 mm Hg) or LG (mean gradient $<$40 mm Hg). The LF-PEF and LF-REF groups corresponded to the diagnosis of paradoxical and classical LF severe AS, respectively. The subgroups were listed as NF-HG, NF-LG, LF-HG, and LF-LG. The LF-LG group corresponded to the diagnosis of paradoxical LF-LG severe AS (**Figure 1**).

STUDY ENDPOINTS. The primary endpoint of this study was cumulative all-cause mortality during follow-up after TAVR procedure and the secondary endpoint was cumulative cardiovascular mortality.