International Journal of Cardiology 190 (2015) 277–281

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Influence of baseline ejection fraction on the prognostic value of paravalvular leak after transcatheter aortic valve implantation☆,☆☆

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ARTICLE INFO

Article history:
Received 12 February 2015
Accepted 23 April 2015
Available online 24 April 2015

Keywords:
Aortic stenosis
Transcatheter aortic valve implantation
Paravalvular leak
Left ventricular ejection fraction
2-Year mortality

ABSTRACT

Background: Moderate or severe paravalvular leak (PVL ≥ moderate) after transcatheter aortic valve implantation (TAVI) is associated with poor outcomes. The aim of this study was to assess whether the baseline ejection fraction (EF) affects the impact of PVL on mortality after TAVI.
Methods: We analyzed 514 consecutive patients with native severe aortic stenosis who underwent TAVI. Patients were divided into two groups: EF <40% group (n = 84) and EF ≥40% group (n = 430) according to baseline EF.
Results: The mean age was 79.5 years and 49% were male. Patients in the EF <40% group were younger and with higher logistic EuroSCORE compared to patients in the EF ≥40% group. Diabetes, coronary artery disease, atrial fibrillation and renal insufficiency were more prevalent in the EF <40% group. Patients in the EF <40% group had more mitral regurgitation. In-hospital mortality was significantly higher in the EF <40% group (8.3% vs. 0.9%, $p < 0.0001$). PVL ≥ moderate was significantly associated with increased 2-year estimated mortality only in the EF <40% group (65% vs. 20%, log-rank $p < 0.0001$) whereas no difference was seen in the EF ≥40% group (24% vs. 19%, log-rank $p = 0.509$). Interaction between PVL ≥ moderate and EF <40% was statistically significant.
Conclusions: The impact of PVL ≥ moderate on mortality after TAVI was significant in the EF <40% group but not in the EF ≥40% group in our study. Even though operators should aim to minimize PVL in all TAVI patients, special attention is required for patients with reduced baseline EF.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is a well-established, effective therapy in patients with severe symptomatic aortic stenosis (AS) who are considered high risk for surgical aortic valve replacement (SAVR) or inoperable [1,2]. However, paravalvular leak (PVL) is a frequent complication after TAVI [3,4] which has been associated with increased early [5] and long term mortality [6–10]. The mechanism of this association is poorly explained.

Functional and structural recovery of the left ventricle (LV) due to the decrease of ventricular afterload after surgical aortic valve replacement is a well-recognized phenomenon [11]. Several studies have demonstrated that the LV undergoes a similar reverse remodeling process after TAVI [12,13]. Since PVL causes LV volume overload [14], PVL may prevent reverse remodeling after TAVI. The aim of this study was to assess whether the baseline ejection fraction (EF) affects the impact of PVL on mortality after TAVI.

2. Methods

2.1. Study population

All patients with severe AS who underwent TAVI at San Raffaele Hospital in Milan between July 2007 and September 2013 were included in the current observational study, with prospectively collected data. A total of 548 patients with severe AS underwent TAVI during this period. We excluded from the current analysis Valve-

☆ This author takes responsibility for all aspects of reliability and freedom from bias of the data presented and their discussed interpretation.
☆☆ Disclosure: Dr. Latib serves on the Medtronic Advisory Board and is a consultant and proctor for Direct Flow Medical. Dr. Montorfano is a proctor Edwards LifeSciences and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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http://dx.doi.org/10.1016/j.ijcard.2015.04.190
0167-5273/

Table 1
Baseline characteristics.

Variable	Overall patients (n = 514)	EF <40% (n = 84)	EF ≥40% (n = 430)	p value
Age, y	79.5 ± 7.3	77.6 ± 7.5	79.9 ± 7.2	0.009
Male	252 (49.0)	50 (59.5)	202 (47.0)	0.042
Hypertension	404 (78.5)	63 (75.0)	341 (79.3)	0.385
Diabetes	152 (29.5)	35 (41.7)	117 (27.2)	0.007
Coronary artery disease	214 (41.6)	48 (57.1)	166 (38.6)	0.002
Previous PCI	112 (21.7)	28 (33.3)	84 (19.5)	0.005
Previous CABG	106 (20.6)	23 (27.4)	83 (19.3)	0.105
Atrial fibrillation	126 (24.5)	30 (35.7)	96 (22.3)	0.012
Renal insufficiency	178 (34.6)	40 (47.6)	138 (32.1)	0.008
COPD	149 (28.9)	23 (27.4)	126 (29.3)	0.793
Logistic EuroSCORE, %	18.3 (10.7–29.0)	32.6 (18.8–50.5)	16.4 (9.8–26.0)	<0.0001
Echocardiographic parameter				
Aortic valve area, cm^2	0.72 ± 0.21	0.67 ± 0.21	0.73 ± 0.20	0.049
Mean pressure gradient, mm Hg	52.5 ± 15.4	44.0 ± 15.8	54.2 ± 14.7	<0.0001
LVEF, %	51.8 ± 12.7	29.0 ± 6.7	56.2 ± 8.0	<0.0001
Baseline AR ≥ moderate	173 (33.6)	32 (38.1)	141 (32.3)	0.377
Baseline MR ≥ moderate	203 (39.4)	47 (56.0)	156 (36.3)	0.001

Values are expressed as n (%), median (interquartile range).
PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; AR = aortic regurgitation; MR = mitral regurgitation.
Renal insufficiency is defined as serum creatinine >1.5 mg/dl.

in-Valve cases (TAVI for degenerated prosthetic valve) (n = 28), patients who died up to 24 h post procedure (worsening heart failure n = 1, aortic rupture n = 3, aortic dissection n = 1) and patients who were converted to open surgery during the procedure (n = 1). Finally, 514 consecutive patients with native severe AS were analyzed. All patients provided written informed consent for the procedure and future follow-up with data collection. The study patients were divided into two groups according to their baseline EF; the EF <40% group and the EF ≥40% group. We chose EF <40% as a cut-off since this is routinely used as the definition for reduced EF in clinical practice [15].

2.2. Echocardiographic examination

Transthoracic echocardiography was performed before the procedure, prior to discharge and 1 month, 6 months, 1 year and 2 years follow-up. The severity of aortic stenosis was assessed by the mean transvalvular pressure gradient and aortic valve area (AVA) calculated with the continuity equation. Left ventricular EF was obtained by Simpson's biplane method. PVL severity was assessed by using multiple imaging windows and a comprehensive approach integrating the parameters suggested by the European Association of Echocardiography and the American Society of Echocardiography recommendations [16] and the VARC-2 definitions [17], focusing the attention on circumferential extent of the leak in the parasternal short-axis view and diastolic flow reversal in the descending aorta. In case of suboptimal parasternal short axis windows, parameters such as jet width, jet density, jet deceleration rate and diastolic flow reversal in the descending aorta were used to assess leak severity. To evaluate PVL before discharge, two experienced echocardiographers performed the examinations. Consensus was obtained between 2 operators in case of discrepancies. For purposes of our analysis, we only used the cut off to discriminate between mild and at least moderate PVL.

Echocardiographers who were performing theses analyses, where unaware of the results of the current study as these scans were part of the regular TAVI follow up visits.

2.3. Follow-up

After discharge, follow-up data were collected prospectively at regular outpatient visits (1 month, 6 months, 1 year, 2 years) or by telephone interview with patients or their relatives. In-hospital death was defined as any death occurred during hospitalization for TAVI, even if the hospitalization was longer than 30 days. Clinical and echocardiographic baseline and follow-up data were recorded in the TAVI database. Cardiovascular events, date, cause of death and functional status according to New York Heart Association [NYHA] classification were recorded. Echocardiographic data included prosthesis function (transvalvular gradient), PVL and EF.

2.4. Statistical analysis

Continuous variables are expressed as mean ± SD or median (25th to 75th percentiles), as appropriate. Categorical variables are expressed as counts and percentages. Differences between two groups were tested using student *t*-test or Mann–Whitney test, for normally and not normally distributed continuous variables respectively. Categorical variables were compared using the Chi-square test.

The severity of PVL assessed before hospital discharge was used in the analysis as a categorical variable: none or mild (PVL ≤ mild), and moderate or severe (PVL ≥ moderate). If a patient died in-hospital, final echocardiography after procedure was used in the analysis. Mortality rates were estimated using the Kaplan–Meier method, and the log-rank test was used to compare estimated mortality rates between the groups. A Cox regression model was used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause mortality and calculate the significance of interaction terms. Variables with a p value <0.1 on univariate analysis were entered into the multivariate models. The intraobserver and interobserver variability of PVL grading was assessed by Cohen's kappa test. All measurements were repeated by the same observer in two sessions and by a second independent observer in 30 randomly selected patients from a series of cardiac cycles digitally stored.

All analyses were tested using 2-sided tests at a significance level of 0.05 and were conducted using SPSS Statistics 21.0 (IBM, Armonk, New York).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the EF <40% group (n = 84, 16.3%) and the EF ≥40% group (n = 430, 83.7%) are presented in Table 1. Patients in the EF <40% group were younger, more frequently males and more likely to have diabetes, coronary artery disease (CAD), renal insufficiency and atrial fibrillation than the EF ≥40% group. The EF <40% group had a higher logistic EuroSCORE. When baseline echocardiographic parameters were

Table 2
Procedural characteristics.

	Overall patients (n = 514)	EF <40% (n = 84)	EF ≥40% (n = 430)	p value
Approach site				
Trans-femoral	440 (85.6)	72 (85.7)	368 (85.6)	0.356
Trans-apical	27 (5.2)	7 (8.3)	20 (4.7)	
Trans-axillary	40 (7.7)	4 (4.8)	36 (8.4)	
Trans-aortic	7 (1.3)	1 (1.2)	6 (1.4)	
Valve used				
SAPIEN	287 (55.8)	43 (51.2)	244 (56.7)	0.643
CoreValve	193 (37.5)	35 (41.7)	158 (36.7)	
Direct flow	34 (6.6)	6 (7.1)	28 (6.5)	
PVL ≥ moderate	120 (23.3)	17 (20.2)	103 (24.0)	0.486
In-hospital death	11 (2.1)	7 (8.3)	4 (0.9)	<0.0001

Values are expressed as n (%), median (interquartile range).
PVL = paravalvular leak.