New-Onset Left Bundle Branch Block After TAVI has a Deleterious Impact on Left Ventricular Systolic Function

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NEW-ONSET LEFT BUNDLE BRANCH BLOCK AFTER TAVI HAS A DELETERIOUS IMPACT ON LEFT VENTRICULAR SYSTOLIC FUNCTION.

New-onset LBBB impact on LVEF after TAVI

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BRIEF SUMMARY

We have assessed the impact of new-onset LBBB after TAVI on the left ventricular ejection fraction (LVEF) evolution. Forty consecutive patients were included following the development of new-onset LBBB after TAVI implantation and were matched (age and LVEF) with 40 patients without. A new-onset LBBB was associated with a decrease in LVEF at 8 months, particularly in patients with an initial LVEF <50%, thereby potentially affecting their prognosis.

ABSTRACT

Background. Transcatheter aortic valve implantation (TAVI) has revolutionized the management of severe aortic stenosis. The development of new-onset complete left bundle branch block (LBBB) is, however, a frequent complication. The objective of the present study was to assess the impact of new-onset LBBB after TAVI on the evolution of left ventricular ejection fraction (LVEF).

Methods. Forty consecutive patients were included following the development of new-onset LBBB after TAVI implantation and were matched for age and LVEF with 40 patients implanted during the same period who did not develop LBBB. The primary endpoint was evolution of the LVEF measured by echocardiography prior to implantation and between 6-12 months after TAVI.

Results. The development of a LBBB was associated with a 5-point decrease in LVEF [-12.5; 2.5], contrary to the non-LBBB group (1.5 [-6.5; 9.5], p = 0.007) at 8 months, with the persistence of the LBBB (n = 23) exacerbating this decrease (-7 [-13; 2], p = 0.009). When left ventricular dysfunction (LVEF <50%) was present prior to TAVI, the appearance of LBBB was associated with a reduction in LVEF (-2 [-8; 2]) contrary to the non-LBBB group (20 [9; 22]), p = 0.02.

In Conclusions, the appearance of new-onset LBBB after TAVI has a pejorative impact on left ventricular systolic function, particularly in patients with an initial LVEF <50%, due to a lack of recovery of the latter, thereby potentially affecting their prognosis.

Key words: TAVI; Heart Valve Prothesis; Left Bundle Branch Block; Ventricular Ejection Fraction, Heart Failure.

INTRODUCTION

Calcified aortic stenosis (AS) is the most common of valvulopathies[1], the incidence of which increases with the increasing life expectancy of the population along with better management of cardiovascular risk factors and heart diseases[2]. Percutaneous transcatheter aortic valve implantation (TAVI) has transformed the management of patients with this disease[3], particularly those with high and intermediate surgical risk[4-6].

Numerous advances in implantation techniques and/or in the design of prostheses (anti-leak paravalvular skirt, rigidity of the prostheses, reduction in the size of the introducers) have considerably limited vascular and functional complications[7]. However, atrioventricular conduction complications are highly common and remain a major problem that is both underevaluated and poorly explored. Indeed, the anatomical proximity of the aortic ring and nodo-ventricular conduction pathways favor the occurrence of a left bundle branch block (LBBB) [higher incidence with self-expandable prostheses (30-60% vs. 6-12%)][8] as well as severe conduction disturbances[9]. The latter are associated with increased post-TAVI morbidity and mortality[10,11]. In the presence of new-onset LBBB, induced electrical asynchrony can lead to ventricular dysfunction or lack of improvement thereof as well as the appearance of high-grade conduction disorders in the long term. The impact of new-onset LBBB after TAVI implantation on left ventricular ejection fraction (LVEF) has never been assessed prospectively. TAVI implantation in patients at intermediate surgical risk and the possible extension of this procedure to low-risk surgical populations under evaluation thus compels cardiologists to anticipate this growing issue.

In light of the above, the objective of the present study was to prospectively assess the impact of the appearance of new-onset LBBB after TAVI on LVEF.

METHODS

This is a prospective cohort follow-up study, conducted between June 8th 2015 and August 1st 2017 as an ancillary of the LBBB-TAVI study (NCT02482844)[12]. The study was approved by the local ethics committee and the National Health Authority (ANSM: 2015-AOO271-48) and the written informed consent of each patient was obtained and archived.

Study Population[16]

Inclusion criteria were as follows: patients older than 18 years of age; implanted with a TAVI according to the 2012 recommendations of the European Society of Cardiology; expected life expectancy greater than 1 year; sinus rhythm; presence of new-onset complete LBBB post-TAVI persisting for more than 24 hours.

Patients were excluded if they had a pre-TAVI pacemaker or if they had a pre-procedural LBBB or lasting <24 hours post-TAVI.

The first 40 patients from the LBBB-TAVI study were included (new-onset LBBB group). During the same inclusion period and within the same center, 40 patients who did not develop an LBBB (non-LBBB TAVI group) were matched to the study population according to age and LVEF (≥50% or < 50%). In both groups, patients were in sinus rhythm and did not require a pacemaker either before or during the follow-up period.

Study Design

In accordance with the LBBB-TAVI study, included patients underwent an electrophysiological study after TAVI and were implanted, depending on the outcome, with a pacemaker (HV interval ≥ 70 ms) or an implantable loop recorder (HV < 70 ms). Patients with a pacemaker, eventually only present in the LBBB group, and presenting a ventricular pacing rate greater than 5% were excluded from this ancillary study. At TAVI post-procedure, patients were divided into two

groups: patients without LBBB (non-LBBB TAVI group) and those with new-onset LBBB after TAVI (new-onset LBBB group).

A transthoracic echocardiography was performed prior to the TAVI procedure as well as between 6 and 12 months after TAVI.

The primary endpoint was evolution of left ventricular ejection fraction on transthoracic echocardiography (TTE) between pre-TAVI and 6 to 12 months after TAVI. The identification of LBBB was validated by two blinded operators.

Definition of LBBB

Left bundle branch block on the electrocardiogram (ECG) was defined according to the AHA recommendations[13], namely by a QRS duration ≥ 120 ms (in at least one lead); a left delay in V5-V6 and aVL leads with a wide, slurred or notched R wave (RR'), and a fast initial ascent; a small R wave in V1-V2, followed by a wide and deep S wave, whose descent is faster than the ascent.

Transthoracic echocardiography

The echocardiographic study prior to the intervention was performed during the preoperative assessment within a maximum of 1 month before the intervention and within a period of 6 to 12 months after the procedure. TTE was performed using a 2.5 to 5 MHz imaging probe connected to a Vivid 9 ultrasonic device (Vingmed-General Electric, Horten Norway) in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Image analysis was subsequently performed by two blinded operators. LVEF was measured from 2D 4-chamber and 2-chamber views (3 loops for each section). The measurement was performed according to Simpson's biplane method described in the recommendations[14]. Aortic regurgitation (AR) was assessed according to recommendations and VARC-II1 criteria [5,16]. Aortic regurgitation after TAVI was considered to be significant if at least moderate.

The change in LVEF was calculated as the difference between the measurement at 6-12 months minus the pre-implantation measurement ($\Delta LVEF = LVEF_{postTAVI} - LVEF_{preTAVI}$). The variation in LVEF values are presented in LVEF percentage points. One operator's analysis were for the analysis. The second operator's analysis were used to evaluate inter-operator reproducibility. Left ventricle EF was obtained with the best loop acquired. Data were analyzed consecutively in groups of 10 patients.

Sample size and Statistical analysis

Sample size were calculated according to Cohen's definitons of effect-size bounds as: small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8: grossly perceptible and therefore large), we estimated that 40 patients in each group would be sufficient to detect a 5% absolute difference in LVEF for an effect size between 0.6 and 0.7 with a two-sided type I error of 5% and a statistical power greater than 80%. Statistical analyses were performed using Stata software, Version 13 (StataCorp, College Station, TX, US). Tests were two-sided, with a Type I error set at α=0.05. Continuous data are expressed as mean ± standard deviation (SD) or median [interquartile range] according to the statistical distribution (assumption of normality assessed using the Shapiro-Wilk test). Categorical parameters (including ischemic cardiomyopathy, beta-blockers, angiotensin converting enzyme inhibitors, AT1 receptors blockers, procedural access) were compared between groups (new-onset LBBB after TAVI *vs.* non-LBBB after TAVI) using chi-squared or Fisher's exact tests. Quantitative variables (including age, LVEF before TAVI) were compared between groups by Student's t-test or the Mann-Whitney test when the assumptions of the t-test were not met (normality and homoscedasticity analyzed using the Fisher-Snedecor test). A multivariable analysis was next conducted in order to determine whether LVEF after TAVI was significantly different between the two groups, taking an adjustment on) LVEF before TAVI, in addition to other covariates fixed according to the univariable results and clinical relevance: time between TTE and TAVI implantation and presence of beta-blockers. Multiple linear conditional regression models were performed, taking into account matching. Before

performing a regression model with time between TTE and TAVI implantation and presence of beta-blockers, we ran separate multivariable regression analyses with each parameter. Then, the two variables were added together in multivariable model. Particular attention was paid to possible interaction. The normality of residuals from these models was studied using the Shapiro-Wilk test. When appropriate, a logarithmic transformation was performed to achieve the normality of dependent outcome. Particular attention was given to LVEF before TAVI, which was also considered as a categorical variable classified according to literature as <50% or ≥50%. Prior to performing subgroup analyses according to LVEF before TAVI, the interaction between groups (new-onset LBBB vs. non LBBB after TAVI) and LVEF before TAVI (< or ≥50%) was studied.

RESULTS

Baseline characteristics (Table 1)

Overall, 534 patients [326(61%) with self-expandable valve and 208(39%) with balloon-expandable valve] underwent a TAVI procedure during the inclusion period. Fifty-one patients (9.6%, n=51) presented new-onset LBBB after TAVI lasting > 24 hours (12.3% new-onset LBBB in patients implanted with self-expandable vs. 5.3% with balloon-expandable TAVI).

A total of 80 patients were included in the present study. We included the first 40 patients of LBBB-TAVI study. Mean age and proportion of male gender were identical in both groups (82.4±4.6 vs. 81.5±5.1 years, p=0.40 and 50% vs. 60% in LBBB and non-LBBB groups, respectively; p=0.37). There were no differences in terms of pre-TAVI symptoms (NYHA class III or IV) [12/40 (30%) in the LBBB group vs. 16/40 (40%) (p=0.35)]. The EUROSCORE also did not differ between the 2 groups (3.8±2.9 in the LBBB group vs. 3.2±1.4, p=0.18). The same was also true for the mean aortic transvalvular gradient in pre-TAVI: 44.2±15.6 mmHg in the LBBB group vs. 43.4±14.3 mmHg (p=0.83). The number of patients implanted with a self-expandable prosthesis was higher in the LBBB group (82.5% vs. 47.5%, p = 0.001).

The rate of moderate or significant aortic regurgitation after TAVI was similar between the 2 groups: 7.5% in the LBBB group vs. 12.5% (p=0.51).

ECG characteristics

Among the patients with new-onset LBBB, 97.5% still exhibited a LBBB at hospital discharge (between D5 and D7), with 58% at TTE follow-up assessment. The mean QRS duration of the LBBB at hospital discharge was 151±17 ms vs. 102±14 ms in the non-LBBB group (p <0.001). Patients who did not present a complete LBBB after TAVI had the following ECG features: 1 patient had a left anterior fascicular block, 3 had an incomplete LBBB <120 ms, 2 had a nonspecific intraventricular conduction delay and 3 had a right bundle branch block ≥120 ms. A total of 34 patients had a narrow QRS <120 ms.

Evolution of left ventricular ejection fraction (Table 2)

LVEF evaluation was performed within a mean delay of 8.1±4.1 months after TAVI in the LBBB group vs. 8.3±5.5 months in the non-LBBB group (p = 0.91).

A decrease in LVEF of 5 percentage points [-12.5; 2.5] was observed in instances of new-onset LBBB in contrast to the non-LBBB group which featured an increase of 1.5 percentage points [-6.5; 9.5], p = 0.007. Among patients with pre-TAVI left ventricular dysfunction (LVEF <50%), the appearance of LBBB was associated with a decrease in LVEF of -2[-8 - 2] as opposed to patients without LBBB who had an increase in LVEF of 20[9; 22], (p = 0.02) (Figure 1).

During follow-up, LVEF of patients with persistent LBBB was reduced by -7 points [-13; 2] (n=23), comparatively to patients who recovered from LBBB (-2 points [-7; 6] (n=17)) and those without new-onset LBBB after TAVI (1.5 [-6.5; 9.5], n=40, p = 0.009), with a regression coefficient of 10.76 [6.01; 15.52] adjusted to pre-TAVI LVEF, QRS duration, valve type and the presence of beta-blockers between persistent LBBB and non LBBB patients (taking into account LBBB and non-LBBB groups matching).

Morbidity and mortality

During the 12-month follow-up, there were no differences in hospitalizations for HF in the new-onset LBBB post-TAVI vs. the non-LBBB groups [2/40 patients (5%) in the new-onset LBBB group vs. 3/40 patients (7.5%), p = 0.65], as well as no difference in mortality rate [1/40 patients (3%) vs. 4/40 patients (10%), p = 0.36].

DISCUSSION

This study is the first to prospectively follow the outcome of patients developing new-onset LBBB persisting for more than 24 hours after TAVI (both self-expandable and balloon-expandable valves) as well as its long-term consequences on left ventricular systolic function. The appearance of a post-TAVI LBBB was associated with a degradation in LVEF limiting the

expected benefits of the intervention. The reduction in LVEF was even more pronounced when LBBB persisted beyond 6 months and in those patients with left ventricular dysfunction (LVEF <50%) prior to TAVI implantation.

The low incidence of conduction disorders (9.6%) and the observed higher prevalence of self-expanding prostheses (82.5%) are comparable to the most recent data in the literature and the reference studies[17]. Although the prevalence of conduction abnormalities varies depending on the studies and type of valve (from 10.5% [PARTNER registry, Edwards® valve] to 37% [France 2 registry, Corevalve Medtronic® self-expanding valves]), such prevalence has tended to decrease with operator experience but also the use of the more recent prostheses (Medtronic Corevalve Evolut R and Edwards Sapiens XT valves).[18] The onset of these abnormalities can be delayed and transient (50% persistence at 6 months)[19]. Similarly, due to its more aggressive conformation in the aortic outflow track, the self-expanding valve is likely to generate more conduction abnormalities without compromising long-term prognosis.

In instances of left ventricular dysfunction, replacement of the aortic valve for severe aortic stenosis is associated with an improvement in LVEF. Whether using the percutaneous or surgical approach, LVEF recovery, including in high-risk patients, evolves towards a near normalization of the parameters depending on the degree of contractile reserve, including in the long term [TVT registry: from 35.7±8.5% to 48.6±11.3% (p <0.0001) 1 year after TAVI and similarly from 38.0±8.0% to 50.1±10.8% (p <0.001) after surgery]. Indeed, left ventricular dysfunction is progressive and often the consequence of an elevation in afterload. Elimination of the outflow obstruction explains the improvement in LVEF in patients undergoing early aortic valve replacement. More generally, an improvement in LVEF or an absence of impairment is also expected when there is no pre-existing left ventricular dysfunction[20].

In the present study, a LBBB after TAVI hindered this recovery. It counterbalanced the improvement expected by the reduction in afterload when LVEF was normal and above all, it did

not allow observing an improvement in LVEF in cases of left ventricular dysfunction. One explanation lies in the electro-mechanical effect of LBBB on left ventricular activation characteristics[21,22]. Electrical activation of the right ventricle by the nodo-Hisian pathways is preserved. On the other hand, both interventricular and intraventricular dyssynchrony (late activation of the left lateral wall) alters the quality of the cardiac contraction[21]. In the long term, it is responsible for reverse left ventricular remodeling with a reduction in LVEF and, in certain cases, heart failure[10].

All of the studies specifically related to the impact of LBBB have reported the degradation or, at the very least, the absence of improvement of LVEF in instances of new-onset LBBB (LVEF at 6 months, narrow QRS 58.1% vs. LBBB 52.8%, p<0.001 PARTNER Study; LVEF at 6 months, narrow post-procedure QRS +4.6±7.8 vs. LBBB-T -2.1±6.9%, p=0.002, Dobson et al.[23], and 7.39±9.05% vs. -0.46±5.63%, p <0.001, Carraba et al.[24]). However, these studies, while akin to LBBB-TAVI, mainly focused on either one type of prosthesis (balloon-expandable[24] or self-expandable[25]) or without a matching of their population[23]. Moreover, these studies were the result of retrospective data and in many instances performed prior to the advent of last-generation valves (in contrast to the Evolut R and Sapiens XT valves included in the present study) and whose hemodynamic and structural characteristics tended to modify their behavior in vivo[19,26 27]. In addition, there are very sparse data on the long-term evolution of LVEF[19,24,26,27].

In the long term, the impact of the reduction in LVEF and of a new-onset LBBB on morbidity and mortality remains nevertheless controversial[26,28-31]. The hemodynamic repercussions of LBBB may be less well tolerated by the remodeled and hypertrophied left ventricle of a patient who is often elderly and with a prior history of aortic stenosis.

These considerations are essential, given that patients with severe aortic stenosis with left ventricular dysfunction account for approximately 10% of the population with aortic stenosis[32] (17.5% in the present study) and the reduction in post-TAVI LVEF appears to be associated with a higher mortality and hospitalization rate in those patients with more severe heart failure[33,34].

Further studies enabling to stratify the management of these patients exhibiting new-onset LBBB is necessary with regard to the rhythmic and hemodynamic outcome of these patients. Indeed, while the LBBB disappears in nearly half of affected patients, there are currently no predictive elements with regard to the persistence of new-onset LBBB after TAVI. Its persistence may ultimately warrant prevention of LVEF dysfunction appearance by bi-ventricular pacing in these patients presenting new-onset LBBB and a left ventricular dysfunction even of moderate grade (e.g. LVEF < 50%). On the other hand, adaptation of the type of valve to be implanted in patients with left ventricular dysfunction could represent an appealing avenue given the notable differences highlighted between self-expandable and balloon-expandable valves[8]. This point is of particular importance in that the newer valves being developed are seemingly more conducive to conductive disorders, albeit with a near zero rate of aortic regurgitation[35,36].

The study has some limitations, mainly the observational design and small sample size. However, the groups were matched on age and LEVF and the sample size seems relevant to meet the primary objective. Due to the relative small population, only large effects could be highlighted, notably to study the secondary objectives and the sub-groups analyses. Residual confounding remains a possibility and there remains a risk of bias, despite the conservative regression analysis. The present study remains the first study conducted prospectively in this frequent population and whose outcome remains uncertain. It moreover represents one of largest cohorts established to date and will help to gain a greater understanding of the underlying mechanisms at play in these patients with new-onset LBBB. Other parameters assessing systolic function such as the Tei index, the measurement of the S' velocity of the mitral annulus at the septal and lateral levels, or as recently described, the study of myocardial deformation or speckle tracking could be more effective and will need to be evaluated[37]. Notwithstanding the latter, LVEF remains the indispensable measurement parameter currently used[38] in cardiology for the assessment, management and stratification of patient risk, and remains a strong and reproducible marker of left ventricular systolic function. None of the

patients in our study were screened for the presence of a contractile reserve (stress echocardiography, MRI). The worsening or lack of improvement of LVEF could be attributable to a reduction in contraction reserve. However, the opposite evolution of LVEF at 6 months in patients without LBBB or who had recovered from LBBB would suggest a minor impact of this particular parameter.

CONCLUSION

The development of new-onset LBBB after TAVI, particularly when persisting beyond 6 months, has a pejorative impact on left ventricular systolic function, especially in patients with an initial LVEF <50%. Complementary studies aimed at decreasing the rate of new-onset LBBB after TAVI procedure but also to guide the management strategy of such patients are necessary.

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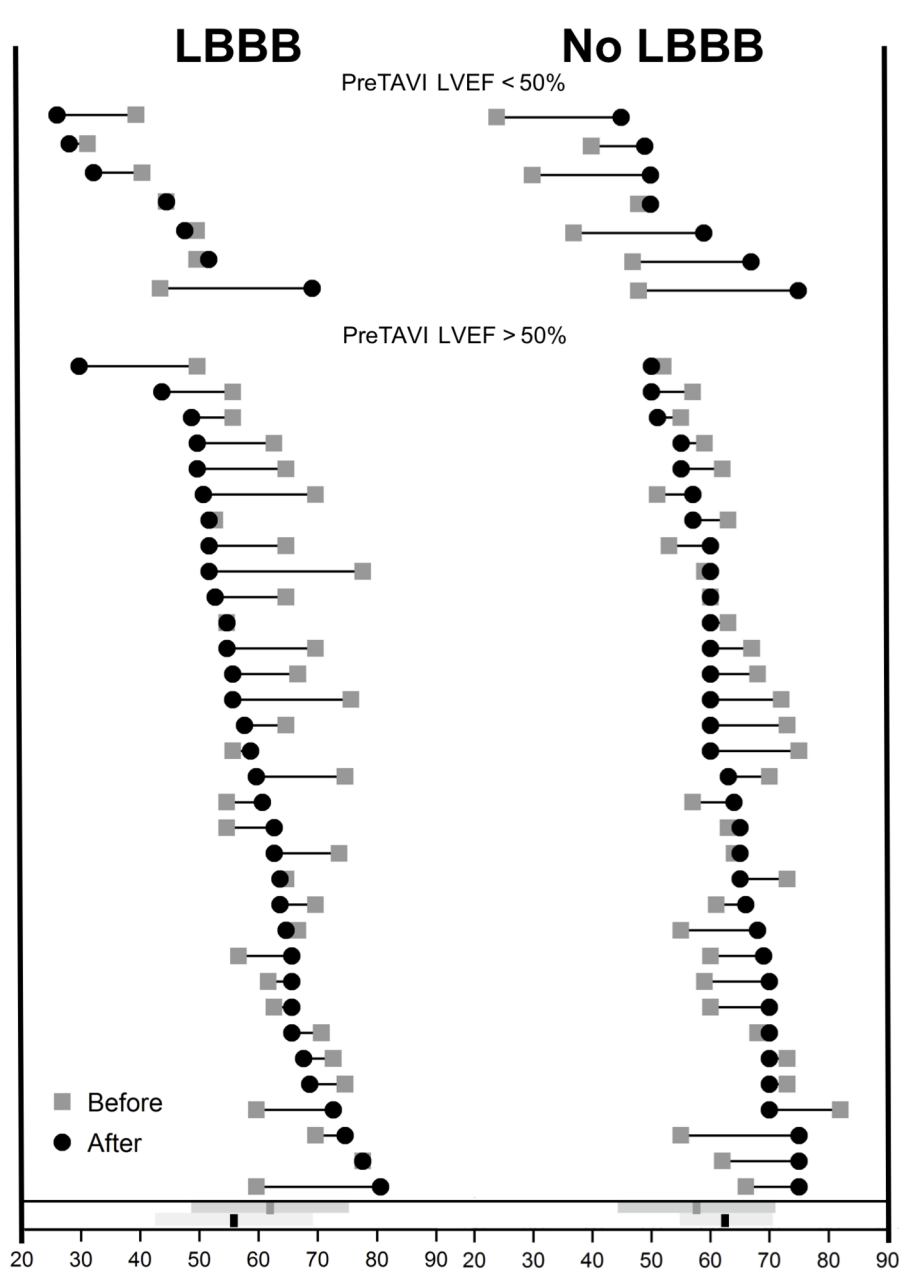
TABLE AND FIGURES

Table 1. Clinical characteristics according to the presence or absence of post-TAVI LBBB. ACE: Angiotensin converting enzyme; AR: Aortic regurgitation; CABG: coronary artery bypass graft; LBBB: left bundle branch block; NYHA: New York Heart Association; MDRD: Modification of diet in renal disease; TAVI: Transcatheter aortic valve implantation.

Table 2. Left ventricular ejection fraction evolution after Transcatheter aortic valve implantation according to left bundle branch block appearance and persistence. LBBB=left bundle branch block; LVEF=Left ventricular ejection fraction, TTE=Transthoracic echocardiography.

Figure. Evolution of left ventricular ejection fraction during follow-up in the presence or absence of post-Transcatheter Aortic Valve Implantation left bundle branch block. LBBB: left bundle branch block; LVEF: Left ventricular ejection fraction, TTE: Transthoracic echocardiography.


LBBB
No LBBB
PreTAVI LVEF < 50%
PreTAVI LVEF > 50%
Before
After
20
30
40
50
60
70
80
90
20
30
40
50
60
70
80
90

	TOTAL (n=80)	LBBB (n = 40)	Non-LBBB (n = 40)	p-value
Clinical characteristics				
Age, years	82.0± 4.9	82,4 ± 4,6	81.5 ± 5.1	0.40
Male gender, n(%)	46 (57.5)	21(52.5)	25(62.5)	0.37
NYHA (III or IV)	28 (35.0)	12 (30.0)	16 (40.0)	0.35
EuroSCORE II	3.5± 2.3	3.8 ± 2.9	3.2±1.4	0.18
EuroSCORE Logistic	12.8±7.7	12.8±8.7	12.8±6.7	0.99
Prior CABG, n(%)	40 (50.0)	3 (7.5)	3 (7.5)	0.99
Hypertension, n(%)	65 (81.2)	37 (92.5)	28 (70.0)	0.01
Diabetes mellitus, n(%)	25 (36.3)	13 (67.5)	12 (30.0)	0.81
Mean aortic valve gradient, mmHg	43.8 ± 14.9	44.2 ± 15.6	43.4 ± 14.3	0.83
Chronic respiratory insufficiency, n(%)	12 (15.0)	6 (15.0)	6 (15.0)	1.00
Renal insufficiency (MDRD clearance < 30 mL/min)	4 (5.0)	3 (7.5)	1 (2.5)	0,62
Ischemic heart disease, n(%)	44 (55.0)	24 (60.0)	20 (50.0)	0.37
Beta-blockers, n(%)	24 (30.0)	14 (35.0)	10 (25.0)	0.33
ACE inhibitors, n(%)	34 (42.5)	19 (47.5)	15 (37.5)	0.37
Procedure-related characteristics				
Medtronic Corevalve or Corevalve Evolut-R	52 (65.0)	33 (82.5)	19 (47.5)	0.001
(vs. Edwards Sapien, Sapien XT or Sapien 3)				
Diameter				
23 mm	15 (18.7)	6 (15.0)	9 (22.5)	0.02
26 mm	30 (37.5)	12 (30.0)	18 (45.0)	
29 mm	27 (33.8)	20 (50.0)	7 (17.5)	
31 mm	8 (10.0)	2 (5.0)	6 (15.0)	
Access route, n(%)				
Femoral	61 (76.2)	32 (80.0)	29 (72.5)	
Subclavian	15 (18.8)	8 (20.0)	7 (17.5)	0.19
Transapical	4 (5.0)	0 (0.0)	4 (10.0)	
Moderate to severe AR after TAVI, n(%)	8 (20)	3 (7.5)	5 (12.5)	0.51
Pre-dilatation, n(%)	35 (28)	20 (8)	50 (20)	0.005
Post-dilatation, n(%)	10 (8)	12.5 (5)	7.5 (3)	0.071

	TOTAL	LBBB (n=40)	Non-LBBB (n=40)	p value	At 6 months		
					No LBBB (n=17)	Persistent LBBB (n=23)	p value
LVEF prior to the procedure							
Mean ± SD	60.0 ± 11.8	60.9 ± 11.6	59.1 ± 12.14	0.50	59.9 ± 9.4	61.6 ± 13.1	0.63
<50%, n (%)	14 (17.5)	7 (17.5)	7 (17.5)	1.00	3 (17.7)	4 (17.4)	0.99
LVEF after to the procedure							
Mean ± SD	59.3 ± 11.0	56.7 ± 12.9	62.0 ± 8.1	0.03	59.3 ± 10.9	54.7 ± 14.1	0.25
<50%, n (%)	10 (12.5)	8 (20.0)	2 (5.0)	0.04	3 (17.7)	5 (21.7)	1.00
Post-procedure TTE delay, months, mean ± SD	8.2 ± 4.8	8.1 ± 4.1	8.3 ± 5.5	0.91	8.7 ± 4.1	7.7 ± 4.1	0.22
Absolute LVEF change							
All patients	-2 [-8 ; 6.5]	-5 [-12.5 ; 2.5]	1.5 [-6.5 ; 9.5]	0.007	-2 [-7 ; 6]	-7 [-13 ; 2]	0.16
Initial LVEF < 50 %	5.5 [-2 ; 21]	-2 [-8 ; 2]	20 [9 ; 22]	0.02	0 [-2 ; 25]	-5.5 [-10.5 ; -0.5]	0.16
Initial LVEF > 50 %	-3 [-11 ; 5]	-6 [-13 ; 3]	-2 [-7 ; 7]	0.05	-3.5 [-12 ; 6]	-7 [-15 ; 3]	0.32