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Mid-term Procedural and Clinical Outcomes of Percutaneous Paravalvular Leak Closure With the Occlutech Paravalvular Leak Device

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Short running title: Transcatheter PVL closure using the Occlutech Paravalvular Leak Device

ABSTRACT

Aims: To assess the efficacy and safety of the Occlutech Paravalvular Leak Device (PLD) for the percutaneous closure of paravalvular leaks (PVL).

Methods and results: Patients with PVL were enrolled at 21 sites from 9 countries. Indications for PVL closure were heart failure and/or hemolytic anemia. Endpoint measures were changes in PV regurgitation grade, NYHA class and requirement for hemolysis-related transfusion. One-hundred thirty-six patients with mitral (67.6%) or aortic (32.4%) leaks were included (mean age 66.7 years, 58% men). Thirty-one percent had multiple PVLs. The proportion of patients with NYHA III/IV decreased from 77.3% at baseline to 16.9% at latest follow-up. The proportion of patients with need for hemolysis-related blood transfusion decreased from 36.8% to 5.9% and 8.3% to 0% for ML patients and AL patients, respectively. All cause mortality was 7.4%. Complications included interference with valve leaflets (0.7%), transient device embolization (percutaneously solved) (0.7%), late device embolization (0.7%), recurrent hemolytic anemia (2.2%), new onset hemolytic anemia (0.7%), valve surgery (2.2%), need for repeat closure (0.7%), complications at femoral puncture site (0.7%) and arrythmias requiring treatment (4.4%).

Conclusions: PVL closure with the Occlutech PLD demonstrated high success rate associated with significant clinical improvement and a relatively low rate of serious complications.

Key words: Imaging modalities; Specific closure device / technique; Transthoracic echocardiogram; Transesophageal echocardiogram

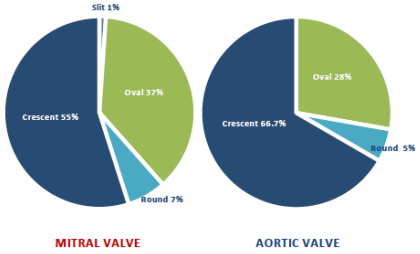
Mid-term Procedural and Clinical Outcomes of Percutaneous Paravalvular Leak Closure With the Occlutech® PLD

Study Enrollment : December 2014 – February 2018

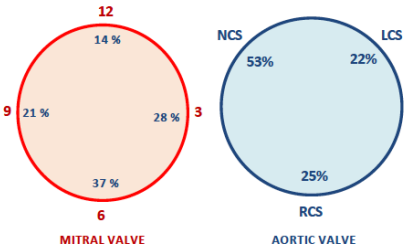
179 Occlutech® PLD were implanted in 136 patients enrolled at 20 sites in 9 countries

Heart Failure: **49.3** %; Hemolysis – Anemia: **4.8**%; Heart Failure + Hemolytic anemia: **43** %
Mitral Leaks, n= **131** (67.6%) Aortic Leaks, n= **53** (32.4%)

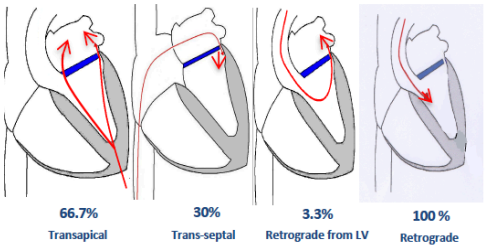
Leak shape



Leak location (valve clockface)

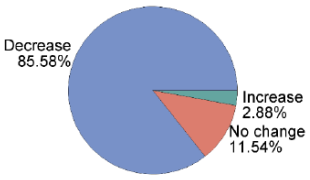


Leak approach



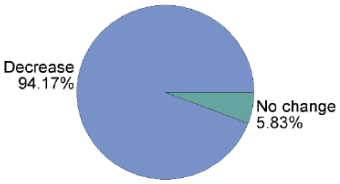
Change in NYHA class

N=106

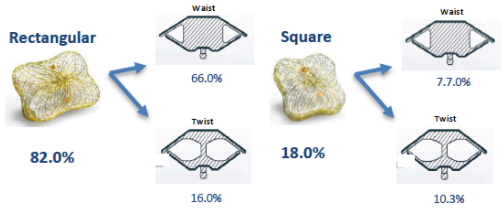


Change in PV Regurgitation

N=106



Device Types used



Transcatheter PVL closure with the specifically designed PLD demonstrated to be effective with a relatively low rate of major complications
Procedural success for ML and AL closure was high with low rate of residual or recurrent leaks
Significant improvement of NYHA class, reduction of hemolytic anemia and transfusion dependency were achieved

Condensed Abstract

With the aim to provide additional clinical data regarding transcatheter PVL closure, we assessed efficacy and safety of the Occlutech Paravalvular Leak Device (PLD). Retrospectively, we included 136 patients who underwent PVL closure with a PLD, of whom 92 (67.6%) had mitral and 44 (32.2%) aortic PVL. Following PVL closure, prevalence of patients with NYHA III-IV symptoms or need of hemolysis-related blood transfusions significantly decreased. All cause mortality during follow-up was 7.4%. PVL closure with PLD was associated with significant clinical improvement.

Abbreviations

AE	Adverse Events
ECG	Electrocardiogram
GA	General Anesthesia
IFU	Instructions for use
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
NT-pro BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PLD	Paravalvular leak device
PVL	Paravalvular leak
SD	Standard deviation
TTE	Transthoracioc echocardiography
TEE	Transesophageal echocardiography

Introduction

Transcatheter closure of PVL, firstly described in 1992 [1], has slowly evolved into a viable and less invasive alternative to surgery in high-risk patients with suitable anatomy [2-4].

Complete PVL sealing is relatively rare due to irregular leak morphology and complex anatomy of the surrounding tissue. This raises the need for dedicated devices ideally available in multiple sizes and shapes for improving procedural efficacy and success.

The Occlutech PLD (Occlutech Holding AG, Switzerland) is the only device specifically designed and certified in Europe (CE marked in 2014) for the treatment of mitral leaks (ML) and aortic leaks (AL). This international, multicenter registry was designed to provide additional clinical data on the efficacy and safety of the PLD in high-risk patients with ML or AL after surgical implantation of prosthetic heart valves.

Methods

This registry considered PLD closure procedures performed in 21 hospitals of 9 EU and outer-EU countries. All centers were contacted to participate in this study, and all agreed to participate. Anonymized data were acquired from medical and electronic records regarding patient medical history, demographics, vital signs, clinical laboratory tests, 12-lead electrocardiography (ECG) and transthoracic and transesophageal echocardiography (TTE/TEE). Signed informed consent was obtained from all patients prior to the procedure. The study plan was approved by an independent Ethics Committee, the International Medical and Dental Ethics Commission (IMDEC).

Procedure

Two and three-dimensional (2D/3D) TEE was used throughout each procedure, particularly in ML for complete and accurate delineation of these defects (Figures 1 and 2). Three-dimensional modalities included real-time 3D zoom and full volume acquisition with and without color flow imaging. The degree of valvular regurgitation was evaluated by Doppler echocardiography using the guidelines recommended by the American Society of Echocardiography [5]. In some cases, ECG-gated cardiac CT angiography was employed to define location, size, shape and trajectory of PVL.

Patients with a moderate-to-severe PVL causing heart failure and/or hemolysis with the need of recurrent blood transfusions who were deemed high risk for surgery by the heart team were considered for closure. Patients were treated according to the device Instructions for use (IFU) and standard clinical practice. Procedures were performed under general anesthesia (GA) or conscious sedation due to the need for intra-procedural TEE guidance. In a subset of patients, transapical catheter-based mitral PVL closure procedures were performed with a fusion of real-time 3D TEE and cardiac fluoroscopy imaging [6].

The Occlutech PLD

The Occlutech PLD is a self-expanding, flexible, double-disc device made from nitinol-braided wires that has been specifically engineered combining and improving several features of previous off-label devices. Two different disc geometries are available, square and rectangular, connected by a waist of different sizes and shapes to improve stability and minimize erosion risk of the surrounding tissue [7,8].

Statistical analysis

All statistical analyses were performed by means of commonly applied descriptive statistics. The study does not allow any confirmatory analyses. The analysis considers safety data of 136 patients. Baseline

and 6-month follow-up analyses consider data from 106 patients. Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range. Differences compared to baseline were assessed using one-sample t-test for normally distributed variables. The Wilcoxon signed-rank test was used for non-normally distributed variables. Categorical variables were compared by Wilcoxon signed-rank test. Two-sided p values <0.05 were considered statistically significant in all analyses. All calculations were done with SAS Version 9.4.

Results

179 PLDs were implanted in 136 consecutive patients in 21 centers of 9 countries (December 2014 – February 2018). Saftey data were collected from 136 patients. Baseline and 6-month follow-up data from 106 patients (69 mitral and 37 aortic) are considered in the following analyses, if not mentioned otherwise. The average patient follow-up time was 153.8 ±80 days.

Baseline Characteristics

Demographic and clinical data for patients with ML and AL are summarizd in Table 1. Mean patient age was 66.2 years (min: 26, max: 84), 58.1% were male and 78.9 % presented with NYHA class III/IV. Main indications were heart failure (49.3%), hemolytic anemia (4.8%) or both (43%). Twenty-five (36.8%) of the ML and three (8.3%) of the AL patients were dependent on blood transfusions.

Procedural details

Table 2 shows procedural details. ML were approached under GA (62.5%) and 3D TEE guidance (63.1%) **via surgical transapical ("hybrid approach")** (66.7%), antegrade transseptal (30.0%) **or retrograde transaortic from the left ventricle (3.3%).** In 20.6% of AL patients, PLD were implanted under GA and

leaks were always accessed via a retrograde transaortic approach (100%). In 36.2% and 21.6% of ML and AL patients, respectively, multiple leaks were treated. Most of ML and AL were closed with one PLD per leak (79.4% and 75.6%, respectively). In several patients, the number of PLD used was less than the number of leaks (10.3% ML patients and 18.9% in AL patients). In most cases, rectangular waist shape PLD were used followed by the rectangular twist shape (Figure 3). Median procedural time for ML closure was 122.5 (110-135) minutes in transapical cases and 62.5 (48-125) minutes in transseptal cases. Median fluoroscopy time was not significantly different between the two access routes (20.5 vs. 25 minutes). Median procedural and fluoroscopy times for AL closure were 90 (70- 110) and 15 (11- 24) minutes, respectively.

Leak characteristics

Table 3 presents details on 131 ML and 53 AL anatomic characteristics and number of PLD used. More than 80% of PVL had a maximum diameter of $\leq$ 10 mm and either crescent or oval shape. ML were located posteriorly in 35.9% of the cases and in a medial position in 29%. Most AL were located in the non-coronary sinus area (55.8%). Intraprocedural TEE showed severe PV regurgitation in 97.1%, moderate in 81.4% and small in 1.4% of ML patients and severe in 91.9% and moderate in 8% of AL patients.

Outcomes

At follow-up, paravalvular regurgitation was severe in 4.5%, moderate in 7.6%, small in 56.1% and absent in 31.8% in ML patients. In AL patients, it was severe in 2.7%, moderate in 10.8%, small in 81.1% and absent in 5.4% (Figure 4). Overall, PVL improved from moderate/severe to no more than mild/small in 87.7% of ML patients and 86.5% of AL patients. One (0.7%) patient underwent repeat closure four months after the index procedure because of significant residual leak. Device success rate, defined as stable implantation and PV regurgitation reduction to $\leq$ mild, was 88.9%.

NYHA class improved in most of the patients over the mean follow-up of 153 ±80 days. The proportion of patients with NYHA III/IV decreased from 86.8% at baseline to 11.4% at follow-up (Figure 5). The proportion of patients with need for hemolysis-related blood transfusion decreased from 36.8% to 5.9% and 8.3% to 0% for ML and AL patients, respectively. Laboratory values of a subset of patients are summarized in Supplemetary Figure 1. The clinical success rate, defined as patients with NYHA I/II or no longer dependency on blood transfusions at 6-month follow-up was 86.5%. All-cause mortality was 7.4%. No death was associated with the device.

One (0.7%) patient with a small residual leak had recurrence of hemolytic anemia requiring transient blood tranfusions. In another case, intraprocedural TEE showed that PLD deployment blocked the movements of the prosthetic valve leaflets and the device was recaptured percutaneously without any complication and successfully replaced with a smaller PDL. Two intraprocedural embolizations occurred during delivery sheath placement for the deployment of an additional PLD. One embolization was managed surgically and one with percutaneous retrieval. One late embolization was detected at follow-up. Complications at femoral puncture site occurred in 0.7%, bleeding complications in 2.9% and arrhythmias requiring treatment in 4.4% of the cases. In 66.7% of the patients, arrhythmias occurred during the procedure or hospital stay (Table 4).

Discussion

The performance endpoint of this study was effective PVL closure, defined as a stable implantation and PVL reduction to no more than mild. The study met this endpoint in 88.9% of the patients. These results compare favorably with those of previous studies, which showed technical success rates ranging between 62% [9] and 87% [10]. In 87.3% of our study patients, PVL was mild or no longer detectable at 6-month echocardiography follow-up. This result is of utmost importance as several studies have shown a direct

correlation between the grade of residual regurgitation and the rate of repeat intervention and survival [3,11-13]. In line with the technical success observed, PVL closure was associated with significant clinical improvement and reduction of blood transfusion need.

As with every interventional technique, transcatheter PVL closure is not free of potential complications [14,15]. Device malpositioning or embolization have been reported in 1% to 5% of large series [12,16]. The main causes are frail tissue around the valve, multiple device deployment and complicated access to PVL combined with imaging limitations. Generally, in such cases snaring and recapture of the device into the delivery sheath can be performed. Only one (0.7%) embolization requiring surgery was reported in our registry.

Interference on prosthetic valve leaflet function is a feared complication of percutaneous PVL closure. It is not rare and clinical studies report rates ranging from 3.6% [3] to 5% [16,17]. In our registry, this occurred in one (0.7%) patient only. Importantly, interference occurred during the procedure and before device release. The very low rate of valve interference may be attributed to the unique design of the PLD, whose concavities of the four edges produce only minimal overlapping with the surgical valve. Undoubtedly, careful image-based assessment of PVL anatomy is of utmost importance for choosing the right size device and for ensuring the proper apposition of the device disc to the surrounding tissue with full sealing [18].

Of note, oversized devices might also have an opposite effect and increase the regurgitant defect.

Regurgitation through a residual leak or the PLD has an important impact on clinical outcome. Indeed, it can be associated with persistent or new hemolysis. We observed new hemolytic anemia in one (0.7%) patient and recurrence of hemolytic anemia in 2.2% of the patients. In two additional patients, who underwent successful PVL closure for hemolytic anemia, transfusion dependency was reduced but not completely avoided. With a moderate or severe residual leak observed in 12.1% of the ML patients and

13.5% of the AL patients, the Occlutech PLD compares favorably with other devices for which moderate or severe residual leaks were reported in 11% to 24% of the cases [3,11]. A repeat procedure was needed in one (0.7%) patient only, a rate lower than that (6%) reported by Calvert et al. [19].

Most of our patients showed clinical benefits as indicated by a significant improvement of NYHA class and a significant reduction of hemolytic anemia and hemolysis-related blood transfusions.

It must be emphasised that percutaneous PVL closure procedure is performed mostly in high-risk patients for whom repeat surgery is not suitable. Accordingly, most patients with PVL have multiple co-morbidities underlining the need for a less invasive procedure. Indeed, the all-cause mortality rate of 7.4% observed in our registry is comparable to that observed in the literature [3, 19] and may be explained by the high-risk characteristics of the patients. It should be noted that a significant improvement in procedural outcomes has been reported with increasing operator experience [12], underlining the importance of the learning curve associated with this complex procedure, which requires commitment and a wide variety of interventional skills.

In summary, choice of an appropriate occluder device along with thorough preprocedural planning using advanced imaging modalities (specifically fusion imaging) and alternative access approaches (transapical "hybrid technique") are critical for achieving high intraprocedural success rate and for reducing major adverse events of this transcatheter procedure.

Study Limitations

This is a retrospective registry. Therefore, there is a theoretical bias associated with such an investigation. There was no evaluation of TEE by a central core laboratory, nor was an audit of the records performed. Having many different centers and investigators with different skills and techniques participating in the

study increases the complexity of comparison of the implantation methods used. Finally, there was no control group comparing this treatment to surgery.

Conclusions

Transcatheter PVL closure with a specifically designed PLD demonstrated to be effective with a relatively low rate of major complications. Procedural success for ML and AL closure was high with low rate of residual or recurrent leaks, and was associated with significant improvement of NYHA class and reduction of hemolytic anemia and transfusion dependency. However, further data are needed to assess the clinical outcome of patients treated with this device at longer-term follow-up.

Impact on daily practice

1. Paravalvular leak is an important complication of valve replacement surgery and is associated with significant morbidity and mortality.
2. For the high-risk symptomatic PVL patient, catheter closure is a viable therapeutic alternative strategy to surgical PVL repair and may represent a first-line treatment for this subset of patients.
3. Transcatheter PVL closure with the specifically designed Occlutech PLD occluder demonstrated to be an effective procedure with a relatively low rate of serious complications.

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Figure Legends

Figure 1. Echocardiographic (A-F) and fluoroscopic imaging (G-J) of transcatheter closure of a postero-lateral, crescent-shaped mitral PVL with severe regurgitation in a patient with a bileaflet mechanical valve prosthesis.

A: 2D TEE color Doppler showing the regurgitant leak (arrowhead);

B: 3D TEE color Doppler images cropped at level of the vena contracta clearly identified the single mitral paraprosthetic leak at 8 o'clock (arrowhead);

C: 3D TEE showing the postero-lateral defect;

D: the wire crossing the PVL hole (arrowhead) seen on 3D TEE images;

E: Post-procedure 2D TEE color Doppler demonstrating no residual regurgitant leak;

F: final position of 12x5 mm PLD rectangular twist (arrowhead) on 3D TEE;

G: Fluoroscopic imaging showing a 5Fr multipurpose catheter (arrow) and an exchange wire (arrowhead) crossing the mitral leak;

H: opening of the distal disc (arrowhead) of the occluder;

I: opening of the waist and the proximal disc (arrowhead) of the occluder;

J: 12x5 mm PLD rectangular twist (arrowhead) successfully deployed.

Figure 2. 2D color Doppler and 3D TEE images before (A-C) and after (D-F) percutaneous closure of a crescent-shaped, postero-lateral (7 o'clock) paravalvular mitral leak in a patient with mechanical Starr-Edwards caged-ball prosthetic valve (arrowhead) and mechanical aortic valve (arrow) + dual-chamber pacemaker; fluoroscopic images (G-J) showing procedural steps of the implantation of a 10x4 mm PLD rectangular waist.

Figure 3. The Occlutech PLD types used for paravalvular leak closure with frequencies. Occlutech PLDs exist in two shapes (rectangular and square) and with two different types of connection between the proximal and distal disc (waist and twist). Frequencies are given. Unit of analysis are individual occluder.

Figure 4. Paravalvular regurgitation in the Mitral and Aortic patient populations before and 6 month following implantation. 6M indicates six-month follow up visit; BL, Baseline visit; Wilcoxon Signed-Rank Test has been applied. Fractions without percent value represent for mitral leaks at BL: small (1.4%) and moderate (1.4%) and at 6M: moderate (7.6%) and severe (4.5%). For aortic leaks at BL: no (0%) and moderate (8.1%) and at 6M: no (5.4%) and severe (2.7%).

Figure 5. NYHA functional classification in the Mitral and Aortic patient populations before and 6 month following implantation. 6M indicates six-month follow up visit; BL, Baseline visit; NYHA, New York Heart Association. Wilcoxon Signed-Rank Test has been applied. Fractions without percent value represent for mitral leaks at BL: class I (1.5%) and at 6M: class IV (4.3%). For aortic leaks at BL: class I (2.8%) and at 6M: class IV (2.8%).

TABLES

Table 1

Table 1 Baseline Characteristics		
	Mitral, N=69*	**Aortic, N=37***
Age [years]	66.7 ±8.3	65.1 ±14.2
Weight (m) [kg]	78.1 ±10.9	77.8 ±11.1
Weight (f) [kg]	69.6 ±16.1	75.6 ±9.4
Height (m) [cm]	176.5 ±7.4	172.6 ±7.6
Height (f) [cm]	162.7 ±6.8	167.2 ±7.7
Male Gender	30 (43.5%)	31 (83.8%)
Pulse rate [bmp]	77.6 ±9.3	72.4 ±9.1
Systolic blood pressure [mmHg]	124.7 ±16.7	130.4 ±14.4
Diastolic blood pressure [mmHg]	71.5 ±9.8	68.6 ±9.6
LVEF [%]	49.3 ±9.3	49.8 ±11.1
PV Regurgitation Grade		
Small	1 (1.4%)	0 (0.0%)
Moderate	1 (1.4%)	3 (8.1%)
Severe	67 (97.1%)	34 (91.9%)
NYHA class		
I	1 (1.5%)	1 (2.8%)
II	8 (11.8%)	12 (33.3%)
III	42 (61.8%)	19 (52.8%)
IV	17 (25.0%)	4 (11.1%)
Transfusion requirement	25 (36.8%)	3 (8.3%)
Indication		
Heart Failure	41 (49.3%)	
Hemolytic anemia	4 (4.8%)	
Heart Failure + Hemolytic anemia	36 (43%)	
Laboratory values		
LDH [U/l] [y]	607.0 ±627.8; (N=47)	
Erythrocytes [Mio/µl] [y]	4.1 ±0.7; (N=73)	
Thrombocytes [Thsd/µl] [y]	196.5 ±62.5; (N=75)	
Leucocytes [/µl] [y]	6698.1 ±1929.5; (N=73)	
Hemoglobin [mmol/l] [y]	7.6 ±1.4; (N=75)	
NTproBNP [pg/ml] [y]	1611.2 ±2680.2; (N=35)	

Values are N (%) or mean ±SD.

*The numbers may not add up to the column totals nor do the percentages add up to 100% because of missing data. Except for laboratory values, in this table continuous data are given with at least 83.3% evaluable data points.

HGB indicates Hemoglobin; LDH, Lactate dehydrogenase; LVEF, Left Ventricular Ejection Fraction; NYHA, New York Heart Association.

[y] Baseline laboratory values are presented unstratified for leak type. N is given per value.

Table 2

Table 2 Procedural Details		
	Mitral, N=69*	**Aortic, N=37***
General Anesthesia	40 (62.5%)	7 (20.6%)
Visualization		
TEE	22 (33.8%)	24 (66.7%)
TTE	1 (1.5%)	0 (0.0%)
TEE+TTE	0 (0.0%)	1 (2.8%)
TEE+3D	41 (63.1%)	10 (27.8%)
TEE+TTE+3D	1 (1.5%)	1 (2.8%)
Approach		
Transseptal	18 (30.0%)	0 (0.0%)
Transaortic	2 (3.3%)	35 (100%)
Transapical	40 (66.7%)	0 (0.0%)
Number of leaks		
1	44 (63.8%)	29 (78.4%)
2	20 (29.0%)	8 (21.6%)
3	5 (7.2%)	0 (0.0%)
PLDs implanted		
1	45 (66.2%)	34 (91.9%)
2	16 (23.5%)	3 (8.1%)
3	5 (7.4%)	0 (0.0%)
Patients with No. of …. No. of …		
Devices = Leaks	54 (79.4%)	28 (75.6%)
Devices < Leaks	7 (10.3%)	7 (18.9%)
Devices > Leaks	7 (10.3%)	2 (5.4%)
PLD type used[Y]		
Square Waist	10 (12.3%)	2 (5.3%)
Square Twist	9 (11.1%)	1 (2.6%)
Rectangular Waist	49 (60.5%)	29 (76.3%)
Rectangular Twist	13 (16.0%)	6 (15.8%)
Procedural Time by approach [min]		
Transseptal	62.5 (48, 125)	n.a.
Transaortic	90.0 (70, 110)	90 (70, 110)
Transapical	122.5 (110, 135)	n.a.
Fluoroscopy Time by approach [min]		
Transseptal	25.0 (19, 38)	n.a.
Transaortic	14.0 (14, 14)	15 (11, 24)
Transapical	20.5 (15, 34)	n.a.
Procedural Time by no. of leaks [min]		
1	70.0 (45, 120)	90 (70, 115)
2	110.0 (90, 175)	95 (75, 103)
3	180.0 (150, 200)	n.a.
Fluoroscopy Time by no. of leaks [min]		
1	20 (14, 30)	17.5 (12, 27)
2	25 (19, 35)	11.0 (9, 28)
3	30 (20, 52)	n.a.
Success rates		
Device success (at D0)[P,Z]	88.9% [95%CI: 80.0%, 94.3%]	
Procedural success (at D0)[P,X]	86.6% [95%CI: 77.4%, 92.5%]	
Clinical success (at 6 month)[J]	86.5% [95%CI: 78.5%, 91.9%]	
Values are N (%), median (Q1, Q3) or mean ±SD. Success rates are % [95%-Confidence Intervals].		

*The numbers may not add up to the column totals nor do the percentages add up to 100% because of missing data. In this table continuous data are given with at least 72.2% evaluable data points. D0 indicates Day of implantation; No, Number; PLD, Paravalvular Leak Device; TEE, Transesophageal Echocardiography; TTE, Transthoracic Echocardiography.

[Y] Unit of analysis are individual occluder. Multiple occluder may refer to a single patient.

[P] Unit of analysis are patients with safety data available (SAF population; N=136).

[Z] Patients with stable implantation and paravalvular regurgitation reduced to ≤ mild (small).

[X] Device Success and no procedure- or device-related major complication.

[J] Patients with NYHA class I/II or patients no longer dependent on blood transfusions at 6 month, who did not experience procedure- o device-related major complication.

Table 3

Table 3 Leak Characteristics		
	Mitral, n=131[y,*]	**Aortic, n=53[y,*]**
Maximum leak diameter		
< 5 [mm]	38 (33.0%)	10 (26.3%)
5-10 [mm]	55 (47.8%)	22 (57.9%)
>10-<15 [mm]	16 (13.9%)	3 (7.9%)
>=15 [mm]	6 (5.2%)	3 (7.9%)
Shape of leaks		
Slit	2 (2.0%)	0 (0.0%)
Oval	36 (36.7%)	6 (28.6%)
Round	6 (6.1%)	1 (4.8%)
Crescent	54 (55.1%)	14 (66.7%)
Location of leak		
Anterior	17 (13.0%)	n.a.
Lateral	29 (22.1%)	n.a.
Medial	38 (29.0%)	n.a.
Posterior	47 (35.9%)	n.a.
LCS	n.a.	11 (21.2%)
NCS	n.a.	29 (55.8%)
RCS	n.a.	12 (23.1%)
Number of devices implanted per leak		
1	104 (88.9%)	36 (94.7%)
2	12 (10.3%)	2 (5.3%)
3	1 (0.9%)	0 (0.0%)

Values are N (%) or mean ±SD.

* The numbers may not add up to the column totals nor do the percentages add up to 100% because of missing data. LCS indicates Left Coronary Sinus; NCS, Non-coronary Sinus, RCS, Right Coronary Sinus.

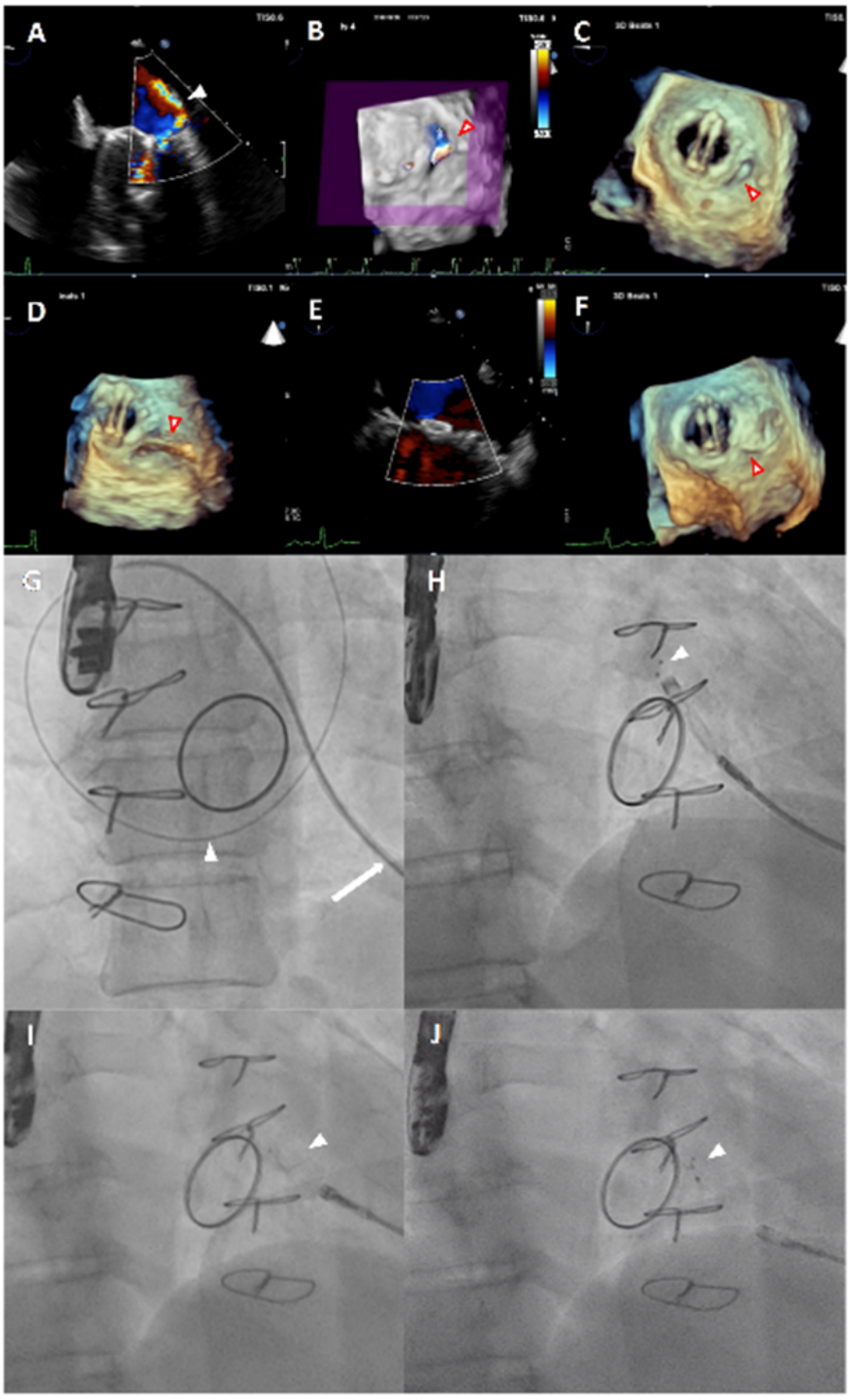
[y] Unit of analysis are individual leaks. Multiple leaks may refer to a single patient.

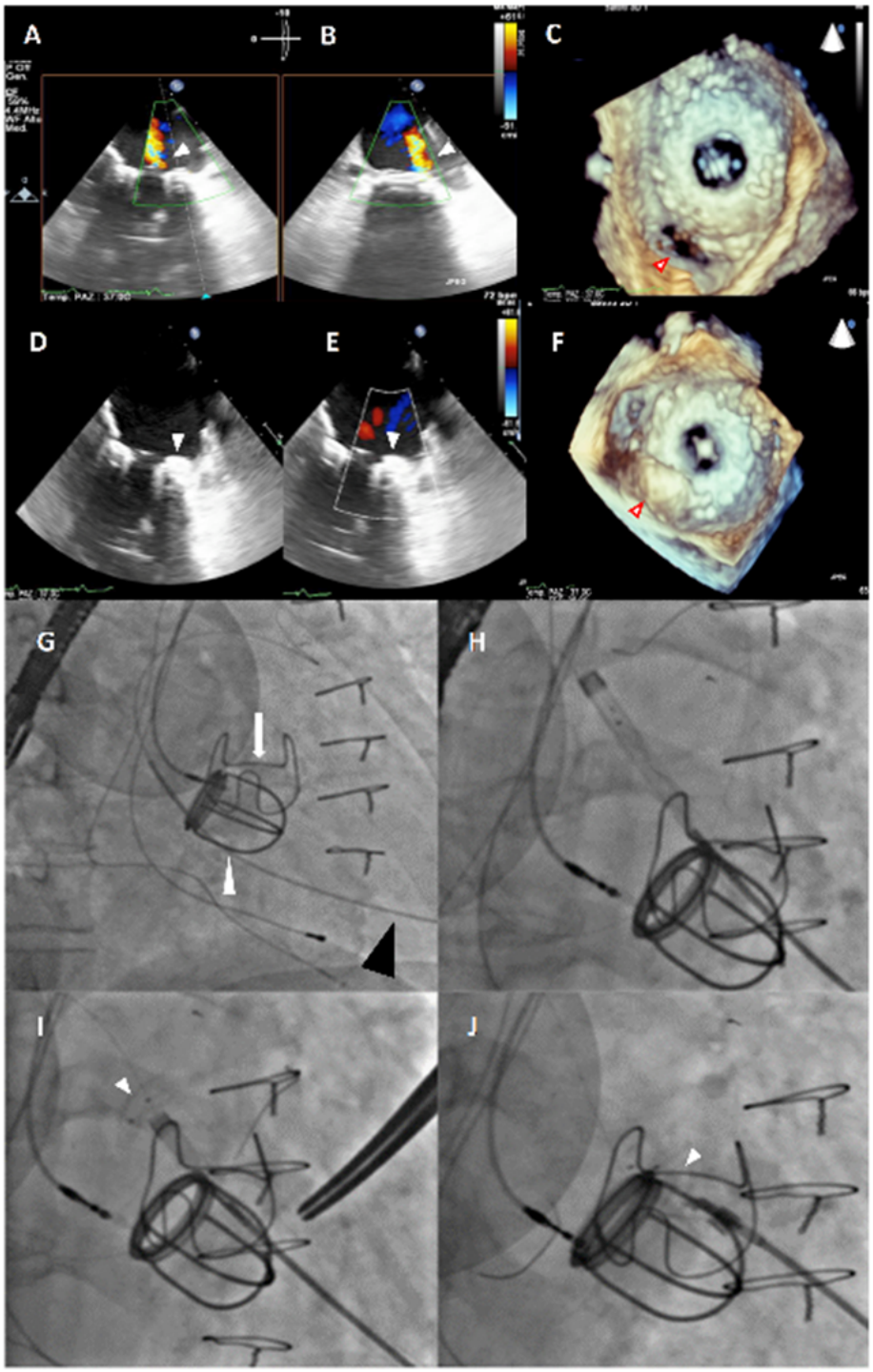
Table 4

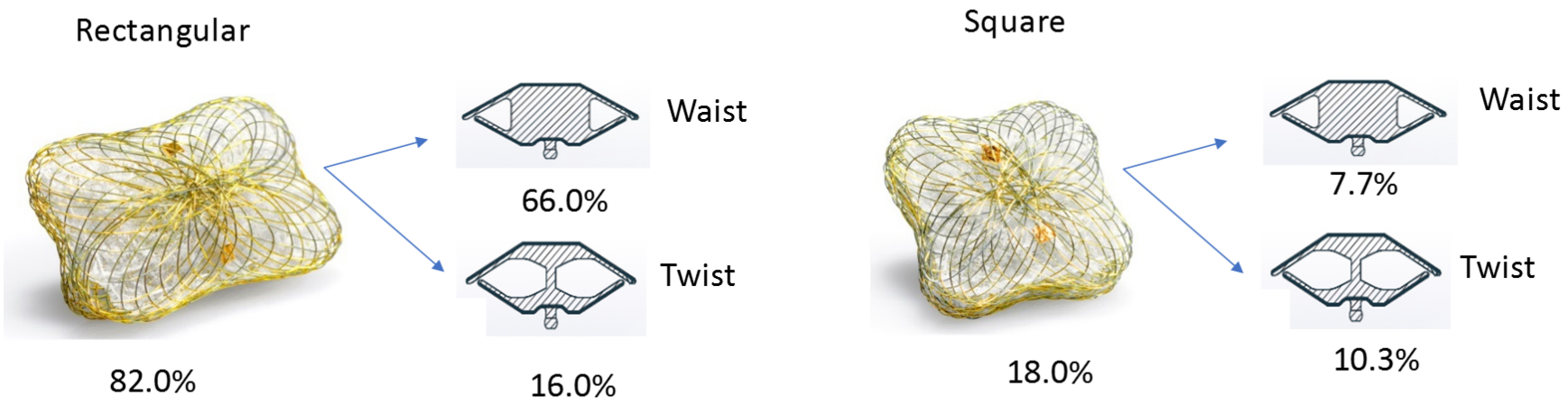
Table 4 Complications

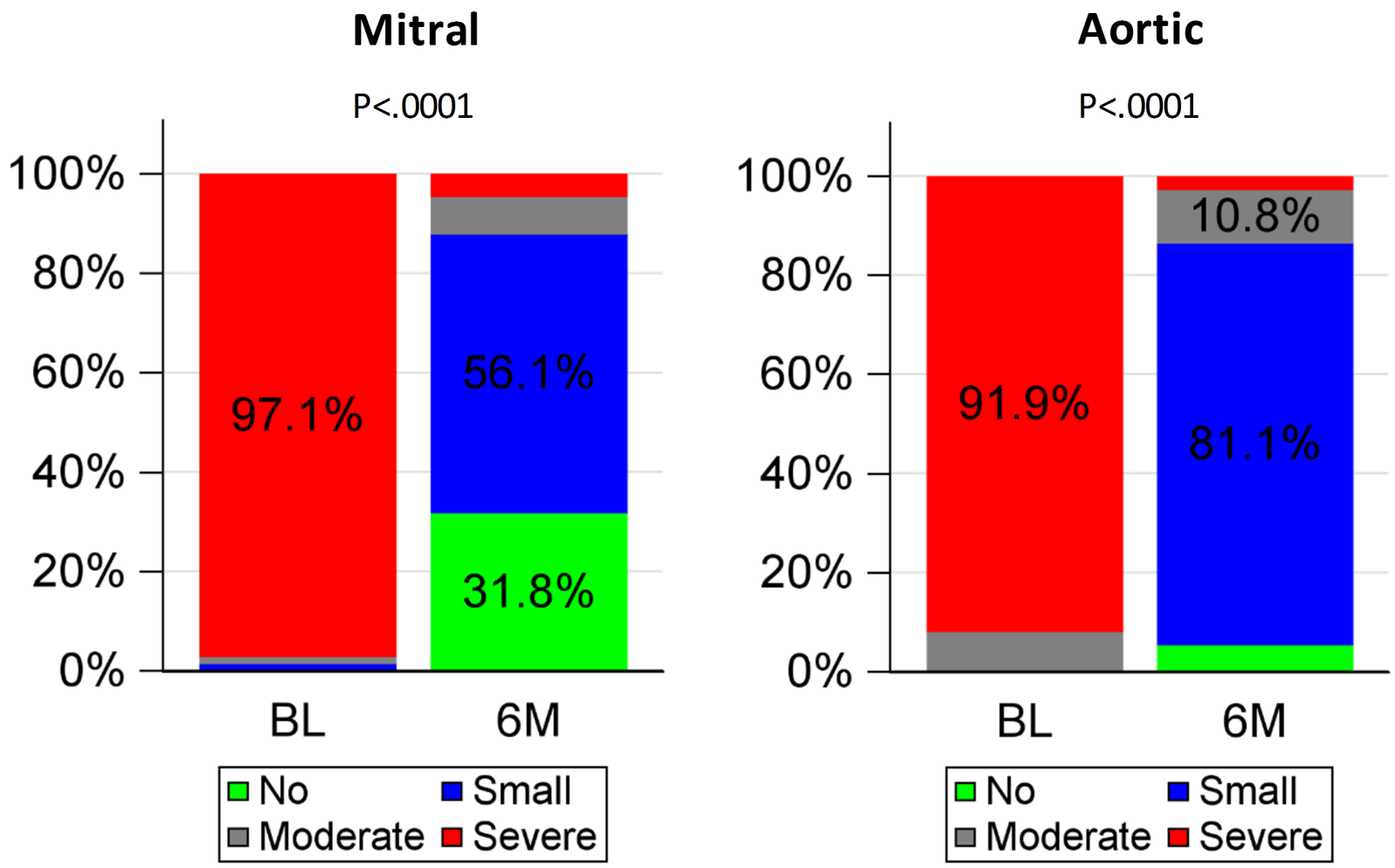
	Mitral, N=92*	Aortic, N=44 *
Device embolization (surgically resolved)	1 (1.1%)	0 (0%)
Device embolization (percutaneously resolved)	1 (1.1%)	0 (0%)
Late Device Embolization	1 (1.1%)	0 (0%)
Interference with prosthetic valve leaflets (surgically resolved)	0 (0%)	0 (0%)
Interference with prosthetic valve leaflets (percutaneously resolved)	1 (1.1%)	0 (0%)
New onset hemolytic anemia requiring transfusions (transient)	1 (1.1%)	0 (0%)
Complication at femoral puncture site	1 (1.1%)	0 (0%)
Need for repeat procedure	1 (1.1%)	0 (0%)
Arrythmia requiring treatment	5 (5.4%)	1 (2.3%)
Bleeding complication	3 (3.3%)	1 (2.3%)
Recurrent hemolytic anemia	3 (3.3%)	0 (0%)
Valve surgeries	2 (2.2%)	1 (2.3%)
Cardiac Resynchronization therapy	1 (1.1%)	0 (0%)
Death following surgical valve replacement	1 (1.1%)	0 (0%)
Sudden unexplained Death	1 (1.1%)	0 (0%)
Stroke Death (1x Hemorragic, 1x Ischemic)	2 (2.2%)	0 (0%)
Death (disease-related)	4 (4.3%)	2 (4.5%)
All-cause mortality	*8 (8.7%)*	*2 (4.5%)*

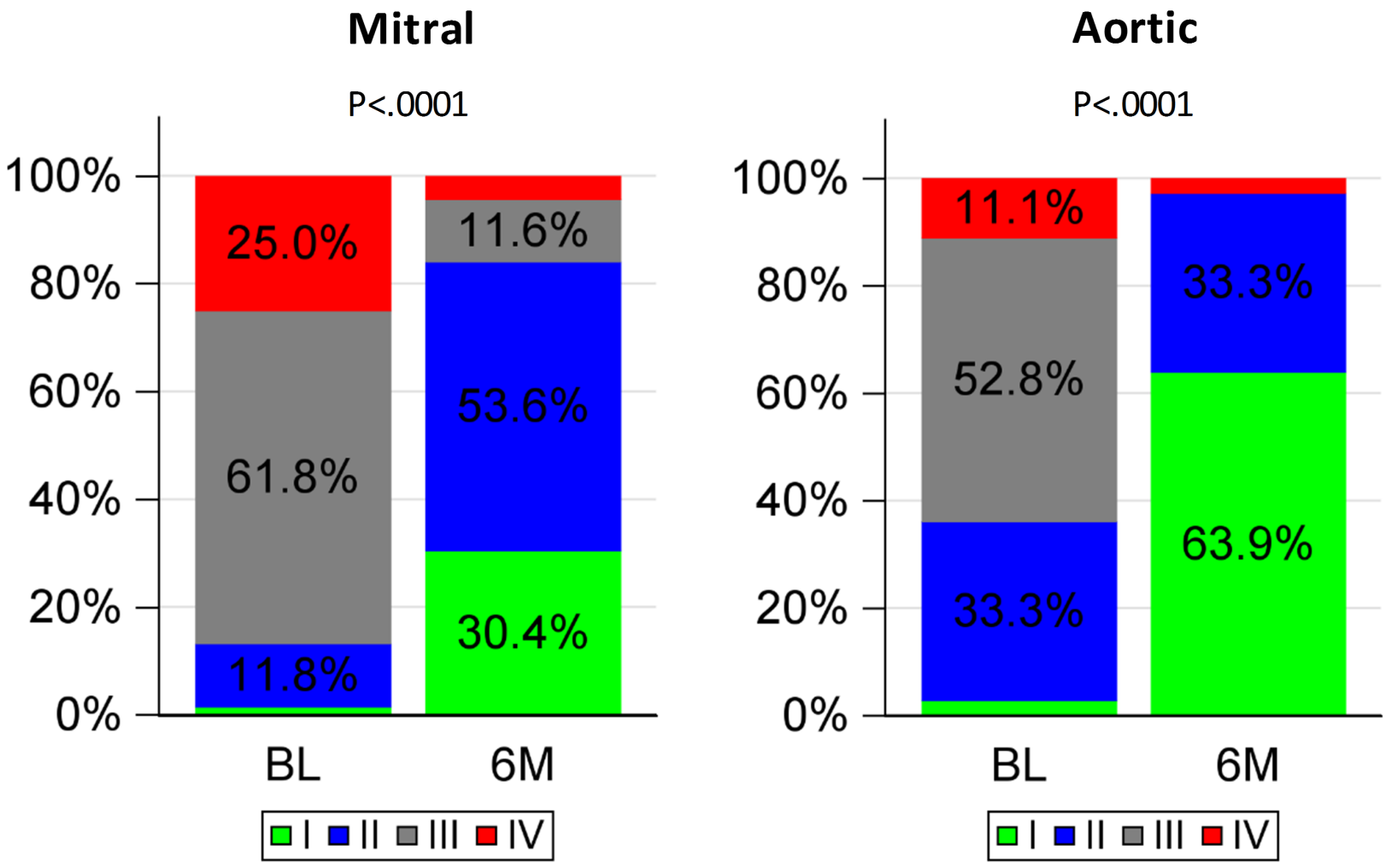
Values are N (%).
* Unit of analysis are patients with safety data available (SAF population).











Supplementary data

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Supplementary Legends

Supplementary Figure 1. Relative change to Baseline in laboratory values and blood cell counts at 6 months following implantation. Abbreviations : ERY, Erythrocytes; HGB, Hemoglobin; LEU, Leucocytes; LDH, Lactate dehydrogenase; NTproBNP, N-terminal prohormone of brain natriuretic peptide; THR, Thrombocytes. N is given per value. Wilcoxon Signed-Rank Test has been applied and * indicates p-values <0.05

Moving image 1. 2D TEE color Doppler showing the significant regurgitant jet through the paravalvular mitral leak.

Moving image 2. 3D TEE color Doppler showing the antero-lateral (9-11 o'clock) mitral paravalvular leak

Moving Image 3. Mitral leak measurements **:** D1 major diameter, D2 lenght of the leak, D3 diameter at

the LA entry, D4 diameter at the LV exit.

Moving image 4. Real-time 3D TEE showing the crescent shape of the mitral leak at 9 - 11 o'clock.

Moving image 5. Fluoroscopic (A) and real-time 3D TEE showing the catheter crossing the leak (arrows) from transapical approach.

Moving image 6. Procedural fluoroscopic steps of the PVL closure procedure using 12x5 mm paravalvular leak device (PLD) rectangular waist: A) distal disc opening; B) waist and proximal disc opening; C) stability test ("pull & push"); D) 12x5 mm PLD in situ.

Moving image 7. 3D TEE color Doppler in two different views showing final position of the occluder device.