Acute and Long-term Outcomes of quadripolar IS-4 versus bipolar IS-1 Left Ventricular Leads in Cardiac Resynchronization Therapy: A Retrospective Registry Study

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Abstract

Background: The implantation procedure of left ventricular (LV) leads and the management of cardiac resynchronization therapy (CRT) patients can be challenging. The IS-4 standard for CRT offers additional pacing vectors compared to bipolar leads (IS-1). IS-4 leads improve procedural outcome and may also result in lower adverse events during follow-up (FU) and improve clinical outcome in CRT patients. Further long-term FU data comparing the two lead designs are necessary.

Methods: In this retrospective, single-center study we included adult patients implanted with a CRT-Defibrillator (CRT-D) or CRT-Pacemaker (CRT-P) with a quadripolar (IS-4 group) or bipolar (IS-1 group) LV lead and with available ≥3 years clinical FU. The combined primary endpoint was a combination of predefined, lead-related adverse events. Secondary endpoints were all single components of the primary endpoint.

Results: Overall, 133 patients (IS-4 n=66; IS-1 n=67) with a mean FU of 4.03±1.93 years were included. Lead-related adverse events were less frequent in patients with an IS-4 lead than with an IS-1 lead (n=8, 12.1% vs. n=23, 34.3%; p=0.002). The secondary outcomes showed a lower rate of LV lead deactivation/explantation and LV lead dislodgement/dysfunction (4.5% vs 22.4%; p=0.003; 4.5% vs. 17.9%; p=0.015, respectively) in the IS-4 patient group. Less patients suffered from unresolved phrenic nerve stimulation with an IS-4 lead (3.0% vs. 13.4%; p=0.029). LV lead-related re-interventions were fewer in case of an IS-4 lead (6.1% vs. 17.9%; p=0.036).

Conclusion: In this retrospective analysis, the IS-4 LV lead is associated with lower lead-related complication rates than the IS-1 lead at long-term FU.

Abbreviations

AVB atrioventricular block

BMI body mass index

CRT cardiac resynchronization therapy

CRT-D cardiac resynchronization therapy defibrillator

CRT-P cardiac resynchronization therapy pacemaker

CS coronary sinus

DCM dilated cardiomyopathy

FU follow-up

HCM hypertrophic cardiomyopathy

HFrEF heart failure with reduced ejection fraction

ICM ischemic cardiomyopathy

IQR interquartile range

LBBB left bundle branch block

LV left ventricle

LVEDD left ventricular end-diastolic diameter

LVEF left ventricular ejection fraction

LVESD left ventricular end-systolic diameter

NICM non-ischemic cardiomyopathy

NYHA New York Heart Association

PNS phrenic nerve stimulation

RA right atrium

RBBB right bundle branch block

RV right ventricle

Introduction

Chronic heart failure patients with left ventricular ejection fraction (LVEF) ≤35% and wide QRS complex, who remain in New York Heart Association (NYHA) functional class II, III or ambulatory IV despite adequate medical therapy, can benefit from cardiac resynchronization therapy (CRT).[1] Clinical improvement is more likely in patients with non-ischemic

cardiomyopathy (NICM).[2] Technically, CRT involves implantation of a left ventricular (LV) pacing lead via the cardiac venous system or thoracotomy.[3] Quadripolar LV leads were introduced in 2010 (featuring an IS-4 connector).[4] The new lead design offers two additional poles for sensing and stimulation, which provides 16-20 selectable pacing vectors, depending on the device model (Figure 1). The bipolar IS-1 lead connector on the other hand possesses only two pacing poles. Several studies that compared bipolar with quadripolar leads for CRT showed improved acute LV lead implantation success rate, shorter implantation time and lower fluoroscopy dose with quadripolar leads.[5-6] Furthermore, CRT with an IS-4 lead tends to provide better clinical outcome and performance parameters.[7-10] However data on long-term clinical outcome and adverse event rates are necessary.

In this retrospective, single-center study, we aimed to compare the adverse event rates between patients implanted with a CRT using IS-4 vs. IS-1 LV leads.

Materials & Methods

Patient Population

This retrospective, single-center study included patients who received endovascular implantation of an IS-1 or IS-4 LV lead for CRT between January 2011 and December 2014. A follow-up (FU) period of at least three years and availability of consistent FU clinical data were inclusion criteria. Patients referred to external cardiologists were only included when FU data were accessible. Patients with documented oral or written refusal to participate were excluded, as were those with congenital heart disease, age < 18 years or epicardial LV lead implantation using a surgical approach. The study protocol was approved by the Ethics Committee of Bern, Switzerland. Patients were classified into two groups: the IS-1 group included patients implanted with a bipolar IS-1 LV lead and the IS-4 group included patients who received a quadripolar IS-4 LV lead.

Device and Lead Characteristics

Patients with implantations of CRT defibrillator (CRT-D) or CRT pacemaker (CRT-P) and transvenous pacing leads at our institution (Inselspital, University Hospital Bern, Switzerland) were included irrespective of the device manufacturer. The choice of the implanted LV lead model (IS-1 or IS-4) was at the discretion of the operator. The implantation procedure and the clinical/device follow-up were performed by experienced device specialists. FU visits were performed at six-month intervals in CRT-D patients and at 12-month intervals in CRT-P patients. In case of adverse events or hospitalizations, clinical follow-ups with device interrogations were performed more frequently and optimized to the patient's clinical needs. Hospital and FU visit records were screened for adverse events. The LV pacing lead was

placed in the most optimal posterolateral branch of the cardiac venous system according to the implanter's decision. The optimal LV lead location was defined as an endovascular position in a posterior, posterolateral or lateral cardiac venous branch offering thresholds <2.75V/0.4ms and the availability of at least one pacing vector without phrenic nerve stimulation (PNS) or a PNS threshold higher than the cardiac stimulation threshold. Inability to implant an LV lead with acceptable thresholds was considered as an implantation failure.

Primary endpoint

The primary endpoint of this study combines lead-related adverse events including (i) occurrence of a new persistent high pacing threshold (>2.75 volts (V) /0.4 milliseconds (ms)), (ii) LV lead dysfunction or dislodgement leading to device re-programming, PNS, or re-intervention, (iii) unresolved PNS, (iv) necessity of re-interventions of the LV lead, and (v) LV lead deactivation or explantation.

Secondary endpoints

All components of the combined primary endpoint were analyzed as a separate secondary endpoint. In addition, secondary endpoints included procedure duration, fluoroscopy duration, duration of hospitalization at implantation, and necessity of LV lead model changes during initial CRT implantation. The procedure time was defined as the duration from the beginning of skin incision to the end of suture. The duration of hospitalization was assessed by counting the number of nights staying in hospital after the implantation procedure. The necessity of active lead fixation and successful LV lead implantation in posterolateral position were analyzed. Intraoperative complications such as cardiac tamponade, dissection of the coronary sinus (CS), and PNS requiring a LV lead position change were also analyzed as secondary endpoints. Postoperative complications included severe and clinically relevant hematoma and postoperative infections within 120 days after implantation.

Clinical Outcome

Echocardiographic and electrical parameters such as LVEF, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and QRS duration were assessed. Device follow-up with echocardiographic or electrocardiographic check-ups were not performed regularly. Therefore, the patient group-sizes vary between different endpoints because of missing data. The exact group-sizes, FU durations and baseline values echographic and electrical parameters can be found in Table 3. Pacing threshold values and NYHA class were assessed in biannual and annual device check-ups for CRT-D and CRT-P devices, respectively. Final pacing configurations were documented at the end of the

implantation procedure, before hospital discharge, and at every FU visit. To be included in the study, outcome data had to be available for least three years after the CRT implantation.

Statistical Analysis

Statistical analyses were performed using SPSS™ Statistics for Windows (IBM™ Corp., 2017, Version 25.0, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median ± interquartile range (IQR) as appropriate. Categorical variables were described by frequency and percentage. The normality of the distribution of continuous variables was examined with the Shapiro-Wilk test and QQ plots. Analysis of statistical difference between the two patient groups was performed using appropriate tests for null hypothesis (Mann-Whitney-U test, Chi^2 test, Fisher's exact test, or Wilcoxon's signed rank test). All tests were performed at a two-sided 5% alpha level. Parametric two-sided 95% confidence intervals are provided. Kaplan-Meier analyses with log-rank test were performed for the primary endpoint and for selected secondary outcome variables (all-cause mortality and explantation or inactivation of the LV lead).

Results

Patient Population

Within a period of 48 months, 188 patients received an endovascular implantation attempt of an IS-1 or IS-4 LV lead for CRT. One patient with congenital heart disease and age <18 years was excluded from this study. Two patients were not included because of missing data. 20 patients (10.8%) had a failed implantation attempt. Reasons were (i) failed CS intubation (n=6), (ii) no successful placing/wedging of the LV lead in a cardiac vein in target zone (n=8), (iii) unacceptable high pacing thresholds (n=5), or hemodynamic instability leading to the termination of the procedure (n=1). Overall, 165 patients (89.2%) underwent a successful implantation. Eight patients with an IS-4 LV lead and 24 patients with an IS-1 LV lead were lost to FU within three years after the implantation procedure and were therefore excluded from data analysis. The final analysis dataset included 66 patients in the IS-4 group and 67 patients in the IS-1 group (Figure 2). The supplemental Figure 6 in the appendix shows the distribution of the implanted LV lead models over time. The IS-1 LV lead was predominantly implanted in the beginning of patient inclusion period (2011/2012). Later (2013/2014), the IS-4 LV lead became the standard-of-care model. Baseline characteristics did not differ significantly between the IS-4 and IS-1 patient groups (Table 1).

Primary endpoint

Mean FU duration of both groups was not significantly different (IS-4 4.02±1.50 years vs. IS-1 4.05±2.28 years; p=0.308). Defined as primary endpoint, lead-related adverse events occurred in patients receiving quadripolar LV leads less frequently than in those with bipolar LV leads (IS-4 n=8, 12.1% vs. IS-1 n=23, 34.3%; p=0.002). The explantation or inactivation of the LV lead was significantly less common in the IS-4 group (IS-4 n=3, 4.5% vs. IS-1 n=15, 22.4%; p=0.003). We found no difference in mortality between the two patient groups (IS-4 n=15, 22.7% vs. IS-1 n=17, 25.4%; p=0.721, Kaplan-Meier analyses are shown in Figure 3, Figure 4, and Figure 5).

Secondary endpoints

No significant differences were observed between the IS-4 and the IS-1 groups regarding median procedural time for CRT device and lead implantation (IS-4 162.5±58 min vs. IS-1 174±90 min; p=0.891), or total fluoroscopy duration (IS-4 27.5±20.5 min vs. IS-1 30±30 min; p=0.511). In the IS-1 group, more patients required an intraoperative LV lead change (manufacturer or model) before achieving an acceptable LV lead position (IS-4 n=3, 4.5% vs. IS-1 n=13, 19.4%; p=0.008). Intraoperative occurrences of PNS necessitated a change of lead model or manufacturer in three cases of IS-4 group and in six cases of IS-1 group (IS-4 n=3, 4.5% vs. IS-1 n=6, 9.0%; p=0.493). All patients in both groups reached an acceptable final LV lead position. No differences were observed in intraoperative complications, such as cardiac tamponade and CS dissection (Table 2). During three IS-1 implantation procedures, active LV lead fixation was used (4.5%). The IS-4 LV lead models did not provide the possibility of active lead fixation. The median duration of post-interventional stay did not vary between the two patient groups (IS-4 1.00±1.00 nights vs. IS-1 1.00±0.00 nights; p=0.064). The chosen manufacturers for the LV lead and devices are listed in table 4 in the appendix.

PNS during FU was more often seen in the IS-1 group and non-invasive elimination of PNS was attempted by reprogramming pacing vectors or an adjustment of pacing threshold. Elimination of PNS was possible in 75.0% (n=6) of IS-4 and 52.6% (n=10) of IS-1 patients with PNS (p=0.405). Unresolvable PNS was more common among patients with a bipolar IS-1 LV lead (IS-4 n=8, 3.0% vs. IS-1 n=19, 13.4%; p=0.029). LV lead dislodgement occurred more often with bipolar leads than with quadripolar leads (IS-4 n=3, 4.5% vs. IS-1 n=10, 14.9%; p=0.044). However, the two groups did not differ in the rate of LV lead dysfunction (IS-4 n=0, 0% vs. IS-1 n=2, 3.0%; p=0.496). Re-interventions of the LV lead was more often necessary in the IS-1 group (IS-4 n=4, 6.1% vs. IS-1 n=12, 17.9%; p=0.036). Results are shown in Table 2.

Clinical Outcome

The NYHA class was assessed before CRT implantation (IS-4 2.79±0.52 vs. IS-1 2.73±0.50; p=0.487) and at the end of FU. The mean reduction of NYHA class did not vary between IS-4 and IS-1 group (IS-4 -0.75±0.57 vs. IS-1 -0.76±0.79; p=0.944).

Electrical Parameters

Changes in the QRS duration after CRT-implantation were evaluated. The initial reduction of the QRS duration post-implantation was similar between the IS-4 and IS-1 groups (IS-4 -31.61±29.38 ms vs. IS-1 -32.78±25.21 ms; p=0.484). This did not change at the last FU. The mean QRS duration with resynchronization was similar between the IS-4 and IS-1 patient groups (IS-4 152.83±25.63 ms vs. IS-1 155.90±30.20 ms; p=0.765).

Mean pacing thresholds at standard pulse duration (0.5 ms or 0.4 ms), were assessed at the end of the implantation procedure. There was no significant difference between the IS-4 and the IS-1 groups (IS-4 1.29±1.01 V vs. IS-1 1.36±0.77 V; p=0.319). At the last FU mean thresholds were not different between IS-4 and IS-1 patients (IS-4 1.10±0.31V vs. IS-1 1.06±0.32V; p=0.509).

Echocardiographic Parameters

At the last FU, both groups showed significant improvement of the LVEF (IS-4 pre-implantation 26.94 ± 6.61%, at end of FU 35.56 ± 12.41%; p=0.001; IS-1 pre-implantation 25.03 ± 6.62%, at the end of FU 35.27 ± 14.93%; p<0.001) compared to baseline. However, there was no significant difference in the increase of LVEF between the study groups. Further results of echocardiographic variables are shown in Table 3.

Discussion

Main findings

In this retrospective study of 133 patients receiving an LV lead for CRT-D/P, quadripolar LV leads (IS-4) were superior to bipolar leads (IS-1) with regard to incidence of acute and long-term lead-related adverse events.

Primary endpoint

Quadripolar leads were associated with lower rates of LV lead inactivation/explantation, LV lead dislodgement, re-interventions affecting the LV lead, and unresolved PNS than bipolar leads. These findings are comparable to those shown in the MORE-CRT randomized

controlled trial, which assessed the rates of lead-related adverse events with the use of both lead systems for a FU period of six months (IS-4 83.0% vs. IS-1 74.4%; p<0.001), as well as other studies.[10-13] In a published registry study, no differences were described in lead-related re-interventions and major complications among bipolar and quadripolar LV leads (34.19 vs. 34.15 events per 100 patient-years; p=0.898).[6] Our data showed that, during long-term FU, patients with an IS-1 lead suffer more from lead associated adverse events. The management and avoidance of LV lead-related adverse events was more effective in case of a quadripolar LV lead. This may be explained by more pacing-vector programming options. The flexibility in IS-4 lead programming may cause lower adverse events. Although the need for re-interventions was not significantly lower with IS-4 leads (p=0.078), even if a trend can be discussed.

Lead Implantation

The endovascular implantation of an LV lead can be technically challenging, as the implantation success depends on the patient's anatomy. As demonstrated in other studies, the implantation success rates were not significantly higher with the IS-4 lead.[11-12] But the IS-4 standard provides additional pacing poles and offers more flexibility in choosing the final pacing vector. Therefore, the necessity of changing a LV lead during an implantation attempt was less frequent when an IS-4 lead was implanted. By contrast, our data could not show any significant difference in median implantation or fluoroscopy duration between patient groups. Intraoperative events such as CS dissection or cardiac tamponade did not occur more frequently in any of the patient groups. Analysis of a large patient cohort (n=124'018) in a registry study showed similar rates of adverse events during the CRT implantation procedure using the quadripolar and bipolar LV leads (IS-4 1.34% vs. IS-1 1.39%; p=0.501).[6]

Phrenic Nerve Stimulation

We showed a lower rate of PNS during FU in IS-4 patients, which facilitates the management of these patients. However, since the pacing vector of IS-4 leads was already optimized during implant, the elimination of PNS by reprogramming was not possible more frequently although more pacing vector options were available compared to IS-1 leads (IS-4 n=6, 75.0% vs. IS-1 n=10, 52.6%; p=0.405). One patient in the IS-4 group was released from PNS by changing to a non-traditional pacing vector, which is only available with a quadripolar lead. The same situation with a bipolar lead would have led to a lead failure. As described in other studies, additional pacing vectors can be useful for the elimination of PNS.[11-12, 14]

Pacing Vectors and Thresholds

We found no difference in mean pacing threshold among patient groups at the end of FU. However, patients with an adaption of pulse duration during FU were excluded from this analysis (IS-4 n=22; IS-1 n=27). Pulse duration change was often performed to avoid high pacing threshold (HPT). This selection bias resulted in lower mean threshold values and were possible in both patient groups. In a prospective, randomized study with a FU duration of one year, similar LV lead pacing capture thresholds at 0.4ms pulse duration for IS-4 and IS-1 LV leads were observed (IS-4 1.03±0.86V vs. IS-1 1.23±0.75V; p=0.46).[15] Analysis of a nonrandomized patient cohort with a six month FU showed lower pacing thresholds for LV IS-4 leads (IS-4 0.9±0.6V vs. IS-1 1.1±0.6V; p=0.04), but information about the pulse duration of measured pacing thresholds were not provided.[11]

72.7% of IS-4 leads in our cohort were programmed to traditional pacing vectors. These patients were paced as if they would have been implanted with an IS-1 LV lead. Other studies showed a similar distribution of pacing vectors.[14, 16] This potential bias is relevant and must be considered when IS-1 and IS-4 leads are compared.

Clinical Outcome

Significant improvements in echocardiographic parameters and/or NYHA class with IS-4 leads were detected in studies with FU duration of 3-6 months.[9, 17-18] In our study with long-term FU (>3 years), no statistical difference was found. No difference in LVEF between the two LV lead models after one year of FU was reported by Keilegavlen and colleagues (IS-4 36.7±7.1% vs. 35.6±9.7%; p=0.64).[19]

Mortality

Recent studies reported contradictory findings regarding differences in mortality associated with IS-4 vs. IS-1 leads. However, prospective randomized clinical trials assessing the mortality rates with IS-4 and IS-1 systems with long-term follow-up are lacking and may suffer from confounding effects due to concomitant heart failure therapy regimen changes over time. One randomized controlled trial with a 6-month FU time[10] and other studies with up to 12 months of FU time showed no significant difference in all-cause mortality rate.[9, 11, 20-24] Interestingly, other retrospective studies with long-term FU (>3 years) or large patient groups showed lower mortality for patients implanted with IS-4 LV leads.[12-13, 25] By contrast, the all-cause mortality rate of the IS-4 and the IS-1 patient group did not show significant difference at a minimum of 3 years FU in our cohort. A potential explanation for these observations can be a modest difference in clinical response to CRT between patient groups that may be detectable in larger sample sizes.

Limitations

This study has several limitations, the most important being its retrospective single-center design. Additionally, patients were excluded from the study cohort if they were lost from FU within three years after implantation. This was more common in the IS-1 patient group (IS-1 n=24; IS-4 n=8) and must be mentioned as a possible bias. In case of a favorable outcome, device follow-up visits were performed by external cardiologists. Some of these patients were excluded from our study because of loss of FU within the first three years after implantation. In case of adverse events, they would have been readmitted to the university hospital. Accordingly, complication rates in both patient groups could be different from reported ones. Our analysis was performed on routinely collected clinical data, resulting in an incomplete dataset for the echocardiographic and electrical parameters. IS-1 LV leads were implanted predominantly in 2011/12, whereas the implantation of the IS-4 model became more frequent in 2013/14. (See Figure 6 in appendix) As a result, for some secondary endpoints the total FU duration was on average longer in the IS-1 group compared with the IS-4 group.

Conclusion

In this retrospective study with a minimal FU duration of three years, we compared the IS-4 LV lead to its preceding model, the IS-1 lead. No significant difference in all-cause mortality rate was detected. However, patients with IS-4 leads had a lower rate of lead-related adverse events than those with IS-1 LV lead.

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Table 1. Baseline characteristics of patients included in the study.

	TOTAL (N=133)	IS-4 (N=66)	IS-1 (N=67)	P-VALUE
AGE [YEARS]	65.27 ± 9.99	65.15 ± 8.92	65.39 ± 11.01	0.692
FEMALES (%)	33 (24.8)	15 (22.7)	18 (26.9)	0.581
BMI* [KG/M^2]	27.32 ± 4.82	27.01 ± 4.24	27.64 ± 5.37	0.519
ECHOCARDIOGRAPHIC / ELECTRICAL PARAMETERS				
LVEF [%]	25.69 ± 6.98	26.06 ± 6.62	25.33 ± 7.35	0.356
LVEDD§ [MM]	68.01 ± 9.54	67.31 ± 8.01	68.76 ± 10.99	0.533
LVESD# [MM]	58.16 ± 11.16	57.80 ± 10.98	58.53 ± 11.46	0.939
QRS DURATION [MS]	187.44 ± 29.55	186.41 ± 31.67	188.46 ± 27.51	0.486
COMORBIDITIES				
HYPERTENSION (%)	90 (67.7)	43 (65.2)	47 (70.1)	0.538
DIABETES MELLITUS (%)	37 (27.8)	14 (21.2)	23 (34.3)	0.091
NYHA CLASS I (%)	2 (1.5)	1 (1.5)	1 (1.5)	>0.999
NYHA CLASS II (%)	33 (24.8)	16 (24.2)	17 (25.4)	0.880
NYHA CLASS III (%)	94(70.7)	46 (69.7)	48 (71.6)	0.805
NYHA CLASS IV (%)	4 (3.0)	3 (4.5)	1 (1.5)	0.619
HEART FAILURE (%)	132 (99.2)	66 (100.0)	66 (98.5)	>0.999
VALVULAR HEART DISEASE (%)	48 (36.1)	21 (31.8)	27 (40.3)	0.309
ISCHEMIC HEART DISEASE (%)	75 (56.4)	36 (54.5)	39 (58.2)	0.670
INDICATION FOR CRT				
INDICATION LBBB (%)	96 (72.2)	45 (68.2)	51 (76.1)	0.307

INDICATION RBBB (%)	1 (0.8)	1 (1.5)	0 (0)	0.496
INDICATION AVB (%)	27 (20.3)	16 (24.2)	11 (16.4)	0.262
INDICATION DCM (%)	5 (3.8)	3 (4.5)	2 (3.0)	0.680
INDICATION HCM (%)	1 (0.8)	0 (0)	1 (1.5)	>0.999
INDICATION ICM (%)	3 (2.3)	1 (1.5)	2 (3.0)	>0.999

Values are mean ± SD, median ± IQR, or n (%). *IS-4 (n=66) and IS-1 (n=65); §IS-4 (n=55) and IS-1 (n=51); #IS-4 (n=44) and IS-1 (n=43); AVB = Atrio-Ventricular Block; IS-1 = IS-1 Patient Group; BMI = Body Mass Index; DCM = Dilatative Cardiomyopathy; HCM = Hypertrophic Cardiomyopathy; ICM = Ischemic Cardiomyopathy; IR = Interquartile Range; kg = Kilogram; LBBB = Left Bundle Branch Block; LVEDD = Left Ventricular End-Diastolic Diameter; LVEF = Left Ventricular Ejection Fraction; LVESD = Left Ventricular End-Systolic Diameter; mm = millimeter; m^2 = square meter; NYHA = New York Heart Association; IS-4 = IS-4 Patient Group; RBBB = Right Bundle Branch Block. SD = Standard Deviation.

Table 2. List of periprocedural, postprocedural, and follow-up complications.

	TOTAL (N=133)	**IS-4 (N=66)**	**IS-1 (N=67)**	**P-VALUE**
PERIPROCEDURAL COMPLICATIONS				
CARDIAC TAMPONADE (%)	0 (0)	0 (0)	0 (0)	n.a.
CS DISSECTION (%)	5 (3.8)	1 (1.5)	4 (6.0)	0.365
LEAD CHANGE* (%)	16 (12.0)	3 (4.5)	13 (19.4)	**0.008**
PNS RESULTING IN LEAD CHANGE§ (%)	9 (6.8)	3 (4.5)	6 (9.0)	0.493
POSTPROCEDURAL COMPLICATIONS				
POSTPROCEDURAL HEMATOMA (%)	2 (1.5)	0 (0)	2 (3.0)	0.496
POSTPROCEDURAL INFECTIONS (%)	2 (1.5)	1 (1.5)	1 (1.5)	>0.999
PRIMARY ENDPOINT	31 (23.3)	8 (12.1)	23 (34.3)	**0.002**
PERSISTING HPT (%)	9 (6.8)	3 (4.5)	6 (9.0)	0.492
LV LEAD DISLODGEMENT (%)	13 (9.8)	3 (4.5)	10 (14.9)	**0.044**

LV LEAD DYSFUNCTION (%)	2 (1.5)	0 (0)	2 (3.0)	0.496
UNRESOLVED PNS (%)	11 (8.3)	2 (3.0)	9 (13.4)	**0.029**
RE-INTERVENTION AFFECTING THE LV LEAD (%)	16 (12.0)	4 (6.1)	12 (17.9)	**0.036**
EXPLANTATION OR INACTIVATION OF LV LEAD (%)	18 (13.5)	3 (4.5)	15 (22.4)	**0.003**
FURTHER ADVERSE EVENTS DURING FU				
FREEDOM FROM REINTERVENTION (%)	109 (82.0)	58 (87.9)	51 (76.1)	0.078
PNS	27 (20.3)	8 (12.1)	19 (28.4)	**0.020**
BATTERY CHANGES (%)	30 (22.6)	12 (18.2)	18 (26.9)	0.231
MORTALITY (%)	32 (24.1)	15 (22.7)	17 (25.4)	0.721
HPT	21 (15.8)	9 (13.6)	12 (17.9)	0.499
RE-INTERVENTION OF LV LEAD (%)	12 (9.0)	4 (6.1)	8 (11.9)	0.237
RE-INTERVENTION OF RV/RA LEAD (%)	8 (6.0)	4 (6.1)	4 (6.0)	>0.999
RE-INTERVENTION OF COMPLETE LEAD SYSTEM (%)	4 (3.0)	0 (0)	4 (6.0)	0.119

Values are n (%). Primary endpoint was defined as lead-related adverse events including (i) persisting HPT, (ii) unresolved PNS, (iii) LV lead dislodgement/dysfunction, (iv) LV lead explantation/deactivation and (v) re-interventions affecting the LV lead. Postprocedural complications occurred within 120 days after implantation. *IS-4 (n=65) and IS-1 (n=65); §IS-4 (n=65) and IS-1 (n=67); IS-1 = IS-1 Patient Group; CS = Coronary Sinus; FU = Follow-up; HPT = High Pacing Threshold; LV = Left Ventricular; n.a. = not applicable; PNS = Phrenic Nerve Stimulation; IS-4 = IS-4 Patient Group; RA = Right Atrial; RV = Right Ventricular.

Table 3. Echocardiographic outcomes.

	TOTAL (N=66)	**IS-4 (N=36)**	**IS-1 (N=30)**	**P-VALUE**
LVEF BASELINE [%]	26.08 ± 6.63	26.94 ± 6.61	25.03 ± 6.62	0.148
LVEF AT END OF FU [%]	35.42 ± 13.50	35.56 ± 12.41	35.27 ± 14.93	0.820

LVEF CHANGE DURING FU [%]	9.35 ± 12.95	8.61 ± 12.76 (p=0.001)	10.23 ± 13.33 (p<0.001)	0.706
FU DURATION [YEARS]	4.45 ± 0.98	4.11 ± 0.84	4.84 ± 1.01	**0.003**
	Total (n=48)	**IS-4 (n=26)**	**IS-1 (n=22)**	**P-value**
LVEDD BASELINE [MM]	67.38 ± 9.88	66.85 ± 7.67	68.00 ± 12.15	0.983
LVEDD AT END OF FU [MM]	61.48 ± 10.58	60.27 ± 12.76	62.91 ± 7.26	0.828
LVEDD CHANGE DURING FU [MM]	-5.90 ± 11.35	-6.58 ± 11.95 (p=0.017)	-5.09 ± 10.82 (p=0.060)	0.641
FU DURATION [YEARS]	4.35 ± 1.00	4.14 ± 0.87	4.60 ± 1.09	0.162
	Total (n=29)	**IS-4 (n=15)**	**IS-1 (n=14)**	**P-value**
LVESD BASELINE [MM]	60.24 ± 9.38	58.73 ± 8.26	61.86 ± 10.52	0.694
LVESD AT END OF FU [MM]	53.24 ± 12.45	48.33 ± 13.23	58.50 ± 9.38	**0.040**
LVESD CHANGE DURING FU [MM]	-7.00 ± 12.65	-10.40 ± 14.35 (p=0.016)	-3.36 ± 9.76 (p=0.258)	0.137
FU DURATION [YEARS]	4.35 ± 0.99	4.14 ± 0.75	4.57 ± 1.19	0.458

Values are shown as mean ± SD. FU duration for LVEF differed between patient groups (p=0.003). IS-1 = IS-1 patient group; FU = follow-up; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; IS-4 = IS-4 patient group; SD = standard deviation.

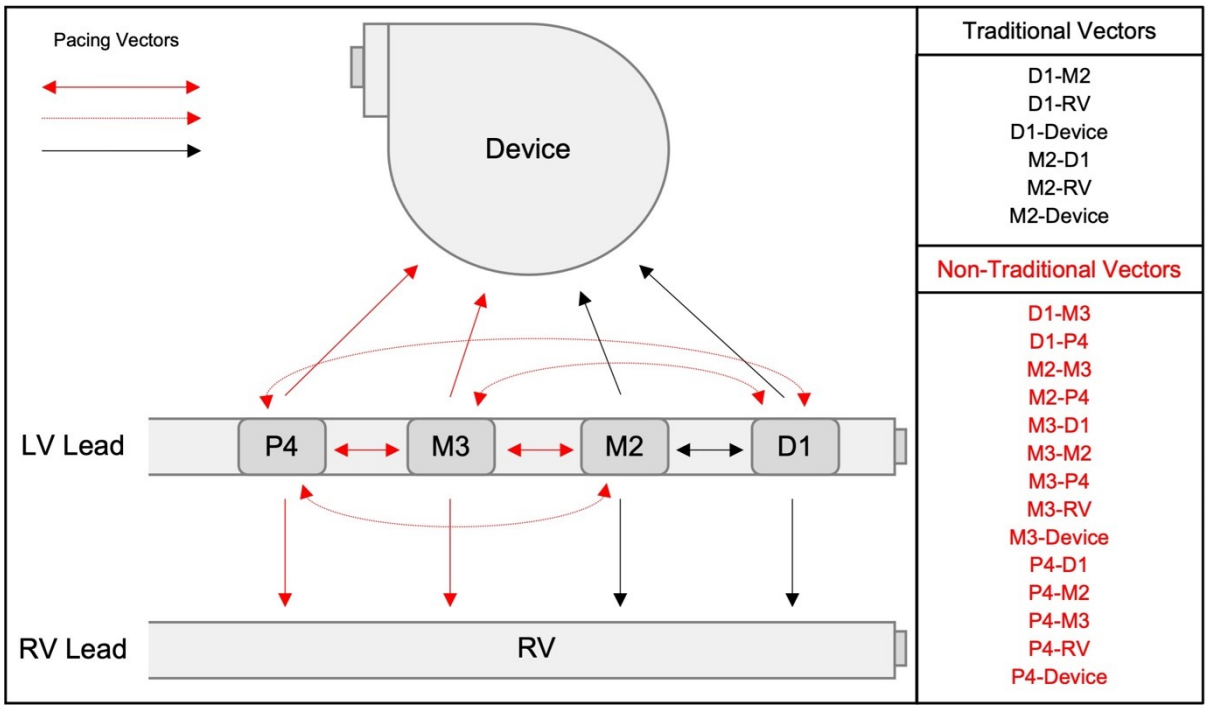

Figure 1. Pacing vectors for cardiac resynchronization therapy (CRT) with quadripolar (IS-4) and bipolar (IS-1) left ventricular leads.

The list of pacing vectors for CRT are shown. Traditional vectors (black) are programmable with IS-1 and IS-4 leads. Non-traditional vectors (red) are only available with an IS-4 lead. Depending on lead manufacturer and lead model, up to 20 pacing vectors are possible.

IS-1 = IS-1 patient group; LV = left ventricle; IS-4 = IS-4 patient group; RV = right ventricle.

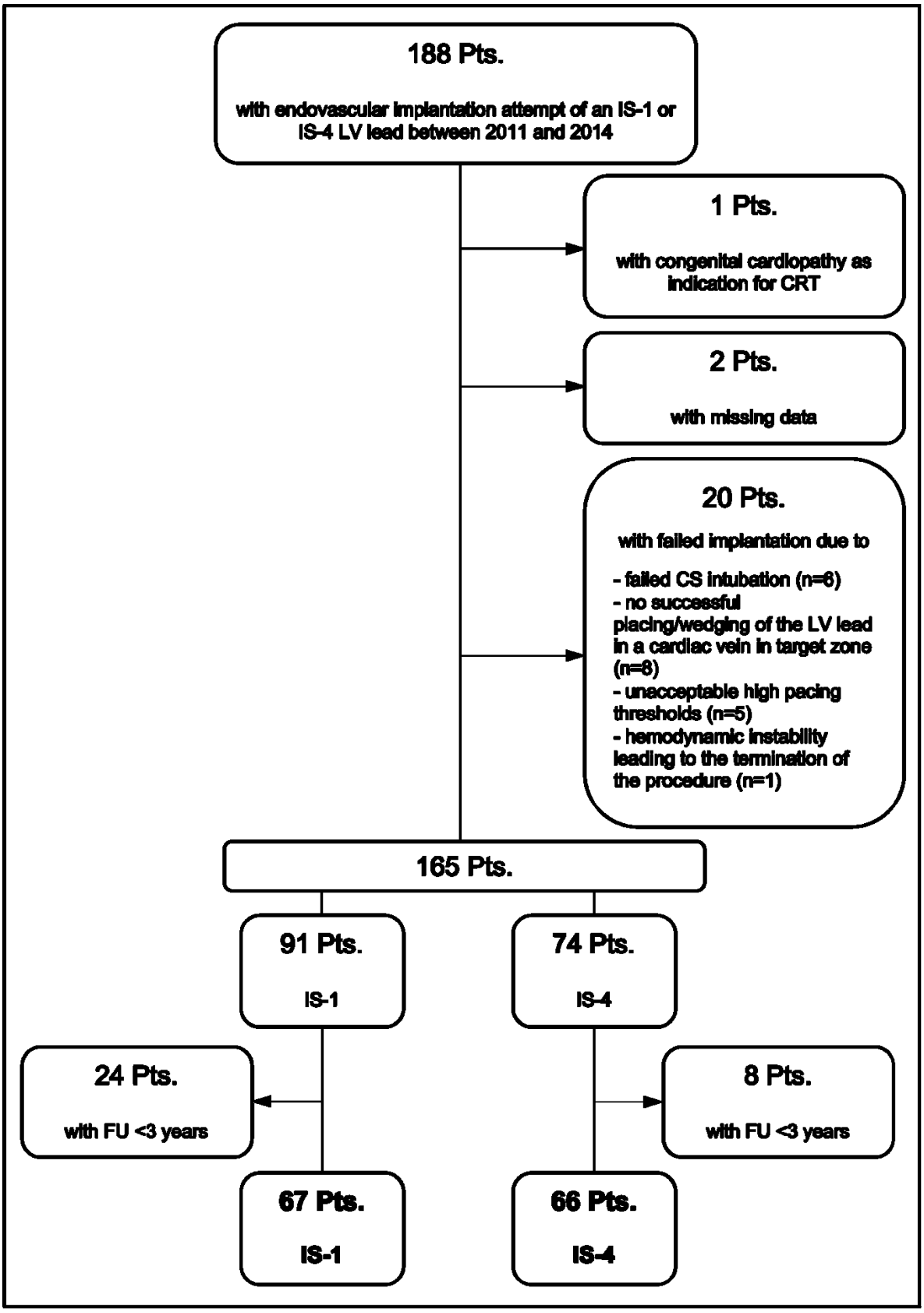

Figure 2. Study flowchart of patients with endovascular IS-1/IS-4 LV lead implanted between 2011 and 2014.

IS-1 = IS-1 patient group; CRT = cardiac resynchronization therapy; CS = coronary sinus; FU = follow-up; LV = left ventricular; Pts. = patient/patients; IS-4 = IS-4 patient group.

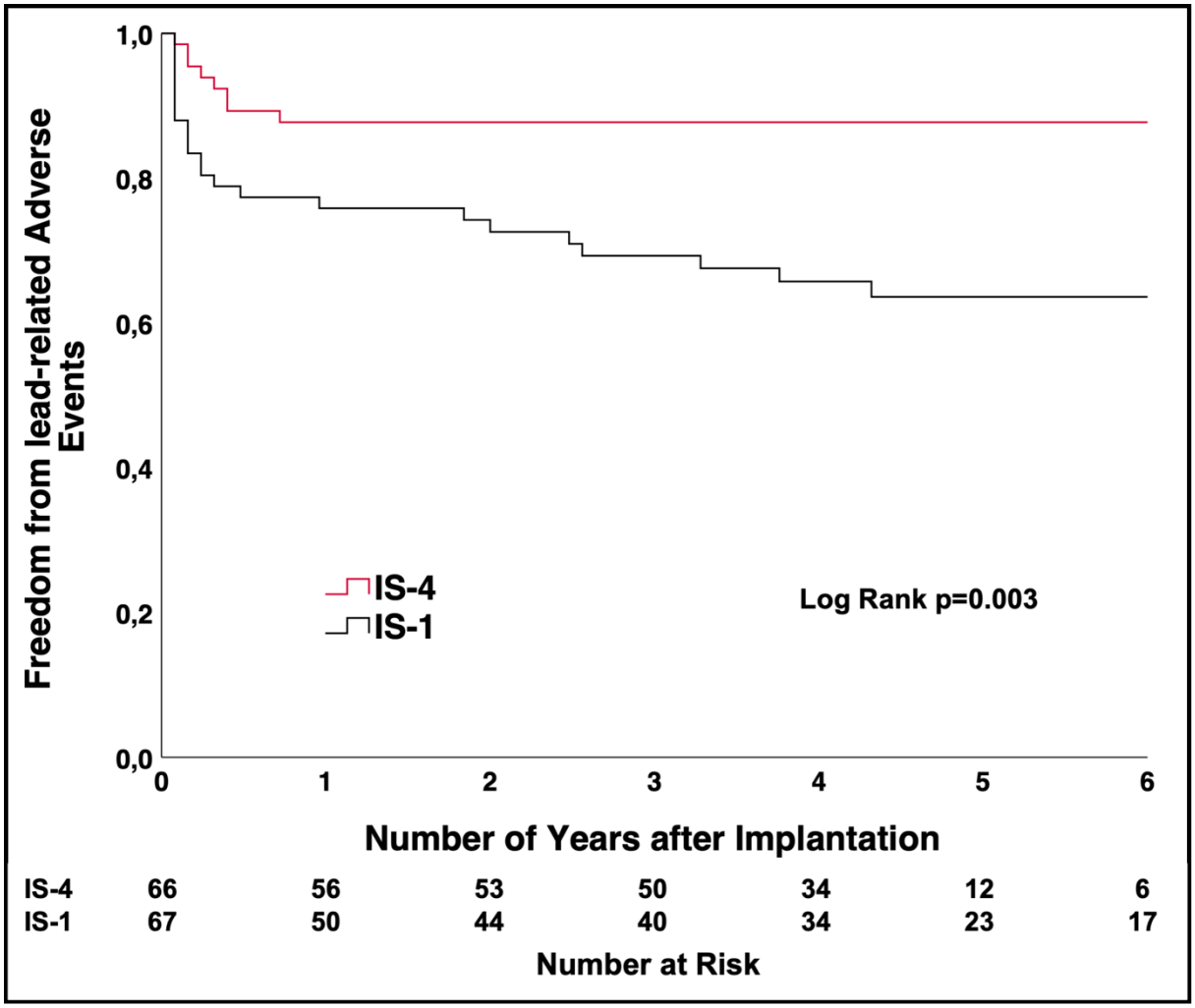

Figure 3. Kaplan-Meier analysis of primary endpoint.

Kaplan Meier survival curves in the quadripolar IS-4 lead group (IS-4) and the bipolar IS-1 lead group (IS-1) for freedom from lead-related adverse events. Censored after six years.

IS-1 = IS-1 Patient Group; LV = Left Ventricular; IS-4 = IS-4 Patient Group.

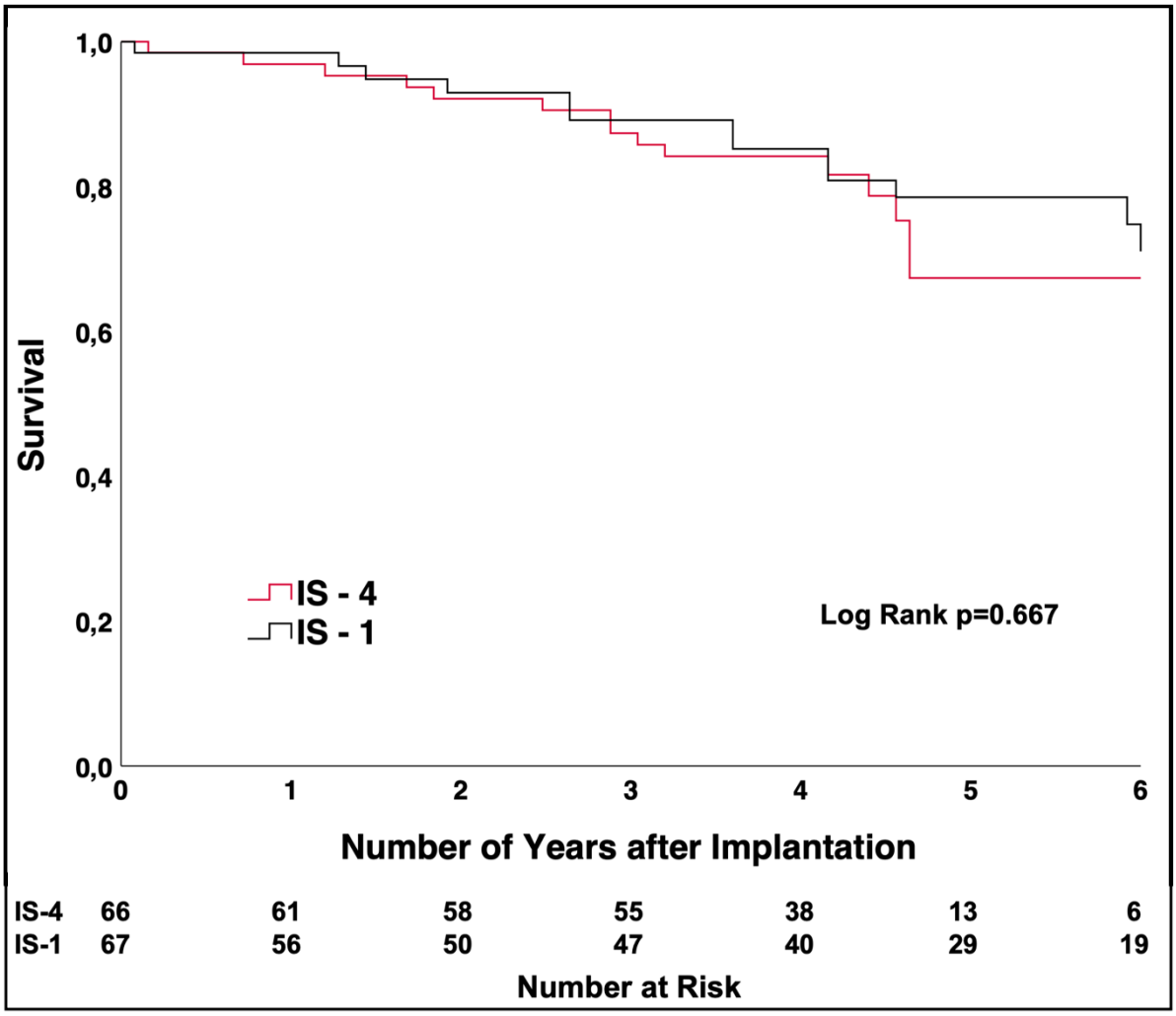

Figure 4. Kaplan-Meier analysis of mortality.

Kaplan Meier survival curves in the quadripolar IS-4 lead group (IS-4) and the bipolar IS-1 lead group (IS-1) for freedom from all-cause mortality. Censored after six years.

IS-1 = IS-1 Patient Group; LV = Left Ventricular; IS-4 = IS-4 Patient Group.

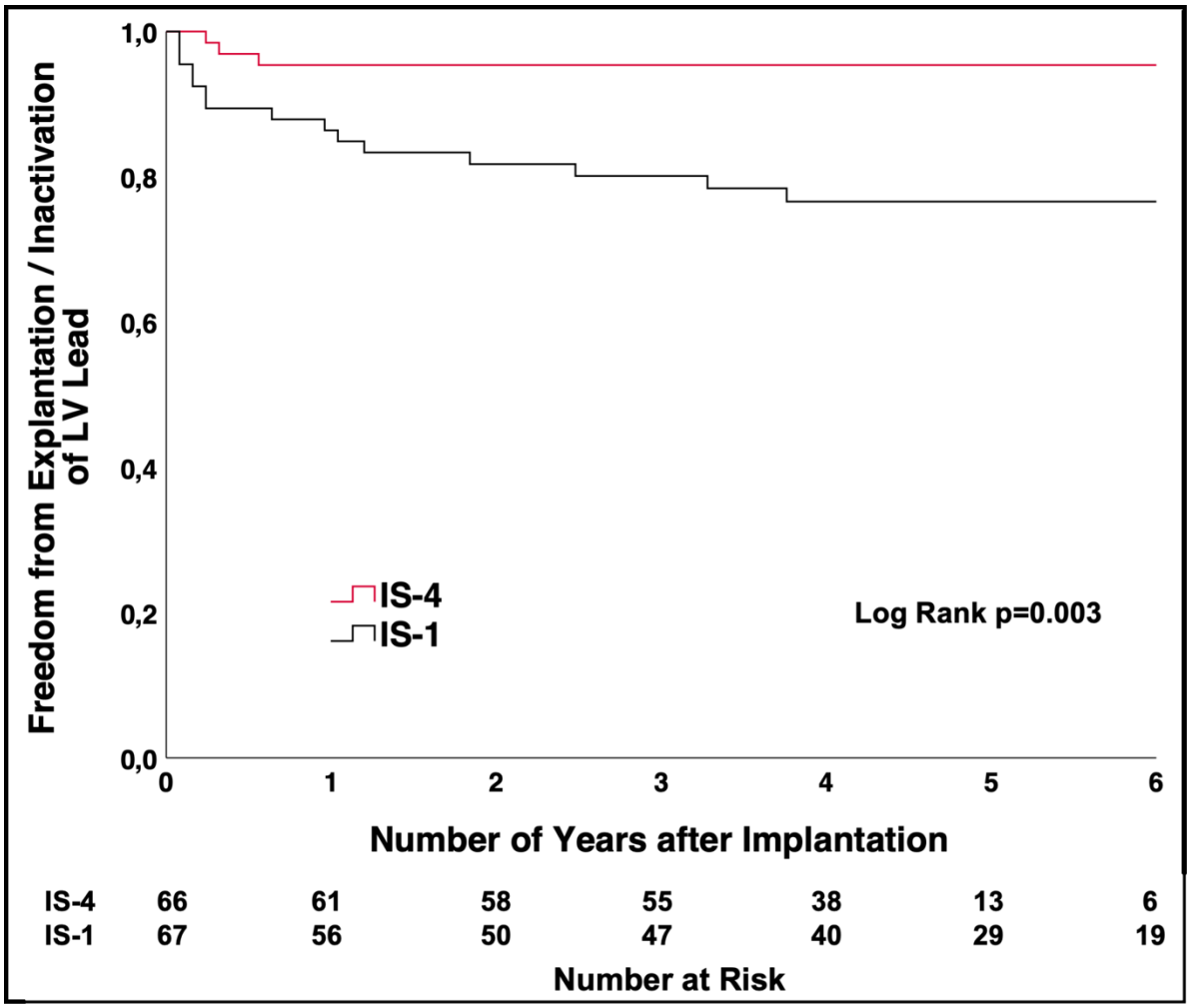

Figure 5. Kaplan-Meier analysis of freedom from LV lead deactivation/ explantation.

Kaplan Meier survival curves in the quadripolar IS-4 lead group (IS-4) and the bipolar IS-1 lead group (IS-1) for freedom from LV lead explantation/deactivation. Censored after six years.

IS-1 = IS-1 Patient Group; LV = Left Ventricular; IS-4 = IS-4 Patient Group.