



## Original Article

# Performance and clinical comparison between left ventricular quadripolar and bipolar leads in cardiac resynchronization therapy: Observational research



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## ABSTRACT

**Aim:** To evaluate Attain Performa (Medtronic, Dublin, Ireland) quadripolar lead performance in clinical practice and, secondarily, to compare its long term clinical outcomes vs bipolar leads for left ventricular (LV) pacing.

**Methods and results:** We retrospectively analyzed clinical, procedural and follow-up data of 215 patients implanted with a quadripolar lead. One hundred and twenty one patients implanted with bipolar lead were selected to compare long-term clinical outcomes. The quadripolar lead was implanted in the target vein in 196 patients (91%) without acute dislodgements. In 50% of patients the chosen final pacing configuration at implant would not have been available with bipolar leads. A dedicated quadripolar pacing vector was chosen more frequently when the LV tip location was apical than otherwise (65.6% vs 42.7%,  $p = 0.003$ ). After a median follow-up of 14 months, the LV pacing threshold was less than 2.5 V at 0.4 ms in 98 patients (90%) with a safety margin between phrenic nerve and LV pacing threshold  $>3$  V in 97 patients (89%). We observed a slight trend toward a lower risk of heart failure worsening and a lower incidence of ventricular arrhythmias and pulmonary congestion in patients implanted with quadripolar leads compared with the control group.

**Conclusion:** Quadripolar leads improve the management of phrenic nerve stimulation at no trade-off with pacing threshold and lead stability. Quadripolar leads seems to be associated with a lower incidence of VT/VF and pulmonary congestion, when compared with bipolar leads, but further investigations are necessary to confirm that this positive effect is associated with better LV reverse remodeling.

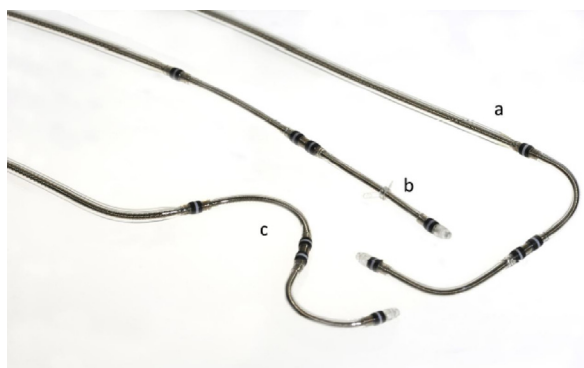
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## 1. Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment in patients with symptomatic heart failure (HF), prolonged QRS duration and impaired left ventricular (LV) systolic function.<sup>1</sup> However, some issues may limit patient response.

Approximately, 30% of patients treated by CRT do not respond in terms of reverse remodeling, and this is associated with worse clinical outcomes.<sup>2</sup> Left-ventricular lead dislodgement from the targeted pacing site, phrenic nerve stimulation, high pacing threshold and suboptimal LV lead position are some of the causes of non-response and altogether these issues may account for failure to provide CRT in up to 15% of patients when unipolar or bipolar LV leads are employed.<sup>3–5</sup> Quadripolar LV leads have been developed to enhance the stimulation of targeted sites while minimizing the risk of phrenic nerve stimulation (PNS) and lead dislodgement.<sup>6</sup> Quadripolar lead designs are different with regard

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**Fig. 1.** Attain Performa Quadripolar lead models: model 4298 (a), model 4398 (b) and model 4598 (c).

to inter-electrode spacing among manufacturers.<sup>6,7</sup> In particular a short inter-electrode spacing between the 2nd and 3rd electrode has been associated with increase in the safety margin between phrenic and LV threshold without affecting the pacing site (Fig. 1).<sup>6</sup>

We performed a multicenter observational study to evaluate whether the utilization of the Attain Performa (Medtronic, Dublin, Ireland) quadripolar lead is safe, effective and possibly associated with improved clinical outcomes when comparison to bipolar leads.

## 2. Methods

### 2.1. Population

We performed a retrospective analysis of all consecutive patients implanted from January 2012 to January 2015 with a Medtronic CRT defibrillator (CRT-D) and a bipolar lead or a quadripolar Attain Performa lead according to ESC guidelines<sup>8</sup> by 14 Italian cardiology centers participating in the ClinicalService<sup>®</sup> project.

### 2.2. Design

Participating centers prospectively collected data of all patients wearing a Medtronic CRT device in the framework of the ClinicalService<sup>®</sup> project [Clinical Trial Registration Information: <http://clinicaltrials.gov/ct2/show/NCT01007474>], ongoing in Italy since 2004. This is a medical care project that aims at evaluating and improving the use of implantable cardiac devices in the clinical practice of Italian sites. The ClinicalService<sup>®</sup> data repository can be also retrospectively interrogated to test specific physicians' hypotheses.

The project was approved by the Ethics Committee or Medical Director of each participating center and complies with the principles outlined in the Declaration of Helsinki. Each patient provided informed consent for data collection and analysis. Since March 2013, after the quadripolar lead was launched in the market, physicians from the 14 centers participating in this study chose to use quadripolar LV lead as the first choice in all consecutive CRT implants. As control group, all patients implanted with standard bipolar leads and included in the ClinicalService<sup>®</sup> project since January 2012 were selected. Follow-up performance and clinical outcomes were compared between the cohorts of patients with quadripolar and bipolar leads whose complete follow-up data was available.

The rate of quadripolar leads was different between the participating centers, but the contribution of each site was not greater than 20% of the total cohort.

### 2.3. Objectives

The primary objective of our analyses was to evaluate the performance of Attain Performa quadripolar lead in clinical practice.

The secondary objective was to compare clinical outcomes and follow-up HF status of patients implanted with quadripolar lead vs. patients implanted with standard Medtronic passive fixation bipolar leads in the year before Attain Performa market release.

### 2.4. Attain performa lead and bipolar lead characteristics

The Attain<sup>®</sup> Performa<sup>™</sup> Quadripolar lead features steroid on all four LV pacing electrodes. Inter-electrode spacing is 21 mm between the first and second electrode and between the third and fourth electrode, while it is 1.3 mm between the second and third electrode. The narrow-spaced electrodes, "Short Bipolar", were designed to reduce the chance of stimulation of the phrenic nerve without compromising pacing capture thresholds.<sup>9</sup>

This lead is intended to be placed into tributaries of the coronary sinus for the provision of CRT. It is available in three shapes: model 4298 is canted with a compound curve at the distal end (Fig. 1a), model 4398 is a straight lead with tines (Fig. 1b) and model 4598 has an offset S-shaped curve at the distal end (Fig. 1c). All three lead models are constructed with an IS4 connector and have 5.3 French (Fr) proximal and 3.9 Fr distal lead body diameters.

The control group consisted of standard Medtronic passive fixation bipolar leads of the Attain Bipolar over the wire (OTW) or Attain Ability families. The Attain Bipolar OTW (model 4194) is a 6 Fr steroid eluting true bipolar lead, with an inter-electrode spacing of 11 mm and a canted distal end for passive fixation into the vein. The Attain Ability is a dual cathode steroid eluting lead, with an inter-electrode spacing of 21 mm and it is available in three models: 4 Fr canted lead (model 4196), 5.3 Fr canted lead (model 4296) and 4 Fr straight tined lead (model 4396).

### 2.5. Clinical and lead data collection

At baseline (prior to CRT-D implantation), patients of both groups were evaluated according to the clinical practice of each center with the collection of available data regarding clinical history, NYHA functional class, 12-lead electrocardiography (ECG) and echocardiography (ECHO). During the implantation procedure of the quadripolar lead, before taking the coronary venogram, the implanting physician determined a target pacing point for the left-ventricular pacing on the 30° right anterior oblique (RAO) view and on the 40° left anterior oblique (LAO) and identified the target pacing site (TPS) as a 2 cm diameter area around the target pacing point (pre-operative TPS selection). TPS selection was not performed using a standardized image-guided approach in all patients, but each physician decided according to his clinical practice: in some patients the target pacing site was chosen a priori (without additional tests) in a posterolateral area, while in others it was decided after a speckle tracking ECHO or magnetic resonance imaging (MRI).<sup>10,11,14</sup>

The coronary sinus (CS) venograms in 40° LAO view and in 30° RAO view were recorded and stored. After the venogram, the implanter determined the presence/absence of a target vein, defined as a suitable cardiac vein leading to the target pacing site.

Before leaving the operating room, the left-ventricular pacing threshold (LVPT) and PNS threshold (PNST) of the quadripolar lead were measured and a final pacing vector was chosen from the 16 available. The final LV pacing site was defined as the location of the cathode of the final pacing vector. Device programming of lower rate limit, rate response, atrioventricular (AV) intervals, ventricular tachycardia or fibrillation (VT/VF) detection intervals and cut-off rates was left to physician discretion.

Patient clinical assessment, electrical parameters of the quadripolar lead (LVPT and PNST), and all adverse events were recorded at routine follow-up. Device diagnostic data retrieved

from the device memory at each ambulatory or remote follow-up were stored in the ClinicalService<sup>®</sup> electronic database.

## 2.6. Device diagnostics data

Device diagnostics stored information about atrial tachycardia or fibrillation (AT/AF), ventricular rate during AF, fluid volume congestion through intrathoracic impedance measurements (OptiVol<sup>®</sup> fluid index), patient activity, night heart rate, heart rate variability (HRV), the percentage of CRT pacing and detected episodes of VT/VF. A close correlation between changes in some of these individual or combined HF diagnostics data and HF events have been shown in several studies.<sup>12,13</sup> We also estimated the PARTNERS-HF index as a combined risk of HF worsening.<sup>13</sup>

Diagnostic data from the first month after implantation were excluded from the analysis.

## 2.7. Statistical analysis

Continuous variables with a normal distribution were expressed as mean and standard deviation, or median and first and third quartile in the case of skewed distributions. Baseline characteristics as well as diagnostic parameters were compared between groups by means of the chi-square test, Fisher exact test, Student's *t*-test or the Wilcoxon-Mann-Whitney test as appropriate. As sensitivity analysis, the two cohorts were propensity matched (see Supplemental Appendix – Table SA1 and SA2). The propensity score was obtained from a logistic model for lead implanted, including age, history of HF and history of atrial arrhythmias. All statistical tests were two sided and deemed to be statistically significant if  $p < 0.05$ . Analyses were carried out using SAS 9.4 version software (SAS Institute Inc., Cary, NC, USA).

## 3. Results

Fig. 2 shows the number of patients included in the two analyses of our project. Median follow-up period was 14 months [25–75 percentile: 8–15 months].

### 3.1. Quadripolar lead performance at implant and follow-up

#### 3.1.1. Quadripolar lead implantation details

A total of 215 patients were implanted with the quadripolar lead in the 14 participating centers in Italy. Baseline characteristics of the patients are described in the second column of Table 1.

Concerning the type of procedure, 176 (80%) were first implants; while ipsilateral upgrading was done in 28 (13%) patients and post-extraction re-implantations were done in 16 (7%) patients. A left-sided access was used in 92.5% of the procedures.

In 158 (74%) cases, the implanter used the 4298 model (dual canted), in 29 (12%) the 4398 (straight) and in 28 (13%) the 4598 (S-shaped).

The choice of target pacing site was a lateral or postero-lateral area by default, without additional testing, in 157 (73%) patients, while additional evaluations, like speckle tracking 2D echo criteria or assessment of scar area using MRI, were made in 63 (27%) patients. The angiogram was performed in 195 patients (96%). In the other patients, the presence of a vein that matched with the target pacing site was tested by advancing a 0.014 Fr angioplasty guidewire. All the patients had at least one target vein. The target vein was lateral in 98 patients (45.6%), posterolateral in 86 patients (40.0%), anterolateral in 21 patients (9.8%) and posterior in 10 patients (4.6%).

The lead was successfully implanted in the chosen target vein in 196 patients (91%). In the other 19 (9%) patients, the Performa lead was placed in a second-choice vein that was nearby the target pacing site: in 16 (7%) patients it was not possible to insert and advance the lead in the target vein, in 3 (2%) patients the target vein was considered too short for the quadripolar lead (with a high risk of dislodgement).

No quadripolar lead acute dislodgements were reported, while 1 acute procedure-related complication occurred in the bipolar control group. A total of 4 (2%) dislodgments (needing a surgical replacement) occurred during the median observation period of 14 months, while 3 (2.5%) in the bipolar control group.

#### 3.1.2. Quadripolar lead placement, pacing vectors and pacing sites

Final lead tip and short bipolar locations are reported in Fig. 3. In 20 patients (9.5%) in the final lead location the proximal electrode (LV4) remained outside the target vein. Among them, in 2 patients a late lead dislodgment occurred during the observation period.

In 50% of patients the chosen final pacing configuration at implant would not have been available with a conventional bipolar lead. In particular a short bipole configuration (LV2-LV3 or LV3-LV2) was programmed in 44 patients (20.4%). The reason for final pacing configuration choice was device longevity for 79% patients, and avoidance of phrenic nerve stimulation for 21% of patients. A dedicated quadripolar pacing vector was chosen more frequently when the LV tip location was apical than otherwise (65.6% vs 42.7%, respectively;

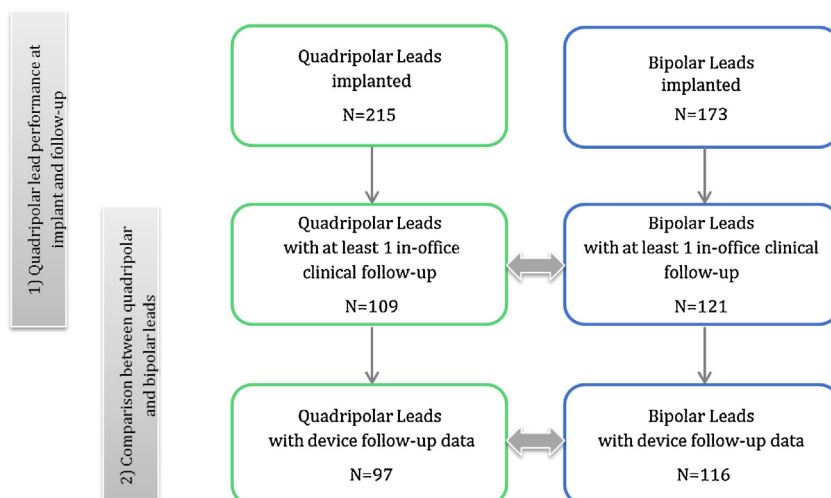
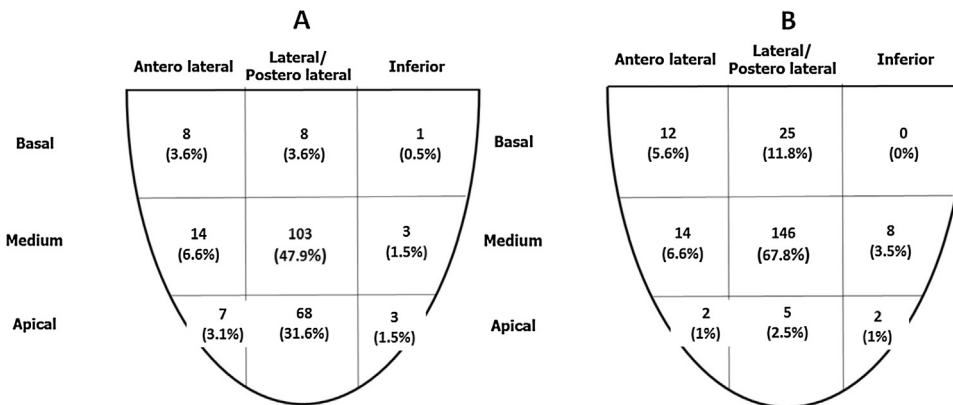


Fig. 2. Patients included in the two analyses.

**Table 1**  
Baseline characteristics of patient population.

Patient Characteristics	First Analysis	Second Analysis		p-value A vs B
	all Quadripolar lead (N = 215)	Quadripolar with follow-up (N = 109) A	Bipolar with follow-up (N = 121) B	
<b>Demographics</b>				
Age at first implant (yrs), mean ± SD	68.8 ± 11.0	69.2 ± 10.1	67.8 ± 10.6	0.608
Gender (Male), % (n)	76.9% (165)	72.5% (79)	80.8% (97)	0.134
<b>Medical history</b>				
History of HF, % (n)	90.6% (195)	90.7% (99)	83.1% (100)	0.094
NYHA 3/4, % (n)	61.5% (132)	72.4% (79)	61.5% (74)	0.087
VT/VF, % (n)	7.6% (16)	8.5% (9)	11.4% (14)	0.472
AT/AF, % (n)	31.6% (68)	29.5% (32)	27.4% (33)	0.732
Ischemic Cardiopathy, (n)	42.8% (92)	48.6% (53)	47.1% (56)	0.813
1st grade AV block, % (n)	14.9% (32)	17.0% (18)	12.4% (15)	0.341
2nd grade AV block, % (n)	3.7% (8)	4.0% (4)	6.1% (7)	0.479
3rd grade AV block, % (n)	8.0% (17)	9.0% (10)	4.4% (5)	0.173
RBBB, % (n)	6.0% (13)	6.0% (6)	10.6% (13)	0.226
LBBB, % (n)	71.6% (154)	68.0% (74)	71.3% (86)	0.599
Left Hemiblock, % (n)	4.5% (10)	6.1% (7)	6.2% (7)	0.968
SND, % (n)	7.8% (17)	7.8% (8)	5.0% (6)	0.405
QRS (ms), mean ± SD	152.2 ± 23.9	150.5 ± 22.9	153.5 ± 29.3	0.918
History of stroke/TIA, % (n)	8.9% (19)	7.5% (8)	5.5% (7)	0.548
Valvular surgery, % (n)	11.2% (24)	11.9% (13)	9.1% (11)	0.482
Hypertension, % (n)	61.2% (132)	66.3% (72)	63.6% (77)	0.671
Diabetes, % (n)	22.3% (48)	23.5% (26)	27.6% (33)	0.514
Chronic kidney disease, % (n)	18.0% (39)	20.8% (23)	12.1% (15)	0.079
COPD, % (n)	19.9% (43)	23.7% (26)	14.0% (17)	0.080
Cardiovascular hospitalizations, % (n/N)	51.8% (1111)	44.2% (48)	31.1% (38)	0.056
<b>Echo at baseline</b>				
LVEF (%), mean ± SD	27.8 ± 6.6	28.0 ± 6.8	28.2 ± 6.1	0.847
LVEDV (ml), mean ± SD	209.8 ± 85.7	209.7 ± 76.0	208.2 ± 57.1	0.903
LVESV (ml), mean ± SD	153.0 ± 71.2	158.7 ± 69.2	146.0 ± 46.6	0.803
Mitral regurgitation, % (n)	91.6% (197)	90.5% (99)	93.3% (113)	0.646
<b>Medication at baseline</b>				
Beta-blocker	75.8% (163)	75.5% (82)	66.1% (80)	0.123
Diuretic	79.5% (171)	81.1% (88)	76.9% (93)	0.432
Anti-platelet	47.0% (101)	53.8% (59)	48.8% (59)	0.451
OAC	63.7% (137)	60.4% (66)	30.6% (37)	<0.001
ACE-inhibitor/ARB2	54.4% (117)	57.5% (63)	63.6% (77)	0.348



**Fig. 3.** Final lead tip (panel A) and short bipolar locations (panel B).

$p = 0.003$ ). During a median follow-up of 14 months, physician changed the pacing configuration at least once in 59 (54.1%) patients. Main reasons for a configuration change were an increased LVPT (62.5% patients), PNS management (12.5%), or optimization of device programming to improve patient response to CRT (25.0%).

Configuration changes from a standard vector (one available in bipolar leads also) to a specific quadripolar pacing vector occurred in 17 (15.6%) patients. In 12 (11.0%) patients the reverse change occurred.

Fig. 4 shows LV-stimulation pacing-site locations at implantation and at last available follow-up. These were basal or middle ventricular in 87.5% of the patients after implantation and in 83.9% of patients at last follow-up, despite the tip of the quadripolar lead is apical in 36.2% of patients (Fig. 3A).

### 3.1.3. Phrenic nerve stimulation and pacing threshold in quadripolar leads

Phrenic nerve stimulation at 8 V at 0.4 ms with the final pacing vector was observed in 54 patients (25.1%) at implantation and in 21 patients (19.4%) at a median follow-up of 14 months, respectively. At implant median LVPT was 1 V at 0.4 ms [25–75 percentile: 0.5V–1.3 V] and it was lower than 2.5 V at 0.4 ms in final pacing configuration in 202 patients (94%) with a safety margin between PNST and LVPT of >3 V in 190 (88%) patients. During the follow-up period, LVPT was 1 V at 0.4 ms [25–75 percentile: 0.75V–1.5 V] ( $p = 0.132$  versus implant) and it was lower than 2.5 V at 0.4 ms in 98 patients (90%) with a safety margin between phrenic nerve threshold and LV of >3 V in

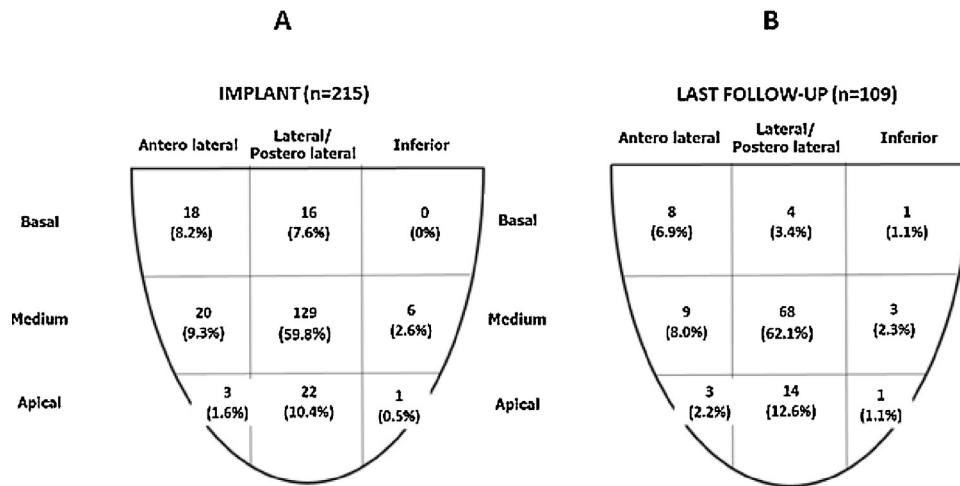


Fig. 4. LV stimulation pacing site locations at implant (panel A) and at last available follow-up (panel B).

97 (89%) patients. In Table 2a and b, we report the percentage of patients with pacing capture threshold of no greater than 2.5 V, according to final pacing configuration, associated with the absence of PNS or a safety margin greater than 3 V in our population, at implant and follow-up.

Both standard vectors, already available in standard bipolar lead, and new vectors specific for the quadripolar lead have been programmed and resulted in a mean LVPT lower than 1.5 V at 0.4 ms and in a guaranteed safety margin between pacing and PNS thresholds of at least 3 V in more than 86% of patients, both at implant and at follow-up.

### 3.2. Comparison between quadripolar and bipolar leads

At long term follow-up 109 patients of the quadripolar group had a clinical follow-up. Among them, 97 had a complete device diagnostics dataset available. We compared these patients with a control group of 121 patients (116 with complete device data collection) with standard bipolar leads. Baseline characteristics of the two patient populations are reported in third and fourth columns of Table 1. There were no statistical differences between the two groups, even if quadripolar group seems to have more patients with chronic kidney diseases, chronic pulmonary obstructive disease (COPD) and pre-implant cardiovascular hospitalizations.

Median follow-up length was 14 months for both groups. No significant differences were observed at follow-up between quadripolar and bipolar group in term of mean LVPT ( $1.19 \pm 0.85$  vs.  $1.44 \pm 1.22$  V at 0.4 ms, respectively), percentage of patients with high LVPT (9.7% vs. 13.3%, with  $LVPT > 2.5$  V at 0.4 ms respectively) and number of patients with PNS requiring surgical intervention (0% vs. 0.8%, respectively). The incidence of clinical and device-derived outcomes is shown in Table 3.

The quadripolar lead group had a lower percentage of patients (27%) with at least 1 day with an OptiVol fluid index higher than 100 in comparison to the bipolar group (44%,  $p = 0.015$ ). Ventricular arrhythmias were detected by the device in a lower percentage of patients of the quadripolar lead group (9%) compared with bipolar lead group (22%,  $p = 0.015$ ). The other device-derived outcomes did not show significant differences. Patients with at least 1 day with PARTNERS-HF worsening HF risk were 65 (67.0%) in the quadripolar lead group and 90 (77.6%) in the bipolar lead group ( $p = 0.084$ ).

Analysis on the propensity-matched cohorts confirmed results on the whole population.

## 4. Discussion

Several factors contribute to either reverse LV remodeling or clinical improvement following CRT delivery. Non-optimal LV

Table 2

Pacing capture threshold and occurrence of phrenic nerve stimulation according to final pacing configuration at implant (A) and last follow-up (B).

a. Implant.					
LVPT and PNS by final configuration					
Final Pacing Configuration	n	Mean LVPT (V @ 0.4 ms)	$LVPT \leq 2.5$ V%pts	$LVPT \leq 2.5$ V and No PNS%pts	$LVPT \leq 2.5$ V and PNST-LVPT > 3 V%pts
Vector available in Bipolar lead	107	$1.15 \pm 0.74$	93.5%	66.7%	87.1%
Vector NOT available in Bipolar lead	108	$1.10 \pm 0.68^*$	94.6%	68.5%	89.1% <sup>†</sup>
- Short Bipole	44	$0.83 \pm 0.35^*$	97.4%	79.5%	89.7% <sup>†</sup>
b. Last follow-up.					
LVPT and PNS by final configuration					
Final Pacing Configuration	n	Mean LVPT (V @ 0.4 ms)	$LVPT \leq 2.5$ V%pts	$LVPT \leq 2.5$ V and No PNS%pts	$LVPT \leq 2.5$ V and PNST-LVPT > 3 V%pts
Vector available in Bipolar lead	47	$1.10 \pm 0.67$	93.6%	78.7%	91.5%
Vector NOT available in Bipolar lead	62	$1.35 \pm 1.05^*$	86.4%	65.9%	86.4% <sup>†</sup>
- Short Bipole	19	$1.09 \pm 0.76^*$	86.7%	80.0%	86.7% <sup>†</sup>

PNST: phrenic nerve stimulation threshold; LVPT: left-ventricular pacing threshold.

\* p-values > 0.01 for comparison vs Vector available in Bipolar lead.

**Table 3**

Patients experiencing clinical and device diagnostics outcomes.

		Quadripolar (N = 97)	Bipolar (N = 116)	P value
Death for any cause	Patients, n (%)	4 (3.7%)	3 (2.5%)	0.230
Cardiovascular or device-related hospitalization	Patients, n (%)	6 (5.5%)	7 (5.8%)	0.927
VT/VF detected episodes	Patients, n (%)	9 (9.3%)	25 (21.6%)	0.015
Thoracic fluid level over threshold Optivol fluid index $\geq 100 \Omega$	Patients, n (%)	27 (27.8%)	51 (44.0%)	0.015
New onset of AT/AF (>6 h spent in AF on at least 1 day)	Patients, n (%)	10 (15.2%)	12 (13.8%)	0.813
High Ventricular rate during AF (daily average ventricular rate occurring during AF on a specific day $\geq 90$ beats/min)	Patients, n (%)	10 (10.3%)	12 (10.3%)	0.993
Low Patient activity (daily average patient activity <1 h on at least 1 day) <sup>a</sup>	Patients, n (%)	63 (64.9%)	73 (62.9%)	0.760
High Night heart rate (average ventricular rate from 12AM (midnight) to 4AM >85 beats/min on at least 1 day) <sup>a</sup>	Patients, n (%)	42 (43.3%)	50 (43.1%)	0.977
Low HRV (HRV <60 ms on at least 1 day) <sup>a</sup>	Patients, n (%)	46 (83.6%)	60 (75.9%)	0.282
CRT pacing percentage <90% on at least 1 day	Patients, n (%)	50 (51.5%)	58 (50.0%)	0.822
	Days/year, Median (Q1–Q3)	49 (4–193)	25 (4–149)	0.514
Risk of worsening HF (PARTNER HF) (at least once between fluid index >100 $\Omega$ days or any 2 of the other criteria listed in this table).	Patients, n (%)	65 (67.0%)	90 (77.6%)	0.084

\*A new onset of AT/AF was defined as no AT/AF episodes reported at baseline visit (in case of first implantation) or in the device memory (in case of device replacement). New onset with more than 6 h of AT/AF a day was considered as an impaired patient clinical condition.

<sup>a</sup> First month after implantation has been excluded from this analysis, to exclude the time of implant hospitalization.

pacing site induced by complex coronary sinus vein anatomy, phrenic nerve stimulation and high pacing threshold may cause CRT non-response.<sup>2–4</sup>

New leads and access tools for LV pacing from cardiac veins have enhanced lead placement into a targeted area improving the success of CRT implantation.<sup>14</sup>

#### 4.1. Main results

Quadripolar leads were associated with 1) high electrical performance, 2) low dislodgement rates, 3) no PNS issues and 4) favorable comparison with bipolar leads in terms of incidence of pulmonary congestion or VT/VF occurrence.

#### 4.2. Electrical performance

Our data show that Attain Performa quadripolar leads have excellent acute and chronic electrical performance confirming previous data; noteworthy 16 patients (7%) with a previous lead extraction needing a right sided re-implantation were included in our cohort. The lack of vessels, the stenosis or thrombosis or narrowing of coronary sinus branches post-extraction did not seem to affect the procedural outcome of quadripolar implant considering our successful experience in the reimplantation setting; a result that favorably compares with previously published experiences with bipolar LV pacing leads<sup>15</sup> and with other quadripolar leads.<sup>7,15</sup>

#### 4.3. Dislodgements

A second challenge in cardiac resynchronization is to prevent LV lead dislodgement. Till date a dislodgement rate of 9–10% has been reported with the use of bipolar leads. Multipolar leads enable the tip to be wedged in the distal part of the vein (improving lead stability) and then to pace at mid and basal sites (this is considered superior to apical pacing).<sup>16</sup> In our cohort of quadripolar leads, it was confirmed that only 12.5% of patients were paced apically (Fig. 4a), despite the tip of the quadripolar lead was apical in 36.2% of the patients (Fig. 3a). The dislodgement rate with the St. Jude's Quartet quadripolar lead has been reported to be around 3.5% at 3 months.<sup>7,16</sup> The rate of dislodgement requiring repeated surgery was 1% in the Attain Performa quadripolar lead family at 6-months follow-up,<sup>6</sup> which is significantly better compared with the bipolar leads<sup>3</sup> and Quartet quadripolar leads.<sup>7,16</sup> Our data also confirms a low dislodgement rate (2%) at 14 months. It is noteworthy to

mention that, while minor dislodgements are treated with cathode reprogramming,<sup>4</sup> the true lead stability may be overestimated and only dislodgements requiring repeated surgery are reported in the literature.

#### 4.4. Phrenic nerve stimulation

PNS poses significant limitations to LV stimulation, as reported.<sup>4,17</sup> In our analysis we showed that, although PNS detection was comparable to literature values, the Attain Performa lead warranted a safety margin greater than 3 V between PNS threshold and LVPT in 88% of patients at implant and 89% at follow-up, which was observed to be advantageous for patients with PNS at implantation.<sup>18</sup> Indeed, a short pacing dipole increases the PNS threshold without affecting the LV threshold.<sup>6,9,18</sup> 20% of our patients were paced by the short-spaced configurations, and 50% of patients with a pacing configuration not available with a bipolar lead. Pacing vectors available in a quadripolar lead were programmed more often when the LV lead tip was in the distal part of the vein to achieve a more proximal stimulation site. A high pacing threshold is frequently associated to PNS management with bipolar LV leads.<sup>19</sup> Because of a high LV threshold when using LV3 and LV4 as cathode, more than 75% of patients with a Quartet lead resulted in a pacing vector available with conventional bipolar leads.<sup>7</sup> In contrast, in our population as well as in Crossley's study,<sup>6</sup> more than 40% of patients were programmed with a pacing vector available with a quadripolar lead only, with LVPT comparable to those of standard bipolar leads and no cases of surgical re-intervention needed to solve PNS. Moreover, several pacing vectors were suitable for LV stimulation below battery voltage, which prolongs device longevity.

#### 4.5. Clinical outcomes

Data on the effect of the quadripolar leads in term of response to the CRT are scarce.<sup>18</sup> Our research compared the outcome of patients implanted with quadripolar leads vs bipolar leads in terms of survival, cardiovascular or device-related hospitalizations, VT/VF occurrence and device-based indexes of worsening HF. We observed a lower incidence of VT/VF and pulmonary congestion in quadripolar leads as compared with bipolar leads. These findings may represent a signal that the use of quadripolar leads improves the possibility to achieve LV reverse remodeling but of course this hypothesis would warrant a solid confirmation in randomized controlled studies. Indeed, it is known that reverse remodeling is

associated with lower occurrence of VT/VF.<sup>20</sup> Behar et al reported an advantage in terms of mortality and PNS management with quadripolar leads compared to bipolar LV leads.<sup>21</sup> Their findings have to be evaluated taking into account that ischemic heart disease and AF were significantly more common in the bipolar leads group and that the LV lead dislodgement and redo surgery rate in the bipolar group could have been associated with a learning curve effect by some centers, later resolved in the quadripolar lead series.

#### 4.6. Limitations

The limitations of multicenter observational studies and retrospective analyses, including factors such as potential bias in patient selection, patient treatment and device programming, apply to our research. Nevertheless, possible biases are mitigated by the fact that data were collected prospectively, the analysis plan and research objectives were designed before opening the dataset and the analysis on the propensity matched cohorts confirmed results obtained in the whole population. Some data, such as echo data or PNS information, were not available for the whole population. The number of patients included in the study is small; however, the inclusion of all-comers, for example also post-extraction patients, allowed us to evaluate quadripolar leads in real clinical practice conditions.

Due to lack of randomization and the use of an historical control group, no evaluation of patient drop-out rate during the implantation because of PNS or lead instability is available, and no comparison of success implant rate or time to LV lead placement and procedural data can be made. In addition, due to the growing use of remote monitoring system for patient follow-up, about 50% of patients did not perform an in-office visit with complete data collection.

## 5. Conclusion

Our data show that Attain Performa quadripolar leads enable implanters to reach a targeted lead positioning even in challenging cases. These short-spaced quadripolar leads improve the management of PNS at no trade-off with pacing threshold and lead stability, which eventually become “minor” problems for CRT provision. In addition, quadripolar leads may be associated with a lower incidence of VT/VF and pulmonary congestion when compared with bipolar leads. However, further investigation through randomized controlled studies is necessary to assess whether this positive quadripolar lead effect is associated with better LV reverse remodeling.

## Conflict of interest

M.Z. received speaker's fees from Medtronic and Boston Scientific; G.B. received speaker's fees from Boston Scientific, Medtronic, St. Jude and Boehringer Ingelheim; M.B. received speaker's fees from Medtronic and Biotronik; D.R. received speaker's fees from Boehringer Ingelheim; G.Z. is a Medtronic Consultant without relevant financial relationship; M.G.B. received speaker's fees from Boston Scientific, Medtronic, Biosense Webster, Spectranetics.

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## Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ihj.2018.05.007>.

## References

1. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
2. Ypenburg C, van Bommel RJ, Borleffs CJ, et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol*. 2009;53:483–490.
3. Biffi M, Bertini M, Ziacchi M, Diemberger I, Martignani C, Boriani G. Left ventricular lead stabilization to retain cardiac resynchronization therapy at long term: when is it advisable. *Europac*. 2014;16:533–540.
4. Biffi M, Moschini C, Bertini M, et al. Phrenic stimulation: a challenge for cardiac resynchronization therapy. *Circ Arrhythmia Electrophysiol*. 2009;2:402–410.
5. Knight BP, Desai A, Coman J, Faddis M, Yong P. Long-term retention of cardiac resynchronization therapy. *J Am Coll Cardiol*. 2004;44:72–77.
6. Crossley GH, Biffi M, Johnson B, et al. Performance of a novel left ventricular lead with short bipolar spacing for cardiac resynchronization therapy: primary results of the Attain Performa quadripolar left ventricular lead study. *Heart Rhythm*. 2015;12:751–758.
7. Tomassoni G, Baker J, Corbisiero R, et al. Postoperative performance of the Quartet(R) left ventricular heart lead. *J Cardiovasc Electrophysiol*. 2013;24(4):449–456.
8. Brignole M, Auricchio A, Baron-Esquivias G, et al. ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;2013(34):2281–2329.
9. Biffi M, Foerster L, Eastman W, et al. Effect of bipolar electrode spacing on phrenic nerve stimulation and left ventricular pacing thresholds: an acute canine study. *Circ Arrhythmia Electrophysiol*. 2012;5:815–820.
10. Abozguia K, Leyva F. Targeting viable myocardium in cardiac resynchronization therapy using a multipolar left ventricular lead. *Circulation*. 2011;123:e617–8.
11. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:1–11.
12. Adamson PB. Using cardiac resynchronization therapy diagnostics for monitoring heart failure patients. *Heart Fail Clin*. 2009;5:249–260.
13. Whellan DJ, Ousdigian KT, Al-Khatib SM, et al. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (program to access and review trending information and evaluate correlation to symptoms in patients with heart failure) study. *J Am Coll Cardiol*. 2010;55:1803–1810.

14. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol*. 2012;59:1509–1518.
15. Zucchelli G, Bongiorni MG, Di Cori A, et al. Cardiac resynchronization therapy after coronary sinus lead extraction: feasibility and mid-term outcome of transvenous reimplantation in a tertiary referral centre. *Europace*. 2012;14:515–521.
16. Thibault B, Karst E, Ryu K, Paiement P, Farazi TG. Pacing electrode selection in a quadripolar left heart lead determines presence or absence of phrenic nerve stimulation. *Europace*. 2010;12:751–753.
17. Biffi M, Bertini M, Ziacchi M, et al. Management of phrenic stimulation in CRT patients over the long term: still an unmet need? *PACE*. 2011;34:1201–1208.
18. Ziacchi M, Saporito D, Zardini M, et al. Left ventricular reverse remodeling elicited by a quadripolar lead: results from the multicenter per4mer study. *PACE*. 2016;39:250–260.
19. Klein N, Klein M, Weglage H, et al. Clinical efficacy of left ventricular pacing vector programmability in cardiac resynchronization therapy defibrillator patients for management of phrenic nerve stimulation and/or elevated left ventricular pacing thresholds: insights from the Efface Phrenic Stim study. *Europace*. 2012;14:826–832.
20. Di Biase L, Gasparini M, Lunati M, et al. Antiarrhythmic effect of reverse ventricular remodeling induced by cardiac resynchronization therapy: the InSync ICD (implantable cardioverter-defibrillator) Italian Registry. *J Am Coll Cardiol*. 2008;52:1442–1449.
21. Behar JM, Bostock J, Zhu Li AP, et al. Cardiac resynchronization therapy delivered via a multipolar left ventricular lead is associated with reduced mortality and elimination of phrenic nerve stimulation: long-term follow-up from a multicenter registry. *J Cardiovasc Electrophysiol*. 2015;26:540–546.