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

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BACKGROUND The Medtronic Attain Performa quadripolar leads provide 16 pacing vectors with steroid on every electrode. This includes a short bipolar configuration between the middle 2 electrodes.

OBJECTIVE A prospective clinical study was conducted to investigate the safety and effectiveness of these new leads in 27 countries.

METHODS Cardiac resynchronization therapy with defibrillator candidates were enrolled (mean age 68 years; 71% men). All implanted subjects were followed at 1, 3, and 6 months postimplant. Pacing capture threshold (PCT) values were measured at each visit. Adverse events were reported upon occurrence.

RESULTS Of 1124 subjects in whom a left ventricular (LV) lead was attempted, 1097 (97.6%) were successfully implanted with an Attain Performa lead. Thirty-six LV lead-related complications were reported (the 6-month LV lead-related complication-free survival rate was 96.9%). Phrenic nerve stimulation (PNS) occurred in 81 subjects (7.2%), with only 3 (0.3%) requiring surgical intervention. At 6 months, the mean PCT at the programmed vector was (1.1 ± 0.8) V and 94.4% of subjects had a PCT of ≤2.5 V. All 16 programming polarities were used in at least 1 patient, and short bipolar configurations were used in 17% of subjects.

CONCLUSION This large multicenter study demonstrated a high success rate for the implantation of Attain Performa quadripolar LV leads with a low complication rate. The PCT was low and stable over time. A low rate of postimplantation PNS was observed, and cases of PNS were readily resolved with reprogramming. Nonstandard vectors were often used for LV pacing.

KEYWORDS Cardiac resynchronization therapy; Quadripolar lead; Defibrillator; Congestive heart failure

ABBREVIATIONS **CRT** = cardiac resynchronization therapy; **CRT-D** = cardiac resynchronization therapy with defibrillator; **LV** = left ventricular; **PCT** = pacing capture threshold; **PNS** = phrenic nerve stimulation; **NYHA** = New York Heart Association

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Introduction

Cardiac resynchronization therapy (CRT) improves heart failure symptoms and mortality in patients with systolic heart failure and a prolonged QRS duration.[1–5] The successful achievement of a stable and effective left ventricular (LV) lead position is critical to the success of CRT.[6–8] An important limiting factor in the implementation of successful CRT are often the variations and limitations of the anatomy of the coronary veins and the position of the cardiac veins relative to the phrenic nerve.[5,9–14] Lead movement after

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implantation and phrenic nerve stimulation (PNS) due to patient posture are challenges that we face. In fact, a 12% rate of CRT failure postoperatively related to either loss of LV capture or PNS has been reported.[15] With a typical unipolar or bipolar LV lead, resolution of these problems often requires surgical intervention with the attendant risks and costs of these procedures.[16] LV leads with more than 2 electrodes have been developed to allow for additional reprogramming options of the pacing vectors to help manage these problems.[10–12,17–20] These leads have been demonstrated to reduce LV lead-related complications at the time of implantation. (Data were orally presented in a late-breaking session at the 2014 European Congress of Cardiology.)

Methods

Device description

The Attain Performa quadripolar leads (Medtronic, Inc, Minneapolis, MN) feature steroid on all 4 LV pacing electrodes with a 21-mm spacing between the first and second electrodes and between the third and fourth electrodes and a 1.3-mm spacing between the second and third electrodes. These leads are intended to be placed into tributaries of the coronary sinus for the provision of CRT. Figure 1 displays the 3 shapes that were developed as a family of Attain Performa LV leads. Model 4298 (Figure 1A) is canted with a compound curve at the distal end; model 4398 (Figure 1B) is the straight lead with tines; and model 4598 (Figure 1C) has an offset S-shaped curve at the distal end. All 3 lead models are constructed with an IS4 connector and have 5.3-F proximal and 3.9-F distal lead body diameters. The leads were implanted with market-released implantation tools and compatible Medtronic Quad CRT-D (cardiac resynchronization therapy with defibrillator) pulse generators (Viva Quad C, Viva Quad XT, Viva Quad S, and Brava Quad), which can be programmed to use any of the 16 different pacing polarities for LV stimulation. The narrow-spaced electrodes, "short bipolar," were designed to reduce the chance of stimulation of the phrenic nerve without compromising pacing capture thresholds (PCTs).[21]

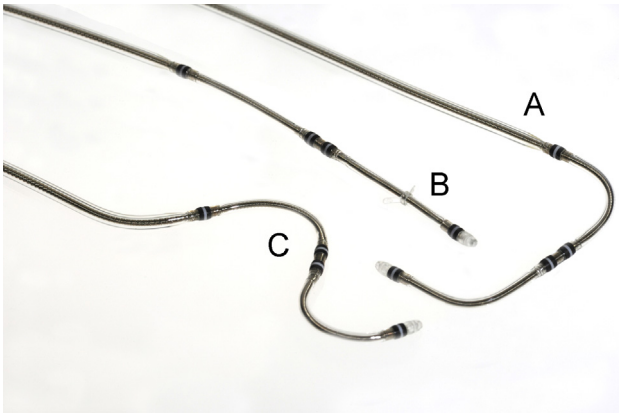

Figure 1 (**A**) Model 4298 canted lead, (**B**) model 4398 straight lead, and (**C**) model 4598 S-shaped lead (Medtronic). The straight lead is tined. In each lead, the interelectrode distance is 21 mm between the first and second electrodes and between the third and fourth electrodes. The interelectrode distance between the second and third electrodes is 1.3 mm.

The VectorExpress feature of the accompanying pulse generator allows for automatic and rapid testing of the PCT and impedance for all possible vectors. This is usually accomplished in less than 3 minutes. There is no negative impact on battery drain associated with VectorExpress because the time required for running VectorExpress is shorter than that required for manual tests. This unique feature also provides relative device longevity estimates for different pacing configurations on the basis of both the threshold and the impedance. The test results may be used to help the clinicians determine which LV lead pacing polarity is most appropriate for their patient, balancing the current drain against the desired anatomic location.

Study design

This was an open-label, prospective, multicenter, clinical trial designed to assess the safety and effectiveness of the Attain Performa lead family (ClinicalTrials.gov ID: NCT01751022). The trial began with the first enrollment in January 2013 and completed enrollment in January 2014. The study was approved by the local governing research authorities (institutional review board, ethics committee, etc). CRT-D implantation candidates were enrolled on the basis of local indications. All subjects gave written informed consent.

All implanted subjects were followed at 1, 3, and 6 months and then every 6 months postimplant. PCT values were measured using either manual or automated testing method. Adverse events were reported upon occurrence and reviewed by an independent physician committee.

Implantation procedure

Any market-released catheter system used for gaining coronary sinus access and compatible with the Attain Performa lead could be used. Coronary sinus venography was required before LV lead placement. The lead choice was determined by the implanting physician on the basis of the visualization of the coronary veins and implanting/lead handling experience, but it was also limited by the availability of various lead models. In geographies where Attain Performa leads were not yet market released, the canted lead was available early in the study and the other 2 models were included later. If the Attain Performa lead was not attempted or could not be implanted, any market-released LV lead could be used.

Follow-up

Lead performance and subject heart failure status were assessed; data were collected at the baseline visit, implant, 1, 3, and 6 months, and then every 6 months until market release in the United States. The study protocol did not require any specific programmed parameters. A substudy was conducted to confirm VectorExpress measurement accuracy against traditional manual tests. Paired

measurements were collected from the first 62 consecutively enrolled subjects.

Study end points

The effectiveness of the lead was evaluated by estimating the probability of a subject having a final programmed LV pacing polarity with a PCT of $\leq$2.5 V with no PNS present at that value. It was assumed that a well-performing LV lead would minimally achieve a success rate greater than 80% (ie, the 95% confidence interval lower bound would be $>$80%). The primary safety end point was Attain Performa LV lead-related complications. Historical clinical studies indicate that the LV lead complication rate postimplantation often ranges between 6% and 8%.[22,23]

Statistical analysis

To evaluate the primary efficacy end point, success was determined for each patient on the basis of the PCT value and PNS threshold (if present) at the 6-month follow-up visit for each subject with a functioning Attain Performa lead. Survival analysis was used to evaluate the primary safety end point as a function of time postimplantation. All subjects who underwent an Attain Performa LV lead implantation attempt were included in the analysis. All reported system or implantation procedure–related events were reviewed by an independent physician panel and classified for relatedness to system component and/or procedure, and severity (complication vs observation). A complication was defined as any adverse event that was resolved by invasive treatment or resulted in patient death or loss of significant functionality of device therapy.

Secondary end points

The occurrence of PNS in all the LV lead pacing polarities at the maximum device output of 8 V was evaluated at implantation as well as at follow-up visits. PNS occurrence rates at the 2 short bpolar configurations were compared with those of the remaining configurations by using the generalized estimating equation models to account for within-subject correlations. At the 6-month visit, the PNS threshold was measured when PNS was detected at 8 V. Implantation success rate, implantation procedure duration, and lead handling characteristics were summarized using descriptive statistics. Device system components and/or implantation procedure–related adverse events were summarized as observations vs complications and the event type by using the Medical Dictionary for Regulatory Activities. Clinical outcomes including death, heart failure–related hospitalization, New York Heart Association (NYHA) functional class, and patient global assessment were obtained.

Results

Patient population

A total of 126 centers in 27 countries from North America, Europe, Australia, Asia, the Middle East, Africa, and South America enrolled a total of 1201 patients. Of those, 46 patients did not undergo an implantation procedure and were subsequently excluded from the study. Of the 1155 subjects who underwent implantation procedures, 1124 attempted Attain Performa leads, and 1097 of the 1124 subjects (97.6%) were successfully implanted with an Attain Performa lead. The distribution of enrolled subjects is shown in Figure 2. As of May 2014, Attain Performa lead recipients were followed for an average of 6.6 $\pm$ 2.8 months. The mean age of patients who underwent implantation procedures was 68 $\pm$ 11 years, 71% were men, and 74% were whites. Most patients were either NYHA class II (27%) or NYHA class III (68%). The mean LV ejection fraction was 27% $\pm$ 7%. The mean QRS duration was 156 $\pm$ 23 ms. Left bundle branch block was reported in 72% of patients. There were no significant differences in these clinical characteristics among patients receiving different lead models.

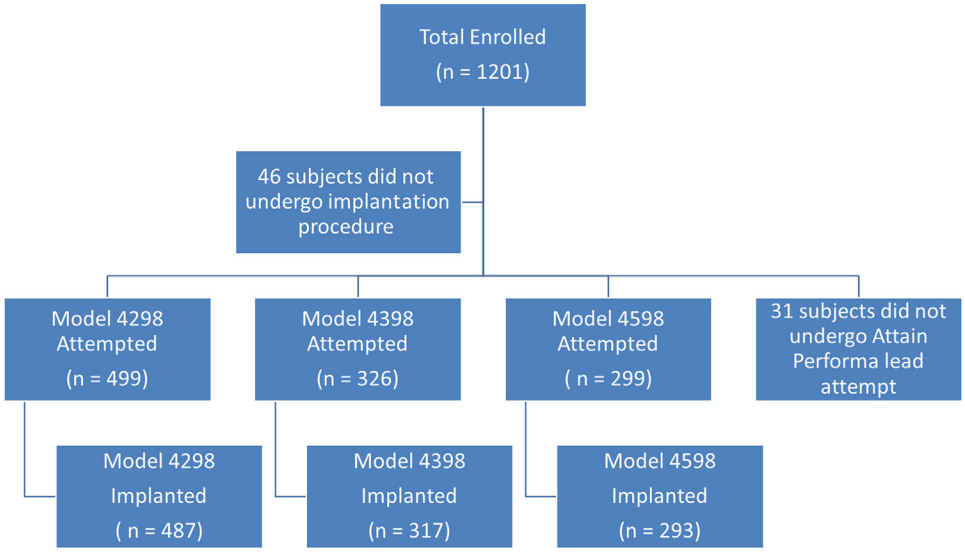

Figure 2 Enrollment flowchart.

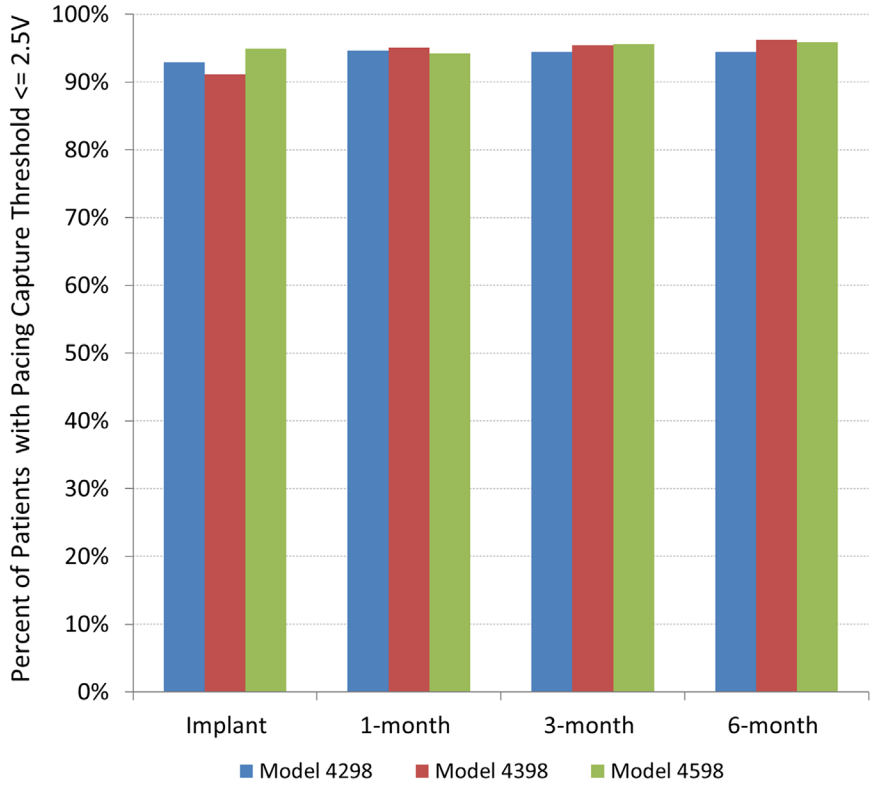

Figure 3 Percentage of patients with a PCT of ≤2.5 V for each lead.

Lead handling

Implanting physicians rated the LV lead handling as acceptable in 98.8% of the cases on the basis of a questionnaire completed after each implantation procedure. LV lead implant times averaged 14 ± 19 minutes.

Electrical performance

The overall percentage of patients with a PCT of ≤2.5 V without PNS at the stimulation voltage was 95.3%, and it was similar for all 3 leads (Figure 3). The mean PCT at the final programmed vector was (1.1 ± 0.8) V at the 6-month postimplantation visit. Table 1 presents the mean PCTs over time. A wide array of the final programmed vectors was chosen (Table 2). The majority of the final chosen vectors were those that were not previously available with a unipolar or a standard Medtronic bipolar lead system. Specifically at 6 months, 17% subjects were programmed to LV1 to RV coil, 18% were programmed to LV1 to LV2, 7% were programmed to LV2 to RV coil, 4% were programmed to LV2 to LV1, and 54% used other pacing polarities. The distribution of PCT and mean PNS threshold (if present) by polarity at the 6-month visit is also given in Table 2. There was

no difference in PCT between patients with ischemic cardiomyopathy and those with non–ischemic cardiomyopathy ($P = .4$).

Figure 4 displays the results of the high output pacing test (ie, PNS at 8-V output) at the 6-month visit. The occurrence of PNS for the 2 short bipolar vectors was significantly lower than that for the other pacing vectors (64% relative reduction; $P < .0001$, generalized estimating equation model estimate).

Safety performance and adverse events

The primary safety end point, freedom from lead-related complication, was 97% at both 3 and 6 months (95%

Table 1 Mean pacing capture thresholds (volt) at the final programmed LV polarities at 0.5 ms

	Model 4298		Model 4398		Model 4598		Combined	
Visit	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Implantation	482	1.2 ± 0.9	316	1.3 ± 1.0	293	1.1 ± 0.8	1091	1.2 ± 0.9
Month 1	468	1.1 ± 0.8	305	1.2 ± 0.8	277	1.1 ± 0.8	1050	1.1 ± 0.8
Month 3	429	1.1 ± 0.7	287	1.2 ± 0.8	271	1.1 ± 0.7	987	1.1 ± 0.8
Month 6	429	1.1 ± 0.7	266	1.1 ± 0.8	265	1.1± 0.8	960	1.1 ± 0.8

Table 2 Attain Performa lead pacing capture thresholds at each polarity and final configuration

	Stimulation threshold (V) (pulse width = 0.5 ms)				PNS threshold (V)*		Final configuration
	Implantation		6 mo		6 mo		6 mo
Polarity	n	Mean ± SD	n	Mean ± SD	n*	Mean ± SD	%
LV1 to RV coil	1066	1.2 ± 1.2	946	1.0 ± 0.9	413	3.7 ± 2.3	16.6
LV1 to LV2	1044	1.6 ± 1.4	934	1.4 ± 1.1	368	4.1 ± 2.2	17.7
LV1 to LV3	1045	1.7 ± 1.4	937	1.4 ± 1.0	369	4.1 ± 2.2	4.4
LV1 to LV4	1032	1.7 ± 1.4	936	1.4 ± 1.1	342	4.0 ± 2.3	5.2
LV2 to RV coil	1033	1.4 ± 1.3	908	1.3 ± 1.2	305	4.0 ± 2.3	7.3
LV2 to LV1	999	2.0 ± 1.4	904	1.7 ± 1.3	305	4.5 ± 2.0	4.0
LV2 to LV3	940	1.7 ± 1.5	820	1.5 ± 1.3	133	4.9 ± 2.0	12.7
LV2 to LV4	972	1.9 ± 1.4	876	1.8 ± 1.4	241	4.3 ± 2.0	4.8
LV3 to RV coil	1008	1.5 ± 1.3	888	1.5 ± 1.3	282	4.0 ± 2.3	4.8
LV3 to LV1	988	2.1 ± 1.4	894	1.9 ± 1.3	312	4.8 ± 2.1	2.0
LV3 to LV2	912	1.9 ± 1.5	775	1.6 ± 1.4	118	4.9 ± 2.0	4.3
LV3 to LV4	960	2.1 ± 1.5	842	1.9 ± 1.4	225	4.3 ± 2.1	6.6
LV4 to RV coil	803	2.4 ± 1.7	683	2.1 ± 1.5	192	4.6 ± 2.3	6.7
LV4 to LV1	918	2.7 ± 1.5	860	2.4 ± 1.3	244	5.3 ± 2.0	1.7
LV4 to LV2	857	2.8 ± 1.6	750	2.6 ± 1.4	191	5.1 ± 2.0	0.2
LV4 to LV3	818	2.8 ± 1.6	731	2.6 ± 1.5	183	4.9 ± 2.0	1.2

PNS = phrenic nerve stimulation.

*Patients with PNS at 8-V output were further tested for PNS thresholds.

confidence interval 96%–98%) and was similar for all 3 of the lead models (Figure 5).

No unanticipated adverse events were reported. A total of 36 LV lead-related complications (3%) were reported among the 1124 subjects who underwent an Attain Performa lead implantation procedure. Lead dislodgement at the last clinic visit was low (1.4%) in this study. It is notable that the straight lead had a relatively lower dislodgement rate compared to the other leads (0.3% in subjects with model 4398 lead vs 2.0% in subjects with model 4298 lead and 1.7% in subjects with model 4598 lead). The occurrence of PNS was 7.2%; 97% of complications were resolved without surgical intervention. The only 3 PNS complications (rate = 0.3%) were all resolved by replacing the LV lead with

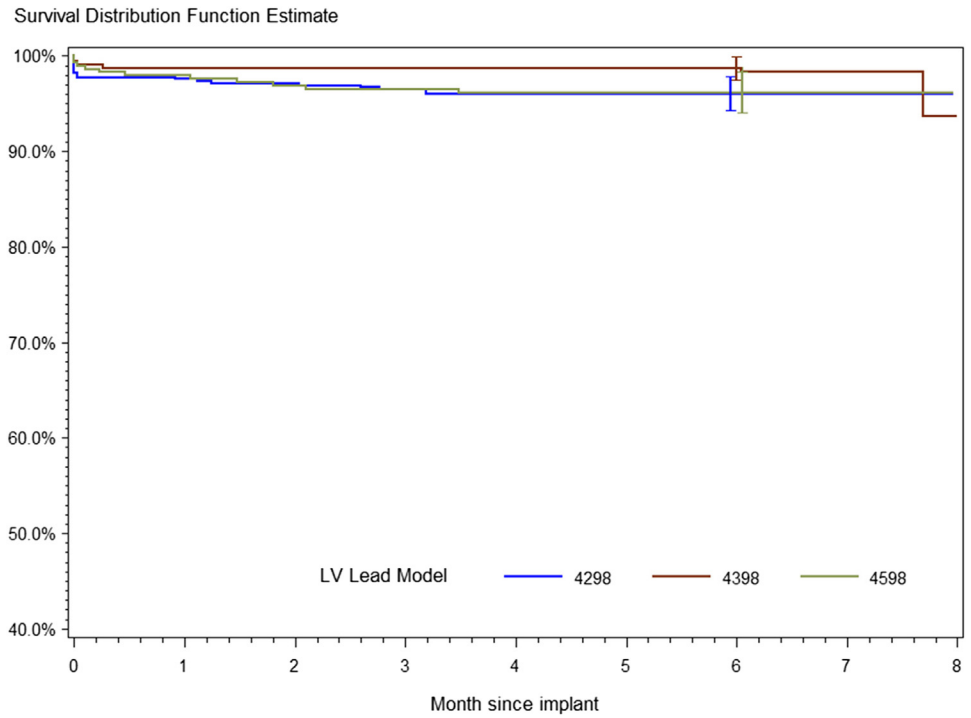

Figure 4 Graph of the freedom from a left ventricular (LV) lead–related complication.

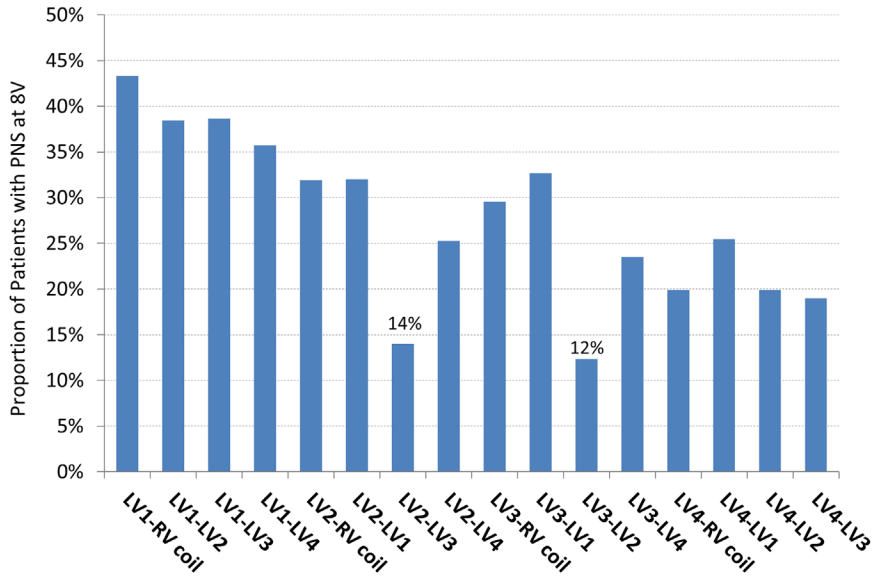

Figure 5 Rate of phrenic nerve stimulation (PNS) with pacing at 8 V is significantly less when the short bipolar electrodes are used. LV = left ventricular; RV = right ventricular.

another Attain Performa lead. The LV lead-related adverse events and observations are summarized in Table 3.

VectorExpress

PCT values were measured at the implantation/prehospital discharge visit after a successful Attain Peforma LV lead implantation. VectorExpress produced results for 790 of 992 possible vectors (80%). The most common reasons why VectorExpress did not provide results for some vectors were a high PCT, short or indistinguishable atrioventricular intervals, competing rhythms, or detection of possible anodal stimulation. Correlation between VectorExpress and manual testing was high ($r = 0.94$; $P < .0001$), with an estimated bias (manual − VectorExpress) of 0.03 V.

Clinical outcome

The clinical composite score method of Packer[24] was adopted to assess CRT response rate at the 6-month visit. Patients were only considered to have improved if, at the 6-month postimplantation visit, they were alive, had not been hospitalized, and experienced at least 1 NYHA functional class improvement or reported favorable response in the patient global assessment question. Patients are considered worse if the patient experienced any of the following events: death, heart failure–related hospitalization, worsening of NYHA class, and/or global assessment by the 6-month visit. Patients are considered unchanged if they were neither improved nor worsened. We observed 80.4% of patients improved, 14.1% of patients worsened, and 5.5% did not change.

There were a total of 54 deaths (4.5%) during the study. Of those deaths, 11 were classified as sudden cardiac (20%), 14 (26%) as non–sudden cardiac, and 24 (44%) as non-cardiac. In 6 subjects, there was insufficient information for classification. Three deaths occurred before implantation procedures, 38 occurred in the first 6 months, and 13 occurred after the 6-month visit.

Discussion

The ultimate goal of LV lead placement is to ensure stable LV stimulation at a desired pacing site. This could be hindered by loss of LV capture in more than 10% of patients because of LV dislodgement, PNS, or high LV threshold.[12–18,20,23,25,26] Achieving a low LV PCT at implantation reduces the likelihood of PNS and increases device longevity. The PCT of these leads were low, with an average of (1.2 ± 0.9) V at implantation and (1.1 ± 0.8) V at 6 months at the final programmed vector. The mean PCT ranged from 1.0 to 2.6 V for all 16 configurations at the 6-month visit. This result compares favorably to other unipolar and bipolar leads[29,30] and appears to be superior to the other commercially available quadripolar leads[31] where nonstandard vectors provide stimulation thresholds greater than 3 V on average. One distinctive construct of the Attain Performa lead is that this lead has a steroid-eluting monolithic controlled release device sleeve/ring at each of the 4 electrodes. While it is well established that the addition of steroid to endocardial leads significantly improves PCTs,[32] the same effect was never previously verified for leads placed in the tributaries of the coronary sinus. The data presented here, as compared with the data on the other market-released quadripolar leads, strongly suggest that steroid elution may improve the performance of all electrodes.[27]

With a low PCT, clinicians targeted more specific pacing sites in proximal or basal regions that are associated with enhanced patient outcomes as compared with apical pacing sites, without compromising battery longevity. In addition, the availability of VectorExpress allowed the opportunity to evaluate 16 pacing vectors and choose a particular vector that

Table 3 Attain Performa lead–related adverse events

Event	Model 4298 (n = 499)	Model 4398 (n = 326)	Model 4598 (n = 299)	Overall (n = 1124)
Complications				
Deep vein thrombosis	0/0	1/1	2/2	3/3
Device capturing issue*	2/2	1/1	0/0	3/3
Device connection issue	3/3	1/1	2/2	6/6
Lead dislodgement	10/10	1/1	5/5	16/16
Increased threshold	2/2	0/0	0/0	2/2
Extracardiac stimulation	1/1	2/2	0/0	3/3
Sepsis	1/1	0/0	0/0	1/1
Subclavian vein thrombosis	0/0	0/0	2/2	2/2
Total	19/19	6/6	11/11	36/36
Observations				
Cardiac vein dissection	0/0	0/0	1/1	1/1
Deep vein thrombosis	2/2	1/1	2/2	5/5
Device damage	0/0	1/1	0/0	1/1
Impedance issue	0/0	1/1	0/0	1/1
Increased threshold	2/2	2/2	1/1	5/5
Extracardiac stimulation	36/32	35/29	21/20	92/81
Dyspnea	1/1	0/0	0/0	1/1
Superior vena cava stenosis	1/1	0/0	0/0	1/1
Ventricular dyssynchrony	1/1	0/0	0/0	1/1
Total	43/38	40/32	25/23	108/93

*The numbers represent the number of events and the number of patients

would be best for patients in a reasonable time during a clinical visit.

During this clinical study, nonstandard vectors were programmed more often than previously published reports on quadripolar leads.[27] We speculate that the high usage of nonstandard vectors was due to the fact that most LV polarities achieved low PCTs, and the unique short bipolar configurations avoid PNS symptoms successfully. The PNS rates elicited by the pacing test at 8 V (Figure 4) were lower, and the PNS − PCT differences (Table 2) were wider at 6 months in the short bipolar configurations compared to other pacing vectors.

Consistent with these findings and previous animal and acute human studies,[21,28] we observed a low incidence of PNS symptoms (7%; Table 3). Biffi and colleagues[28] reported that in a group of 1307 patients with bipolar and unipolar leads the incidence of PNS was 12.9%, while Tomassoni et al[27] reported a similar PNS event rate of 13.5% at 3-month follow-up by using another lead. Thus, Attain Performa leads enhance PNS management at no compromise with the LV capture threshold.

The overall implantation success with this system was also favorable. The 97.6% successful implantation rate compares favorably with previous studies, such as CARE-HF (89%),[29] the combined MIRACLE, MIRACLE ICD, and InSync II (92%),[30] Starfix (94%),[31] and EASYTRAK (88%).[32,33] Implantation times have not been widely reported for previous leads, but our results of 13.9 ± 19 minutes compare favorably with the results reported by others.[27,31,34]

Study limitations

This is an observational study that reports the results of these leads alone. It is neither a randomized study comparing results with those of unipolar or bipolar LV leads nor did it evaluate physician's choice of different models of the lead family. However, the study performance criteria were determined on the basis of the performance of previous market-released LV leads.

Conclusion

The Attain Performa LV leads, coupled with Quad CRT-D devices, were demonstrated to be safe and effective. The suite of technologies has the potential to enhance CRT delivery. It includes 16 selectable pacing vectors that provide more options for noninvasive postoperative treatment; a pair of short bipolar configurations that reduce the incidence of PNS symptoms; steroid elution on every electrode that achieves low pacing thresholds for all pacing vectors during both acute and chronic phases; and the VectorExpress software that provide clinicians rapid and accurate measurements for all LV pacing configurations, allowing for a more efficient follow-up. This combination allows physicians to deliver CRT while potentially increasing the battery life and reducing the risk of reoperation for PNS.

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Appendix

Supplementary data

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.hrthm.2014.12.019.

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CLINICAL PERSPECTIVES

By using this steroid-eluding quadripolar lead, we were able to achieve successful left ventricular pacing while maintaining excellent pacing capture thresholds. This is in contrast to the existing quadripolar leads that demonstrate high thresholds on the third and fourth electrodes. We also demonstrated that the use of the narrowly spaced pair of electrodes was associated with a remarkable avoidance of phrenic nerve stimulation. By using this novel technology, physicians should be able to accomplish efficacious cardiac resynchronization therapy without sacrificing thresholds and worsening longevity of the pulse generator and without sacrificing lead position for the sake of lead stability. Translation of these results into clinical practice should be easy since the leads are now available in most geographies.