Cost-Effectiveness Analysis of Quadripolar Versus Bipolar Left Ventricular Leads for Cardiac Resynchronization Defibrillator Therapy in a Large, Multicenter UK Registry

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ABSTRACT

OBJECTIVES The objective of this study was to evaluate the cost-effectiveness of quadripolar versus bipolar cardiac resynchronization defibrillator therapy systems.

BACKGROUND Quadripolar left ventricular (LV) leads for cardiac resynchronization therapy reduce phrenic nerve stimulation (PNS) and are associated with reduced mortality compared with bipolar leads.

METHODS A total of 606 patients received implants at 3 UK centers (319 Q, 287 B), between 2009 and 2014; mean follow-up was 879 days. Rehospitalization episodes were costed at National Health Service national tariff rates, and EQ-5D utility values were applied to heart failure admissions, acute coronary syndrome events, and mortality data, which were used to estimate quality-adjusted life-year differences over 5 years.

RESULTS Groups were matched with regard to age and sex. Patients with quadripolar implants had a lower rate of hospitalization than those with bipolar implants (42.6% vs. 55.4%; p = 0.002). This was primarily driven by fewer hospital readmissions for heart failure (51 [16%] vs. 75 [26.1%], respectively, for quadripolar vs. bipolar implants; p = 0.003) and generator replacements (9 [2.8%] vs. 19 [6.6%], respectively; p = 0.03). Hospitalization for suspected acute coronary syndrome, arrhythmia, device explantation, and lead revisions were similar. This lower health-care utilization cost translated into a cumulative 5-year cost saving for patients with quadripolar systems where the acquisition cost was < £932 (US $1,398) compared with bipolar systems. Probabilistic sensitivity analysis results mirrored the deterministic calculations. For the average additional price of £1,200 (US $1,800) over a bipolar system, the incremental cost-effective ratio was £3,692 per quality-adjusted life-year gained ($5,538), far below the usual willingness-to-pay threshold of £20,000 (US $30,000).

CONCLUSIONS In a UK health-care 5-year time horizon, the additional purchase price of quadripolar cardiac resynchronization defibrillator therapy systems is largely offset by lower subsequent event costs up to 5 years after implantation, which makes this technology highly cost-effective compared with bipolar systems. (J Am Coll Cardiol EP 2016;–:–) © 2016 by the American College of Cardiology Foundation.
Cardiac resynchronization therapy (CRT) is an efficacious and cost-effective (1) treatment for patients with symptomatic heart failure with poor left ventricular (LV) function and prolonged QRS duration (2-4). Despite improvements in implantation delivery equipment and accumulation of user experience over the past 2 decades, approximately 30% of patients do not derive symptomatic benefit (5,6). Post-implantation complications such as high capture thresholds, phrenic nerve stimulation (PNS), lead displacement, and infection reduce the effectiveness of this therapy (7-10). The recent introduction of multipolar (quadripolar) LV leads has demonstrated a reduction in PNS through more proximal pole reprogramming, the presence of sustained lower capture thresholds, and easy deliverability (11).

However, new technology is usually provided at a higher purchase price than the conventional standard of care, which means that cost-effectiveness and affordability must be considered (12). Furthermore, the need for £22 billion in savings by 2020 in the United Kingdom (13) and an increased focus on efficiency as a result (14) further highlight the importance of cost-effective care. Multiple small clinical studies have demonstrated the clinical effectiveness of quadripolar leads at implantation and early follow-up (8,15). Implant and 6-month follow-up data recently presented from the randomized MORE-CRT (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges) trial (16) have confirmed the superioritity of quadripolar leads, mainly from a reduction in intraoperative complications. We have previously demonstrated elimination of PNS and an associated lower all-cause mortality in patients implanted with a quadripolar lead in a large multicenter UK registry (17) (Online Figure 1).

We set out to assess the cost-effectiveness of quadripolar LV leads compared with bipolar LV leads in patients implanted with a cardiac resynchronization defibrillator therapy device (CRTD) within our previously published registry. We analyzed longer-term health-care utilization costs in terms of hospitalizations that occurred within the 5-year follow-up period to investigate whether the higher purchase price of this new technology was offset by expected reductions in cost arising from a reduction in hospitalizations. We also used mortality, acute coronary syndrome, and heart failure hospitalization data to estimate quality-adjusted life-year (QALY) differences.

METHODS

Clinical data were taken from a registry of patients with conventional CRT criteria who received device implants at 3 UK centers (Guy’s and St Thomas’ NHS Foundation Trust; John Radcliffe Hospital, Oxford University Hospital NHS Foundation Trust; and Great Western Hospital, Swindon) between January 2009 and January 2014. All patients provided fully informed consent. We have previously published the results of 5-year follow-up of patients, in which we compared patients with CRTD systems with a quadripolar versus a bipolar LV lead in terms of PNS, lead complications, and all-cause mortality (17).

For the purposes of the current study, hospitalization episodes for each patient in the clinical registry were reviewed and assigned to the following categories based on diagnosis: acute coronary syndrome (ACS), arrhythmia, heart failure hospitalizations, infection requiring system explantation and reimplantation, generator replacement, and revision of any lead. These were compared between patients implanted with a CRTD incorporating a quadripolar LV lead versus those with a bipolar LV lead. Quadripolar leads in the current analysis were exclusively the Quartet lead (St. Jude Medical, Sylmar, California). Only individuals with complete hospitalization data that included coding of the cause of hospitalization were included; as such, the cohort comprised 606 patients (quadripolar, n = 319; bipolar, n = 287).

We performed an economic analysis of the registry data using all hospitalizations that occurred during the follow-up period. The rates of hospitalizations in each year from implantation were multiplied by the national tariff that pertained to the cause of
hospitalization (Table 1). There was no extrapolation of data or event rates beyond the 5-year follow-up after implantation. Event rates were those that were observed to have occurred in each year; we did not derive transition probabilities that could be used for a Markov model. All events were counted, and some events occurred more than once in individual patients. A probabilistic sensitivity analysis was also undertaken to help understand the impact of parameter uncertainty and determine the probability that quadripolar CRTD was cost-effective. Probabilistic analysis was conducted by inputting data as probability (beta) distributions rather than point estimates and randomly sampling 1,000 values from these distributions. This was performed for all hospitalization episodes in addition to mortality data from our previous work (17). Comparative purchase costs were estimated between the quadripolar Quartet leads (St. Jude Medical) and the mean purchase cost of bipolar leads used in the clinical registry (QuickFlex, St. Jude Medical; AttainAbility, Medtronic; Easytrak, Boston Scientific). A National Health Service (NHS, the UK health system) perspective was used, which means that wider societal impact was not considered. Costs and effects beyond year 1 were discounted at 3.5%, following the methodology recommended by the UK’s National Institute of Health and Care Excellence (NICE) (20). A model diagram (Figure 1) demonstrates the differing probabilities of hospitalization event rates (per cause) for year 1 post-implantation in those with quadripolar and bipolar systems. The same approach was used for years 2 to 5 in the analysis, and rates for all years are shown in Online Table 1.

**COSTS.** National tariff “enhanced tariff option” prices for 2015 to 2016 (18) were applied to ACS hospitalization, arrhythmia hospitalization, heart failure hospitalization, and lead revision procedures. The base tariff price was multiplied by the local cost factor (market forces factor) for each NHS hospital that implants CRT devices, and the mean of these values was used in the model. Table 1 shows the mean unit cost data used in the calculations per hospitalization, including local cost factors. Online Table 2 shows the equivalent costs in US dollars using a simple conversion of £1 = $1.50. Where there were different tariff values for elective/nonelective procedures and different values for complication/comorbidity splits, averages weighted by the number of admissions for each were calculated. Costs for CRTD implantation, device removal and reimplantation for wound infection, and CRT generator replacement were taken from the data used to inform the economic evaluation that underpinned NICE’s 2014 Technology Appraisal Guidance (19). The additional purchase cost of quadripolar technology was estimated to be £1,200 ($1,800) for the base-case analysis (market estimate, St. Jude Medical) but varied between zero and £2,400 ($3,600) to assess sensitivity, because acquisition price may vary according to local procurement arrangements. Quadripolar device removal and reimplantation for infection was uplifted by the additional acquisition cost for the quadripolar device, on the assumption that the same type of device would be reimplanted. Quadripolar generator replacement was costed at bipolar cost plus 0.67 of additional quadripolar system costs. Quadripolar lead revision was costed at bipolar cost plus 0.33 of additional quadripolar system costs.

**QUALITY-ADJUSTED LIFE YEARS.** The use of QALYs allows clinical effectiveness to be expressed in a common unit, to which a cost can be applied to estimate the value of health-care interventions. The EQ-5D questionnaire is commonly used to determine the quality-of-life utility values that can be translated into QALYs (21). Hawkins et al. (22) discussed this approach in the context of cardiac interventions, and it is a standard part of NICE’s methodology (20).

### Table 1: National Tariff Tables: Hospitalization Pricing by Coding Category

| Cost Item                  | Value ($) | Description                                      | Source (Ref. #) |
|---------------------------|-----------|--------------------------------------------------|-----------------|
| ACS hospitalization       | 3,421     | EB01Z (actual or suspected MI), nonelective       | ETO 2015-2016 (18) |
| Arrhythmia hospitalization| 887       | Activity-weighted average of EBO7H (arrhythmia or conduction disorders with CC) and EBO7I (arrhythmia or conduction disorders without CC) | ETO 2015-2016 (18) |
| Heart failure admission   | 2,756     | Activity-weighted average of EBO3H (heart failure or shock with CC) and EBO3I (heart failure or shock without CC) | ETO 2015-2016 (18) |
| Lead revision procedure   | 2,952     | Activity-weighted average of elective/nonelective HRG EA932 (pacemaker procedure without generator implant; includes removal and reimplantation of cardiac pacemaker system) | ETO 2015-2016 (18) |
| Bipolar CRTD device       | 12,615    | NICE technology appraisal (19)                   |                 |
| Additional cost of         | 1,200     | Base-case value, varied between £0 and £2,400 in sensitivity analysis | Market estimate 2015 |
| quadripolar CRTD device    |           |                                                  |                 |
| Device removal and         | 23,506    | Base value for bipolar device                    | NICE technology appraisal 2014 (19) |
| reimplantation for         |           |                                                  |                 |
| infection                  |           |                                                  |                 |
| CRTD generator revision    | 15,990    | Base value for bipolar device                    | NICE technology appraisal 2014 (19) |

See Online Figure 1 for equivalent cost in US dollars.

ACS = acute coronary syndrome; CC = complications and comorbidities; CRTD = cardiac resynchronization defibrillator therapy device; ETO = extended tariff option (the national tariff scheme used by most English trusts in 2015-2016); MI = myocardial infarction; NICE = National Institute for Health and Care Excellence.
The incremental cost-effectiveness ratio (ICER) is obtained by dividing the additional cost of using the new device by the incremental QALYs gained and can be used to estimate a value for decision-making purposes. NICE’s methods guide (20) suggests an ICER of £20,000 ($30,000) to £30,000 ($45,000) is the range in which cost-effectiveness is acceptable in terms of effective use of NHS resources; therefore, this was the benchmark used to assess the results of the current study.

Only the mortality difference used in our previous report (17), utility loss attributable to ACS events, and utility loss attributable to heart failure hospitalizations were used to assess QALY differences between bipolar and quadripolar devices, similar to the methods used in the economic analysis that informed NICE’s recent technology appraisal of implantable cardioverter-defibrillators and CRT (19). A baseline EQ-5D utility of 0.8808 was used for a patient with heart failure and a CRT device (range: 0.85 to 0.903), with utility loss because of death being taken as a loss from this value to zero. The utility loss associated with a heart failure admission was calculated, from the work of Swinburn et al. (23) and Lewis et al. (24), to be 0.1197, persisting for 18 days (average length of stay plus 7 days post-discharge). The utility loss associated with ACS events was calculated, from the work of Lewis et al. (24) and Matza et al. (25), to be 0.1035, persisting for 10.4 days (average length of stay plus 7 days post-discharge). A range of input parameters were varied by ±95% confidence interval to show the impact of each on the base-case ICER, and the results are shown on a tornado plot (Figure 2).

**STATISTICAL ANALYSIS.** Continuous variables are expressed as mean ± SD. Comparisons were made with a Student t test. Categorical data were expressed as an absolute number of occurrences and associated frequency (%); analysis was performed with a chi-squared test. A probability value of <0.05 was considered significant. Statistical analysis was performed with the Statistics Package for the Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, Illinois). Economic analysis was undertaken in Microsoft Excel.
RESULTS

A total of 606 patients were included in this analysis and were matched with regard to age and sex. Patients in the bipolar group had a higher prevalence of ischemic heart disease (quadripolar vs. bipolar: 181 [56.7%] vs. 190 [66.2%]; \( p = 0.02 \)), and fewer were in sinus rhythm (quadripolar vs. bipolar: 303 [95.0%] vs. 48 [83.3%]; \( p < 0.001 \)) before implantation. Mean QRS duration was similar between groups (159 ± 6.2 ms vs. 160 ± 5.1 ms, quadripolar vs. bipolar, respectively; \( p = 0.07 \)), as was the proportion of patients in New York Heart Association functional class III (183 [76.9%] vs. 145 [72.1%], quadripolar vs. bipolar, respectively; \( p = 0.10 \)). Mean percentage of biventricular pacing throughout the follow-up period was similar between groups (Q: 94.6 ± 1.6% vs. B: 94.4 ± 1.5%, \( p = 0.11 \)). Length of stay after implantation was similar between groups, irrespective of whether they were elective admissions (1.2 ± 2.3 days vs. 1.2 ± 1.6 days, quadripolar vs. bipolar, respectively; \( p = 1.00 \)) or existing inpatients (5.0 ± 8.5 days vs. 5.2 ± 7.2 days, quadripolar vs. bipolar, respectively; \( p = 0.76 \)), as shown in Table 2.

Patients implanted with a quadripolar lead had a significantly lower absolute number of all-cause hospitalizations (quadripolar: 191 admissions among 309 patients; bipolar: 225 admissions among 287 patients; \( p < 0.001 \)), as shown in Table 3. Moreover, the proportion of patients hospitalized at least once was also significantly lower in those implanted with a quadripolar compared with a bipolar lead (42.6% vs. 55.4%, respectively; \( p = 0.002 \)), as shown in Table 4. This was primarily driven by a significantly lower number of hospitalizations for heart failure (51 admissions among 309 patients with a quadripolar device vs. 75 among 287 patients with a bipolar device; \( p = 0.003 \)) and CRTD generator replacement (9 admissions among 309 patients vs. 19 among 287 patients, respectively; \( p = 0.03 \)). Hospitalizations for suspected ACS, arrhythmia, device explantation, and

### Table 2 Demographic Data

|                      | Quadripolar (n = 319) | Bipolar (n = 287) | p Value |
|----------------------|-----------------------|-------------------|---------|
| Age (yrs)            | 70.4 ± 11             | 68.7 ± 10         | 0.06    |
| Female               | 50 (15.7)             | 48 (16.7)         | 0.74    |
| Ischemic heart disease| 181 (56.7)           | 190 (66.2)        | 0.02    |
| Sinus rhythm         | 303 (95.0)            | 48 (83.3)         | <0.001  |
| QRS duration (ms)    | 159 ± 6.2 (n = 238)   | 160 ± 5.1 (n = 201)| 0.07    |
| NYHA functional class III symptoms | 183 (76.9) (n = 238) | 145 (72.1) (n = 201) | 0.10    |
| Mobitz II/complete heart block | 9 (2.8) | 14 (4.9) | 0.21    |
| % Biventricular pacing| 94.6 ± 1.6           | 94.4 ± 1.5        | 0.11    |
| LV lead upgrade      | 8 (2.5)               | 61 (21.3)         | <0.001  |
| Length of stay post-implantation days (elective) | 1.2 ± 2.3 | 1.2 ± 1.6 | 1.00    |
| Length of stay post-implantation days (inpatient) | 5.0 ± 8.5 | 5.2 ± 7.2 | 0.76    |

Values are mean ± SD or n (%).
LV = left ventricular; NYHA = New York Heart Association.
TABLE 4

| Event                                      | Quadripolar (n = 319) | Bipolar (n = 287) | Odds Ratio (95% CI) | p Value |
|--------------------------------------------|----------------------|-------------------|---------------------|---------|
| ACS                                        | 35 (11.5%)           | 21 (7.3%)         | 1.40 (0.57-3.46)    | 0.34    |
| Arrhythmia                                 | 59 (18.6%)           | 65 (22.7%)        | 0.75 (0.47-1.21)    | 0.24    |
| Heart failure                              | 51 (16.1%)           | 75 (26.1%)        | 0.69 (0.42-1.12)    | 0.18    |
| System explantation and reimplantation     | 5 (1.6%)             | 6 (2.1%)          | 0.75 (0.23-2.47)    | 0.83    |
| Generator replacement                      | 8 (2.5%)             | 19 (6.6%)         | 0.36 (0.15-0.84)    | 0.02    |
| Lead revision (RA/RV/LV)                   | 30 (9.5%)            | 32 (11.2%)        | 0.83 (0.49-1.40)    | 0.50    |
| Hospitalization (any cause)                | 136 (42.6%)          | 159 (55.4%)       | 0.59 (0.43-0.83)    | 0.002   |

Values are n (%). CI = confidence interval; other abbreviations as in Table 3.
4. The calculated cost-effectiveness using real-world clinical data (deterministic model) was closely mirrored by the probabilistic sensitivity analysis, which reaffirms confidence in the results.

Multipolar LV leads for CRT delivery have demonstrated high implant success, good capture thresholds at implantation and follow-up, and a low rate of lead displacement (11,26). Rates of intra-procedural lead complications appear lower than with conventional bipolar leads (27). Reduction or even elimination in PNS during medium-term follow-up provides invaluable utility in CRT delivery (9,15). We have recently shown a reduction in all-cause mortality associated with quadripolar leads compared with a bipolar lead (17). Furthermore, rates of reintervention for lead repositioning were lower in those implanted with a quadripolar compared with a bipolar lead (2% vs. 5.2%, p = 0.03), and the radiation dose during implantation was almost half (1,028 cGy cm² vs. 1,950 cGy cm²; p < 0.001).

The lower rates of hospitalization associated with a quadripolar lead in the current study could be driven by the improved efficacy in CRT delivery (attributable to PNS reduction and fewer reinterventions for lead displacement). Our previous study (17) also demonstrated lower implantation capture energy with quadripolar than with bipolar leads (0.95 μJ vs. 1.08 μJ; p = 0.003). Pacing systems consistently delivering higher-output voltages to capture the LV will have a reduced longevity (28), and this could explain the current findings of a

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significantly lower number of generator replacements among those implanted with a quadrripolar system. This might be of significant clinical importance given the higher prevalence of device-related infections after generator replacement (29), which might allow leads to be implanted more distally in posterolateral or lateral veins for stability purposes (8,17), with the ability to stimulate the LV more basally from the proximal poles, which in turn could contribute to more optimal CRT delivery and could result in fewer heart failure hospitalizations and reduced mortality.

**COMPARISON WITH PREVIOUS STUDIES.** Forleo et al. (32) have reported reduced rates of heart failure hospitalizations and LV lead revision among patients implanted with a quadrripolar lead in a single-center Italian registry (events per patient per year: 0.15 vs. 0.32, quadrripolar vs. bipolar; p = 0.04). Non-heart failure hospitalization rates were similar among groups. This study demonstrated lower health-care utilization costs associated with the quadrripolar group (434 euros/patient-year vs. 1136 euros/patient-year; p = 0.02). However, the study by Forleo et al. (32) used Italian cost data that cannot be directly translated into the UK health-care setting, used only single-center data, had a much shorter follow-up period, included a smaller number of patients (193 vs. 606), and did not include as wide a range of clinical events in the follow-up costing. In the present study, the time to each event was calculated individually from the time of original implantation. In addition, the present study recorded and coded for all relevant acute and elective hospitalizations, not just heart failure and LV lead revisions, including admissions with ACS, arrhythmia, generator replacements, device extractions/reimplantation, and all right atrial and right ventricular lead revisions. Our calculated cumulative 5-year cost analysis was paralleled by the 5-year follow-up data, which provides confidence in the clinical relevance and accuracy of this study.

Furthermore, we undertook a probabilistic sensitivity analysis similar to that by Forleo et al. (32), and the results for the base-case ICER closely mirrored the value calculated in the deterministic model. The only other contemporary UK-specific cost-effectiveness analysis was published recently by NICE (33). Recommendations made by NICE in a 2014 review of CRT and implantable defibrillators
The results showed ICERs for quadripolar systems of up to £20,288 ($30,432) per QALY gained. Had data been available to include QALY adjustments for arrhythmia admissions, device removal and reimplantation for wound infection, generator changes, and lead revisions, it is likely that the ICERs would have been lower, because the rates of these events favor the quadripolar system. This analysis is therefore conservative with respect to the cost-effectiveness of quadripolar CRTD.

**STUDY LIMITATIONS.** The data used as the basis of this economic evaluation were derived from a multicenter clinical registry, and the choice of whether quadripolar or bipolar leads were implanted was not subject to a randomization process. However, the approach we have taken reflects current demands in which real-world data are becoming more important to assess the impact that new technologies have actually had on patients and health systems. We took real clinical events that occurred in NHS practice and applied NHS tariffs to them to determine the actual charge and cost-effectiveness. This was an in-study cost-effectiveness analysis, not an extrapolation to a lifetime horizon. We therefore did not assume event rates and did not model beyond the time for which we had gathered follow-up data. We did not perform a Markov model. Wider societal benefit was also not taken into account, which might be a further limitation.

As might be expected, the incremental acquisition cost of quadripolar technology is a strong determinant of the overall incremental cost-effectiveness of the 2 therapies. We therefore made an estimate of base cost and performed an analysis either side of the additional purchase cost to account for the variation in procurement acquisition costs. With respect to QALYs, the mortality difference was the strongest driver of the QALY gain associated with quadripolar CRTD. There was a significant difference in the proportions of patients with ischemic heart disease and those not in sinus rhythm (with more such patients in the bipolar group); however, this was corrected for in the multivariate analysis, and mortality remained significantly different.

**CONCLUSIONS**

In a 5-year time horizon calculated from a UK healthcare system perspective, the additional purchase price of quadripolar CRTD systems is substantially offset by lower health-care utilization costs, which suggests this technology is highly cost-effective compared with bipolar systems.

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