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Cost-effectiveness of implantable cardiac devices in patients with systolic heart failure

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Abstract:	Objective To evaluate the cost-effectiveness of implantable cardioverter-defibrillators (ICD), cardiac resynchronisation therapy pacemakers (CRT-P) and combination therapy (CRT-D) in patients with heart failure with reduced ejection fraction based on a range of clinical characteristics. Methods Individual patient data from 13 randomised trials were used to inform a decision analytic model. A series of regression equations were used to predict baseline all-cause mortality, hospitalisation rates and health related quality of life (HRQoL) and device-related treatment effects. Clinical variables used in these equations were age, QRS duration, NYHA class, ischemic aetiology, and LBBB. A UK NHS perspective and a lifetime time horizon were used. Benefits were expressed as quality adjusted life years (QALYs). Results were reported for 24 subgroups based on LBBB status, QRS duration and NYHA class. Results

	At a threshold of £30,000 per QALY gained, CRT-D was cost-effective in 10 of the 24 subgroups including all LBBB morphology patients with NYHA I/III/III. ICD is cost-effective for all non-NYHA IV patients with QRS duration <120ms and for NYHA I/II non-LBBB morphology patients with QRS duration between 120 and 149ms. CRT-P was also cost-effective in all NYHA III/IV patients with QRS duration >120ms. Device therapy is cost-effective in most patient groups with LBBB at a threshold of £20,000 per QALY gained. Results were robust to altering key model parameters. Conclusions At a threshold of £30,000 per QALY gained, CRT-D is cost-effective in a far wider group than previously recommended in the UK. In some subgroups ICD and CRT-P remain the cost-effective choice.

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Cost-effectiveness of implantable cardiac devices in patients with systolic heart failure

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Abstract (250 words)

Objective

To evaluate the cost-effectiveness of implantable cardioverter-defibrillators (ICD), cardiac resynchronisation therapy pacemakers (CRT-P) and combination therapy (CRT-D) in patients with heart failure with reduced ejection fraction based on a range of clinical characteristics.

Methods

Individual patient data from 13 randomised trials were used to inform a decision analytic model. A series of regression equations were used to predict baseline all-cause mortality, hospitalisation rates and health related quality of life and device-related treatment effects. Clinical variables used in these equations were age, QRS duration, NYHA class, ischemic aetiology, and LBBB. A UK NHS perspective and a lifetime time horizon were used. Benefits were expressed as quality adjusted life years (QALYs). Results were reported for 24 subgroups based on LBBB status, QRS duration and NYHA class.

Results

At a threshold of £30,000 per QALY gained, CRT-D was cost-effective in 10 of the 24 subgroups including all LBBB morphology patients with NYHA I/II/III. ICD is cost-effective for all non-NYHA IV patients with QRS duration <120ms and for NYHA I/II non-LBBB morphology patients with QRS duration between 120 and 149ms. CRT-P was also cost-effective in all NYHA III/IV patients with QRS duration >120ms. Device therapy is cost-effective in most patient groups with LBBB at a threshold of £20,000 per QALY gained. Results were robust to altering key model parameters.

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Conclusions

At a threshold of £30,000 per QALY gained, CRT-D is cost-effective in a far wider group than previously recommended in the UK. In some subgroups ICD and CRT-P remain the cost-effective choice.

Keywords

Cardiac Resynchronisation, Implantable Cardioverter Defibrillator, Cost-effectiveness, Cost-utility, CRT, ICD

Key questions

What is already known about this subject?

Clinical guidelines on ICD/CRT in HF make recommendations for ICD, CRT-P and CRT-D based on a range of clinical parameters. These include NYHA class, LVEF, ischaemic aetiology status, QRS duration, and presence or absence of either AF or LBBB. ICD and CRT therapy are not indicated in all patient groups of interest.

ICD, CRT-P and CRT-D have been shown to represent a cost-effective use of UK health care expenditure when compared to medical therapy, and when evaluated in patient groups determined by individual trial inclusion criteria.

What does this study add?

We have compared the devices to each other, as well as no device therapy in a much wider set of patients than has previously been evaluated in order to provide an answer to the question 'in which patients are ICD/CRT-P/CRT-D cost-effective?'.

Data from multiple RCTs rather than single studies were used to inform the cost-effectiveness analysis hence results are more reflective of the totality of the clinical data. Results are stratified by a series of commonly used clinical parameters and present health care decision makers with much more information than was previously available.

Device therapy is cost effective at a threshold of £30,000 per QALY gained in all sub-groups examined. CRT-D is cost effective in 10 of the 24 subgroups, and is cost effective for all LBBB morphology patients with NYHA I-III. ICDs are cost effective for all NYHA I-III patients with a QRS duration <120ms and for NYHA I-II patients with non-LBBB morphology and a QRS duration between 120 and 149ms. CRT-P is cost-effective for all NYHA IV patients evaluated.

How might this impact on clinical practice?

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The results from our work will allow health care decision makers to make more informed decisions on which devices to offer patients taking in to account both clinical and economic factors.

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Introduction

In addition to guideline directed medical therapy, implantable cardiac devices have an established role in the treatment of heart failure with reduced ejection fraction (HFrEF). International clinical guidelines[1-3] make recommendations for implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy pacemakers (CRT-P), and the combined device, CRT-D, based on the presence of specific patient characteristics, recognising that the extent of clinical benefit associated with these devices varies across subgroups within the broader population of patients with HRrEF.

Health care systems internationally are seeking evidence on the value for money of medical interventions, and ICD and CRT have been the subject of a number of economic evaluations[4-9] and health technology assessments (HTAs)[10-12]. In general, the conclusion has been that ICD and CRT are cost-effective when compared to medical therapy, and that CRT-D is marginally cost-effective when compared to standalone CRT-P.

Clinical guidelines on ICD/CRT in HF make recommendations based on a range of clinical parameters. These include New York Heart Association (NYHA) class, Left Ventricular Ejection Fraction (LVEF), ischaemic aetiology status, QRS duration, and presence or absence of either Atrial Fibrillation (AF) or Left Bundle Branch Block (LBBB).[2;3] Guidance issued by HTA organisations such as the National Institute for Health and Care Excellence (NICE)[13;14] is based on a subset of these parameters. The great majority of published ICD/CRT economic evaluations, however, including those informing NICE decisions, have been based on data or populations from single clinical trials. These analyses do not, therefore, reflect the totality of randomised controlled trial evidence available, and have only limited information with which to explore the potential for cost-effectiveness (and decisions based on cost-effectiveness) to vary by patient sub-groups.

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This paper reports a unique collaboration between manufacturers, clinicians and health economists to pool individual patient data from all major randomised controlled trials of these devices (N=12,638). This database of studies has been used to inform a range of research studies.[15;16] We report its use to develop a cost-effectiveness analysis for submission to NICE as part of their comprehensive review of ICD and CRT designed to answer the question 'in which patients are ICD/CRT-P/CRT-D cost-effective?'.[16] Unlike previous studies, the analysis is based on a synthesis of evidence across trials and reflects important differences between sub-groups, hence guiding health systems' resource allocation decisions regarding these devices.

Methods

Decision analytic modelling

The analysis is based on a typical UK HFrEF patient population, starting age of 66 years, all NYHA classes), and LVEF ≤35%. The cost-effectiveness analysis follows the methods recommended by NICE.[17] Costs considered are those of the UK NHS, and outcomes are expressed as quality-adjusted life-years (QALYs). An annual discount rate of 3.5% is applied to both costs and benefits.[17]

The analysis is based on a decision analytic model which comprises a series of regression equations to predict: mortality, hospitalisation rates and health related quality of life (HRQoL). The regression equations include covariables representing patients' baseline prognostic characteristics. The first regression equation predicts the probability of death in patients who only receive medical therapy. This is combined with estimates of the treatment effects of ICD, CRT-P and CRT-D based on the results of a network meta-analyses[15] to derive device-specific mortality probabilities. A second equation is used to predict the monthly probability of experiencing a hospitalisation event for any reason. A final equation estimates a patient's HRQoL given their characteristics and treatment. All living patients potentially incur other costs

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related to device implant and replacement, background medication and routine clinical visits.

Cost-effectiveness results are generated in a two-stage process. In the first stage, costs and QALYs are estimated for all interventions for all possible sets of patient characteristics ('patient profiles'). In the second, these are collapsed to 24 subgroups defined by NYHA class, QRS duration and presence or absence of LBBB. Due to clinical contra-indications or a paucity of evidence, not all treatments are evaluated for each of the 24 sub-groups (see **supplementary material, Appendix 1**, for details).

Expected (mean) costs and QALYs are estimated for all relevant treatments in each sub-group, and the following standard 'decision rules' are followed to identify the cost-effective intervention in each sub-group.[18] Firstly, any option that is less effective and more costly than one or more others is removed from consideration (dominated). Secondly, the extra cost per additional QALY (the incremental cost effectiveness ratio (ICER)) of a more effective treatment is calculated and any treatment that is less effective than another with a higher ICER is removed from consideration (extended dominance). The remaining options lie on a cost-effectiveness 'frontier' which runs from least to most costly/ effective. ICERs are calculated between each progressively more costly and effective option.

Estimating model inputs

The baseline mortality risk (patients receiving medical therapy alone) was estimated using relevant individual patient data from the included trials.[15] Parametric survival analysis was used to extrapolate these mortality risks beyond the follow-up periods in the trials in order to generate lifetime estimates. The following candidate baseline covariables were selected based on data availability, a review of risk scores, clinical guidelines, RCT subgroup analyses and clinical advice: age, QRS duration, LVEF, gender, NYHA class, ischaemic aetiology, LBBB status and a binary geographic indicator to track whether or not patients were from a North American centre. Final covariable selection in all regression models was via a stepwise procedure unless

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otherwise stated. Estimation of the treatment effects of the devices on all-cause mortality has been detailed elsewhere.[15] Mortality treatment effects were assumed to be maintained for 7.5 years (the maximum follow up period in the trials) after which they would decline so that, by 20 years, there was no impact on mortality.

The expected number of all-cause hospitalisations per month for patients on medical therapy, together with the treatment effects of the devices, was estimated from the 11 trials reporting relevant data (full list of studies reported in **supplementary material, Appendix 2**). Hospitalisation rates were assumed constant over a patient's lifetime. Excluding LBBB morphology, the covariates of interest were as for all-cause mortality. NYHA I-II patients were considered together due to paucity of data on NYHA I patients. For the analysis of the effect of devices on hospitalisation rates, study specific intercepts were included as well as device related main effects with interaction terms used to identify treatment effect modifiers.

HRQoL estimates expressed on a zero (equivalent of dead) to one (equivalent of good health) scale are necessary to quality-adjust survival and calculate QALYs.[18] Baseline HRQoL conditional upon patients' characteristics was estimated using data from the three trials reporting EQ-5D data (relevant studies listed in **supplementary material, Appendix 2**). The treatment effects of devices are estimated as the change from baseline (to first follow-up) in the treatment arms of the included trials, minus the change from baseline in patients allocated to medical therapy. This HRQoL treatment effect is assumed to be maintained for five years based on information in the CARE-HF trial,[19] and then to decline to zero by ten years. Throughout the model, a decline in HRQoL is applied to reflect ageing, estimated using UK general population data.[20]

Hospitalization costs are based on information on hospitalization type from a UK based population study.[21] The typical HF medications for each NYHA class are estimated based on a review of the clinical literature and expert opinion. With the exception of those relating to device

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systems, all costs are taken from national databases.[22-24] The total implant cost for CRT-P is based on a relevant Healthcare Resource Group (HRG) code. For CRT-D and ICD, no such codes exist, so cross-manufacturer average selling prices for both systems and leads were made available by the Association of British Healthcare Industries (ABHI) for the purpose of this analysis (**supplementary material, Appendix 3**).

Device longevity estimates are based on data from the Central Cardiac Audit Database (CCAD). Parametric survival models are used to model time to first and subsequent device replacements (**supplementary material, Appendix 3)**.

A range of sensitivity and scenario analyses are undertaken to quantify the importance of the key modelling assumptions. Of particular importance is the uncertainty in assumptions regarding the duration of the mortality and HRQoL treatment effects. Alternative values explored as sensitivity analyses were: i) a constant, lifetime mortality effect (as in previous UK reimbursement models[10;12]); ii) a five year time period; and iii) the mean follow up period from the studies included in the data analyses (2.54 years). A sensitivity analysis was also conducted using lifetime treatment effect durations for both all-cause mortality and HRQoL (as per previous UK reimbursement models). Further sensitivity analyses were undertaken including varying key costs, increasing device longevity, the use of an alternative approach to modelling all-cause hospitalisation and the use of NYHA class as a modifier of all-cause mortality treatment effect.

Software

All mortality related analyses were performed in R (www.r-project.org), with all analysis of hospitalisation and HRQoL performed in STATA V12 (StataCorp. College Station, TX: StataCorp LP). The economic model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA).

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Results

All-cause mortality

Full details of the mortality model are reported in the **supplementary material (Appendix 4).** The risk of death was higher in patients who are older, male or with ischaemic aetiology. The risk of death was also found to increase across NYHA classes, and was more than three times higher in individuals in NYHA class IV than those in NYHA I/II. The risk of mortality was lower in patients with a normal (<120ms) vs. longer QRS duration (hazard ratio = 0.84) and decreased as LVEF increased. Long term survival predictions for each subgroup and treatment are presented in the **supplementary material (Appendix 5)**. Allowing for variations in within-group sample size and covariate mix the results are broadly internally consistent and in line with the published literature.

All cause hospitalisation

Full details of the baseline hospitalisation model are reported in the **supplementary material (Appendix 4)**. Patients in NYHA classes III and IV were 2.1 and 4.4 times, respectively, more likely to be hospitalised than those in NYHA I/II. Ischaemic aetiology increased the rate of hospitalisation by 9% and wide QRS complex increased the rate by 22% (120-149ms) and 6% (150ms or more), respectively.

The model predicted that ICDs reduced monthly hospitalisation rates by 20% in patients with NYHA I/II/III HF. CRT-P was associated with reductions in monthly hospitalisation rates of 32% and 40%, respectively, in patients with NYHA III/IV HF. CRT-D was associated with a monthly rate reduction of 30% in patients with NYHA I-IV HF. In NYHA III/IV patients the treatment effects arising from the patient level data for CRT-D compared to those generated for CRT-P were considered clinically implausible. For the base case analysis of these patients we therefore assumed equivalence of efficacy for CRT-D and CRT-P. Subgroup/ treatment specific lifetime

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hospitalisation counts are reported in **supplementary material (Appendix 5).** These data require careful interpretation since subgroups with longer overall survival have more hospitalisation events.

Health related quality of life

Full details of the HRQoL model are reported in the **supplementary material (Appendix 4).** Statistically significant ($p<0.05$) but modest improvements from baseline were observed for ICD and CRT-D in patients with NYHA I or II heart failure, and CRT-P in NYHA Class III (+0.02, +0.03 and +0.091, respectively). No significant impact was observed on HRQoL with ICD or CRT-D therapy in patients in NYHA Class III. Meaningful results for patients with NYHA IV HF could not be generated due to the very low numbers of patients in the clinical trials.

For the purposes of economic modelling, equivalence of HRQoL benefit for CRT-P and CRT-D was again assumed in NYHA III and IV HF. This assumption can be justified on the basis of a review of external sources and trial specific Minnesota Living with Heart Failure data.[16]

Cost effectiveness – base case

The base case results for all subgroups are presented in **Table 1.** For each patient sub-group, the order of treatments on the cost-effectiveness frontier is shown, and the ICERs for each option which is not subject to dominance or extended dominance. **Table 2** shows the cost-effective option for each sub-group (cost-effectiveness threshold: £30,000 per QALY gained). Device therapy is cost effective at this threshold in all sub-groups examined. CRT-D is cost effective in 10 of the 24 subgroups, and is cost effective for all LBBB morphology patients with NYHA I/II/III. ICDs are cost effective for all non-NYHA IV patients with a QRS duration <120ms and for NYHA I/II, non-LBBB morphology patients with a QRS duration between 120 and 149ms. CRT-P is cost-effective for all NYHA IV patients evaluated.

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Results generated using a more stringent threshold value (£20,000 per QALY gained) are presented in **Table 3**. CRT-D is only cost-effective in two patient groups (NYHA I or II, QRS duration ≥150ms, with LBBB); ICD is only cost-effective in two patient groups (NYHA I or II, QRS duration between 120 and 149ms, no LBBB); and CRT-P is cost-effective in six patient groups (NYHA III or IV, QRS duration >120ms, and LBBB and also NYHA III/IV, QRS duration ≥150ms and no LBBB).

The nature of the cost-effective intervention is dependent upon the cost effectiveness threshold (**Figure 1**)**.** Beyond a threshold value of approximately £24,500 per QALY gained, for patients without LBBB morphology the treatments identified in the base case analysis are largely robust to changes in threshold. For patients with LBBB morphology there is generally less sensitivity to changes in threshold, with the cost-effective treatments presented in **Table 2** largely unchanged beyond a threshold value of approximately £22,000 per QALY.

Results in NYHA I and IV patients are subject to additional uncertainty due to the numbers of patients informing these analyses and the nature of the trial inclusion criteria for NYHA I patients, these issues are described in the discussion.

Sensitivity analyses

The choice of cost-effective therapy was, in general, unchanged when varying the duration of maximum all-cause mortality treatment effect (**Table 4**, threshold value £30,000 per QALY gained). A similar outcome was noted when the assumption of lifetime treatment effect durations for both all-cause mortality and HRQoL improvements was made (**Table 4**). A detailed breakdown of the fully incremental ICERs generated in this latter analysis is presented in the **supplementary material (Appendix 6)**. The corresponding results generated using a threshold value of £20,000 per QALY gained are presented in **Table 5**.

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The impact of varying key costs, increasing device longevity, the use of an alternative approach to modelling all-cause hospitalisation and the use of NYHA class as an all-cause mortality treatment effect modifier on the choice of devices at thresholds of £20,000 and £30,000 per QALY gained was modest. Hence, the model was robust to changes in these parameters.

Discussion

The clinical efficacy of CRT and ICD therapy has been investigated in numerous studies, and these technologies are established therapies for HFrEF individuals in international practice. The uniqueness of the database created for the purpose of this analysis lies in the ability to explore the clinical efficacy of CRT and ICD in detail, and in particular to pursue a thorough investigation of the impact of key clinical variables on both the baseline risk of death and the efficacy of each treatment option in reducing mortality.[15] The database also facilitated the incorporation of clinical sub-groups into the cost-effectiveness assessment so the devices representing best value for money for patients with different sets of clinical characteristics could be identified.

This collaboration can serve as a model for similar collaboration across manufacturers. Pooling together clinical data across manufactures can help manufactures, physicians, and policy makers become more confident in the clinical- and cost-effectiveness of a therapy and get a better understanding of how this varies across patients.

The analysis presented here was used to inform the recent NICE guidance regarding the use of these technologies. The committee developing the NICE recommendations recognized this analysis as “a rich and important data source”[25], and based its decision making on it. The guidance issued by NICE in 2014 reflected the findings of this cost-effectiveness analysis in almost all subgroups,[25] with the exception of CRT-D in patients with NYHA III and QRS 120-149ms without LBBB morphology and CRT-D in asymptomatic (NYHA Class I) patients with

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QRS 120-149ms. ICD was recommended in both cases due to concerns about reduced effectiveness and a lack of symptomatic benefit of CRT in these subgroups.

The major source of uncertainty identified during the NICE appraisal of these technologies was the duration of treatment effect on all-cause mortality. The duration of effect used in this analysis (7.5 years) is supported by a number of long-term studies. Recently published data from the CARE-HF study[19] found that, at a mean follow-up of 56 months in the CRT-P and 50 months in the medical therapy arms, the hazard ratio for all cause-mortality (CRT-P vs. OPT) was 0.77 [95% CI 0.63, 0.93], despite 39% of control patients crossing-over to a CRT device during follow-up. In addition, long-term follow-up from the MADIT-II study[26] found that, at a median follow-up of 7.6 years, the hazard ratio for all cause-mortality (ICD vs. non-ICD) was 0.77 [0.65, 0.91], although 34% of control patients crossed-over to a device during follow-up. Attempts to adjust statistically for cross-over resulted in treatment effect estimates of 0.67 [0.56, 0.80] and 0.66 [0.56, 0.78], in CARE-HF and MADIT-II, respectively.[19,26]

The results from our analysis, generated using a cost-effectiveness threshold of £30,000 per QALY gained broadly agrees with guidelines issued by the European Society of Cardiology.[3,27] In patients with QRS<120ms, NYHA II-III and EF≤35%, ICD is recommended and cost-effective according to our analysis. In ambulatory NYHA IV patients with prolonged QRS duration, CRT-P is recommended and cost-effective. Our analysis provides information on where scarce resources should be targeted in patients with QRS prolongation and in NYHA class II or III where several possible device options are recommended. In particular, it suggests that CRT-D is cost-effective in NYHA II-III patients with LBBB morphology, and that, in patients with non-LBBB morphology, CRT-D is cost-effective in all groups with the exception of NYHA II patients with a QRS duration of 120-149ms. Unlike previous guidelines, the current analysis suggests implantable devices may be cost-effective in asymptomatic patients (NYHA Class I). However,

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given the small number of patients in these groups in the trials, results in NYHA Class I, and in particular in relation to CRT-D in this patient group, should be regarded with caution.[15]

Comparison of the results from the current analysis with previous UK HTA models of ICD and CRT is challenging due to the different model structures and evidence used. The earlier models used aggregate level evidence, whereas the current model was based on access to a large amount of individual patient data. Accepting these differences, the results from the sensitivity analysis performed with the removal of all tapering effects on treatment effect durations are the most comparable with earlier models. This showed that the ICERs from the current analysis are lower (i.e. better value for money) than those considered acceptable in previous NICE guidance. The reasons for this are likely to be increases in average device longevity and a reduction in hardware acquisition costs. In many cases, where ICD was historically recommended, the current analysis suggests patients should be offered a CRT-D device as the most clinically and cost-effective option.

A number of limitations arose from the choice of modeling approach and data on which the analyses were based, with the main area of potential concern being that some of the patient groups modeled were sparsely represented in our database. The primary groups of concern relate to patients in NYHA Class I and IV HF (regardless of LBBB status). Cost-effectiveness results in these groups may have been influenced by the small patient numbers and should be treated with caution. In addition, NYHA I patients in trials may be atypical of those observed in clinical practice as specific inclusion criteria were used to focus on patients who were easily identifiable.[28,29]

Omitting previous HF hospitalisations as a predictor of subsequent monthly hospitalisation events represents a limitation of our analysis. However, the total event rates predicted are low and the choice of modelling approach is therefore unlikely to have had a substantive impact on the model results.

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In conclusion, from a UK NHS perspective, at a threshold of £30,000 per QALY gained our analysis has shown that CRT-D is cost effective in a far wider group of patients than previously recommended and that, for most other patients, ICD is a cost-effective treatment alternative. Our analysis also showed that CRT-P was cost-effective in all patients with NYHA III/IV and a QRS duration >120ms. Device therapy is cost-effective in most patient groups with LBBB at a threshold of £20,000 per QALY gained.

Acknowledgements and affiliations

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Figure legends

Figure 1: Graphic display of cost-effective option across cost-effectiveness threshold values (base case)

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Text tables

Table 1: Base case results. Cost-effectiveness sequence relates to the order in which interventions appear on the cost-effectiveness frontier. "N/A" represents fewer than four interventions being considered. Options labelled as "Dominated" or "Ext Dominated" do not lie on the frontier

	Cost-effectiveness sequence				Incremental cost-effective ratios			
Patient group	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Individuals without LBBB morphology								
NYHA I, QRS duration <120ms[a]	MT	ICD	N/A	N/A	Referent	£24,074	N/A	N/A
NYHA I, QRS duration≥120ms and <150ms[a]	MT	CRT-D	ICD	N/A	Referent	Dominated	£16,253	N/A
NYHA I, QRS duration≥150ms[a]	MT	ICD	CRT-D	N/A	Referent	£21,102	£21,759	N/A
NYHA II, QRS duration<120ms	MT	ICD	N/A	N/A	Referent	£24,465	N/A	N/A
NYHA II, QRS duration≥120ms and <150ms	MT	CRT-D	ICD	N/A	Referent	Dominated	£16,813	N/A
NYHA II, QRS duration≥150ms	MT	ICD	CRT-D	N/A	Referent	£20,602	£23,738	N/A
NYHA III, QRS duration<120ms	MT	ICD	N/A	N/A	Referent	£27,826	N/A	N/A
NYHA III, QRS duration≥120ms and <150ms	MT	CRT-P	ICD	CRT-D	Referent	£20,178	Ext Dominated	£23,349
NYHA III, QRS duration≥150ms	MT	ICD	CRT-P	CRT-D	Referent	Dominated	£13,930	£25,200
NYHA IV, QRS duration<120ms	MT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
NYHA IV, QRS duration≥120ms and <150ms	MT	CRT-P	CRT-D	N/A	Referent	£22,578	£40,052	N/A
NYHA IV, QRS duration≥150ms	MT	CRT-P	CRT-D	N/A	Referent	£17,175	£35,811	N/A
Individuals with LBBB morphology								
NYHA I, QRS duration≥120ms and <150ms[a]	MT	ICD	CRT-D	N/A	Referent	£20,677	£21,672	N/A
NYHA I, QRS duration≥150ms[a]	MT	ICD	CRT-D	N/A	Referent	Ext Dominated	£17,470	N/A
NYHA II, QRS duration≥120ms and <150ms	MT	ICD	CRT-D	N/A	Referent	Ext Dominated	£20,704	N/A
NYHA II, QRS duration≥150ms	MT	ICD	CRT-D	N/A	Referent	Ext Dominated	£17,664	N/A
NYHA III, QRS duration≥120ms and <150ms	MT	ICD	CRT-P	CRT-D	Referent	Dominated	£14,215	£24,875

NYHA III, QRS duration≥150ms	MT	ICD	CRT-P	CRT-D	Referent	Dominated	£10,496	£28,646
NYHA IV, QRS duration≥120ms and <150ms	MT	CRT-P	CRT-D	N/A	Referent	£18,664	£37,104	N/A
NYHA IV, QRS duration≥150ms	MT	CRT-P	CRT-D	N/A	Referent	£14,500	£40,449	N/A

MT: Medical therapy; ICD: Implantable cardioverter-defibrillator; CRTP: standalone CRT device; CRTD: combined CRT and ICD device; N/A: Not applicable; a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Table 2: Summary of cost-effectiveness recommendations arising from the base case analysis (threshold value: £30,000 per QALY gained)

NYHA	QRS duration<120ms	QRS duration 120-150ms	QRS duration>150ms
		Patients without LBBB morphology	
I[a]	ICD	ICD	CRT-D
II	ICD	ICD	CRT-D
III	ICD	CRT-P / CRT-D[b]	CRT-P / CRT-D[b]
IV	Medical therapy	CRT-P	CRT-P
		Patients with LBBB morphology	
I[a]		CRT-D	CRT-D
II		CRT-D	CRT-D
III		CRT-P / CRT-D[b]	CRT-P / CRT-D[b]
IV		CRT-P	CRT-P

a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text. b) Instances where NICE recommended two devices based on fully incremental results and a threshold of £30,000 per QALY gained. CRT-P values are relative to medical therapy and CRT-D values relative to CRT-P.

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Table 3: Summary of cost-effectiveness recommendations arising from the base case analysis (threshold value: £20,000 per QALY gained)

NYHA	QRS duration<120ms	QRS duration 120-150ms	QRS duration>150ms
		Patients without LBBB morphology	
I[a]	Medical Therapy	ICD	Medical Therapy
I	Medical Therapy	ICD	Medical Therapy
III	Medical Therapy	Medical Therapy	CRT-P
IV	Medical Therapy	Medical Therapy	CRT-P
		Patients with LBBB morphology	
I[a]		Medical Therapy	CRT-D
II		Medical Therapy	CRT-D
III		CRT-P	CRT-P
IV		CRT-P	CRT-P

a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Table 4: Impact of duration of treatment effect on treatment choice (threshold £30,000 per QALY gained). Changes from base case highlighted in bold

Subgroup	Duration of mortality treatment effect				Lifetime mortality and constant HRQoL
	Lifetime	7.5 years	5 years	Mean f/up	
Individuals without LBBB					
NYHA I, QRS <120ms[a]	ICD	ICD	ICD	ICD	ICD
NYHA I, QRS ≥120ms and <150ms[a]	ICD	ICD	ICD	ICD	ICD
NYHA I, QRS ≥150ms[a]	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA II, QRS <120ms	ICD	ICD	ICD	ICD	ICD
NYHA II, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD	ICD
NYHA II, QRS ≥150ms	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA III, QRS <120ms	ICD	ICD	ICD	**MT**	ICD
NYHA III, QRS ≥120ms and <150ms	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA III, QRS ≥150ms	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA IV, QRS <120ms	MT	MT	MT	MT	MT
NYHA IV, QRS ≥120ms and <150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
NYHA IV, QRS ≥150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
Individuals with LBBB					
NYHA I, QRS ≥120ms and <150ms[a]	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA I, QRS ≥150ms[a]	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA II, QRS ≥120ms and <150ms	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA II, QRS ≥150ms	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA III, QRS ≥120ms and <150ms	CRT-D	CRT-D	CRT-D	CRT-D	CRT-D
NYHA III, QRS ≥150ms	CRT-D	CRT-D	**CRT-P**	**CRT-P**	CRT-D
NYHA IV, QRS ≥120ms and <150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
NYHA IV, QRS ≥150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P

MT: Medical Therapy; a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Table 5: Impact of duration of treatment effect on treatment choice (threshold £20,000 per QALY gained). Changes from base case highlighted in bold

Subgroup	Duration of mortality treatment effect				Lifetime mortality and constant HRQoL
	Lifetime	7.5 years	5 years	Mean f/up	
Individuals without LBBB					
NYHA I, QRS <120ms[a]	ICD	**MT**	**MT**	**MT**	ICD
NYHA I, QRS ≥120ms and <150ms[a]	ICD	ICD	ICD	ICD	ICD
NYHA I, QRS ≥150ms[a]	CRT-D	**MT**	**MT**	**MT**	CRT-D
NYHA II, QRS <120ms	ICD	**MT**	**MT**	**MT**	ICD
NYHA II, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD	ICD
NYHA II, QRS ≥150ms	CRT-D	**MT**	**MT**	**MT**	**ICD**
NYHA III, QRS <120ms	MT	MT	MT	MT	MT
NYHA III, QRS ≥120ms and <150ms	CRT-P	**MT**	**MT**	**MT**	CRT-P
NYHA III, QRS ≥150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
NYHA IV, QRS <120ms	MT	MT	MT	MT	MT
NYHA IV, QRS ≥120ms and <150ms	MT	MT	MT	MT	MT
NYHA IV, QRS ≥150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
Individuals with LBBB					
NYHA I, QRS ≥120ms and <150ms[a]	CRT-D	**MT**	**MT**	**MT**	CRT-D
NYHA I, QRS ≥150ms[a]	CRT-D	CRT-D	CRT-D	**MT**	CRT-D
NYHA II, QRS ≥120ms and <150ms	CRT-D	**MT**	**MT**	**MT**	CRT-D
NYHA II, QRS ≥150ms	CRT-D	CRT-D	CRT-D	**MT**	CRT-D
NYHA III, QRS ≥120ms and <150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
NYHA III, QRS ≥150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
NYHA IV, QRS ≥120ms and <150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P
NYHA IV, QRS ≥150ms	CRT-P	CRT-P	CRT-P	CRT-P	CRT-P

a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Figure 1

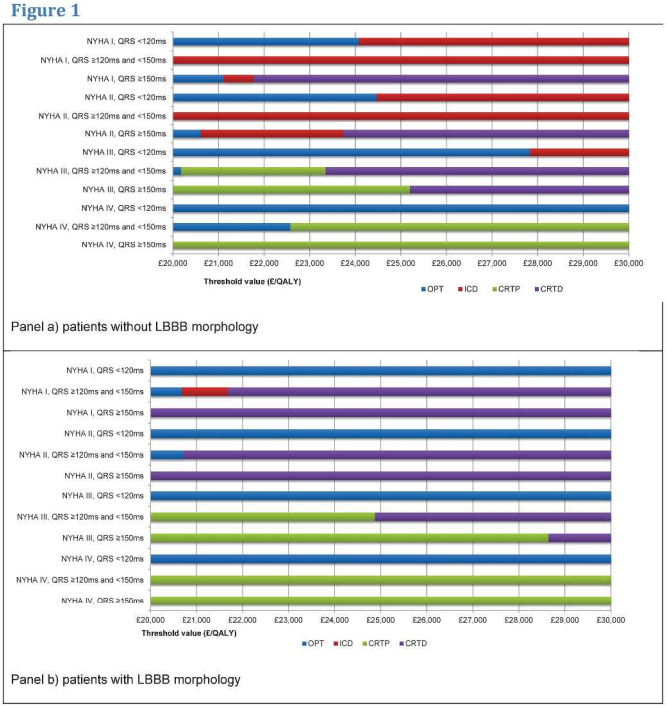

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Figure 1: Graphic display of cost-effective option across cost-effectiveness threshold values (base case)
297x420mm (300 x 300 DPI)

SUPPLEMENTARY ONLINE MATERIAL

Appendix 1: Rational for excluding interventions from some subgroups

Table S1: Rationale for excluding interventions from some subgroups

Treatment option	Subgroup from which excluded	Rationale/ justification
Medical Therapy	None	
ICD	NYHA IV	Minimal IPD data available from clinical trials *(of 12,638 patients included in IPD database only 77 (0.6%) were NYHA IV and randomised to an ICD)*
CRT-P	NYHA I/II	Minimal IPD data available from clinical trials *(of 12,638 patients included in IPD database only 74 (0.6%) were NYHA I-II and randomised to a CRT-P)*
	QRS duration<120ms	Prolonged QRS duration required for consideration of device insertion. No evidence of benefit from CRT in patients with normal QRS duration
CRT-D	QRS duration<120ms	Prolonged QRS duration required for consideration of device insertion. No evidence of benefit from CRT in patients with normal QRS duration

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Appendix 2: List of studies contributing information to all-cause hospitalisation and health related quality of life analyses

All-cause hospitalisation

Abraham WT, Fisher WG, Smith AL, DeLurgio DB, Leon AR, Loh E et al. Cardiac resynchronization in chronic heart failure. *New England Journal of Medicine* 2002; 346(24):1845-1853.

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Beshai JF, Grimm RA, Nagueh SF, Baker JH, Beau SL, Greenberg SM et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *New England Journal of Medicine* 2007; 357(24):2461-2471.

Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De MT et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *New England Journal of Medicine* 2004; 350(21):2140-2150.

Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New England Journal of Medicine* 2005; 352(15):1539-1549.

Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA et al. Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients with Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias. *Journal of the American College of Cardiology* 2003; 42(8):1454-1459.

Linde C, Abraham WT, Gold MR, St John SM, Ghio S, Daubert C et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *Journal of the American College of Cardiology* 2008; 52(23):1834-1843.

Moss A. MADIT-CRT: The multicentre automatic defibrillator implantation trial-cardiac resynchronization therapy. *European Journal of Heart Failure* 2009; 11(12):1217-1219.

RHYTHM ICD. St. Jude Medical® Epic™ HF System including the Epic™ HF Model V-338 Cardiac Resynchronization Therapy Defibrillator, the Aescula™ LV Model 1055K Lead, the QuickSite™ LV Model 1056K Lead, and the Model 3307 v4.5m Programmer Software - P030054. US Food and Drug Administration

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Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *New England Journal of Medicine* 2010; 363(25):2385-2395.

Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA : the journal of the American Medical Association* 2003; 289:2685-2694.

Health Related Quality of Life

Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New England Journal of Medicine* 2005; 352(15):1539-1549.

Moss A. MADIT-CRT: The multicentre automatic defibrillator implantation trial-cardiac resynchronization therapy. *European Journal of Heart Failure* 2009; 11(12):1217-1219.

Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *New England Journal of Medicine* 2010; 363(25):2385-2395.

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Appendix 3: Additional model parameters

Table S2: Background medication by NYHA class (% patients receiving each drug)

	NYHA I	NYHA II	NYHA III	NYHA IV
Atorvastatin	20%	20%	20%	20%
Simvastatin	55%	55%	55%	55%
Warfarin	10%	15%	25%	40%
Clopidogrel	15%	15%	15%	15%
Ramipril	90%	90%	90%	90%
Carvedilol	85%	85%	75%	70%
Spironolactone	0%	30%	30%	30%
Digoxin	5%	25%	25%	25%
Furosemide	75%	80%	90%	95%
Eplerenone	0%	30%	30%	30%

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Table S3: Medication p*urchase costs (all data taken from the British National Formulary*[24]*, cost year 2012)*

Drug	Tablets per pact	Daily dose	Pack price
Atrovastatin (Liptor®)	28	10mg	£13.00
Simvastatin	28	10mg	£0.90
	28	20mg	£1.01
	28	40mg	£1.32
	28	80mg	£2.29
Warfarin	28	0.5mg	£1.49
	28	1mg	£0.93
Clopidigrel	30	75mg	£3.40
	28	75mg	£3.17
Ramipril	28	1.25mg	£1.10
	28	2.5mg	£1.18
	28	5mg	£1.25
	28	10mg	£1.41
Carvedilol	28	3.125mg	£1.10
	28	6.25mg	£1.25
	28	12.5mg	£1.37
	28	25mg	£1.84
Spironolactone	28	25mg	£1.55
	28	50mg	£2.11
	28	100mg	£2.46
Digoxin	28	62.5	£2.03
	28	125	£1.12
	28	250	£1.13
Furosemide	28	20	£0.81
	28	40	£0.84
	28	500	£4.05
Eplerenone	28	25	£42.72

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Table S4: Hospitalisation event costs (cost year 2012)

Item	Cost	Source
Day in hospital (HF)	£655.71	NHS Schedule of reference costs[16,22]
Day in hospital (non-HF)	£699.50	NHS Schedule of reference costs[16,22]
Day in hospital (leads)	£794.41	NHS Schedule of reference costs[16,22]
HF hospitalisation event	£2,295	NHS Schedule of reference costs[16,22]
Non-HF hospitalisation event	£2,448	NHS Schedule of reference costs[16,22]
Outpatient visits[a]	£110.00	Unit costs of health and social care[16,23]

a) Applied every six months to all patients alive regardless of device option in addition to any other hospitalisation event costs.

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Table S5: ICD and CRT system costs (source Association of British Healthcare Industries unless otherwise stated, cost year 2012)

Item	Cost	Source
	System costs	
CRT-P whole system costs (device and leads)	£3,411	Association of British Healthcare Industries*
CRT-D whole system costs (device and leads)	£12,293	Association of British Healthcare Industries*
ICD whole system costs (device and leads)	£9,692	Association of British Healthcare Industries*
CRT Leads	£510	Association of British Healthcare Industries*
CRT-P pulse generator	£2,600	Association of British Healthcare Industries*
CRT-D pulse generator	£11,752	Association of British Healthcare Industries*
ICD generator	£9,149	Association of British Healthcare Industries*
	UK Tariff values	
CRT-P	£8,281	NHS Schedule of reference costs[16,22]
ICD/CRT-D non-purchase costs	£5,556	NHS Schedule of reference costs[16,22]
Revisions not requiring new device	£2,748	NHS Schedule of reference costs[16,22]

* Data on file

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Table S6: Device costs used in the model (cost year 2012)

Item	Cost	Components
Initial implant operation (ICD)	£15,248	ABHI system costs (incl. leads) and UK tariff EA12Z
Initial implant operation (CRT-P)	£8,281	UK Tariff E07Z
Initial implant operation (CRT-D)	£17,849	ABHI system costs (incl. leads) and UK tariff EA12Z
Replacement (ICD)	£14,705	ABHI system costs (excl. leads) and UK tariff EA12Z
Replacement (CRT-P)	£8,281	UK Tariff E07Z
Replacement (CRT-D)	£17,308	ABHI System costs (excl. leads)* and UK tariff EA12Z
Device related infection (ICD)	£18,964	See footnote
Device related infection (CRT-P)	£12,541	See footnote
Device related infection (CRT-D)	£21,568	See footnote
Battery replacement (ICD)	£12,004	ABHI generator costs (excl. leads) and UK tariff EA39Z
Battery replacement (CRT-P)	£8,381	UK Tariff EA07Z
Battery replacement (CRT-D)	£14,672	ABHI generator costs (excl. leads) and UK tariff EA39Z

As per previous NICE appraisal of CRT, for the purpose of costing we have assumed that treatment of a device related infection involves explanation of the existing device and a *de novo* device reimplantation as well as an additional outpatient visit. Detailed breakdown of the relevant resource use protocol can be found in the ABHI NICE submission dossier.[16]

Table S7: Parameter estimates which to inform Weibull models (time to first device failure)[a]

Parameter	ICD	CRT-P	CRT-D
Log-Lambda	-15.784	-14.287	-15.465
Gamma	1.943	1.689	1.935

a) Full details on source data and the modelling of device longevity to be found in the relevant NICE submission[25]

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Appendix 4: Clinical baseline risk equations

Table S8: Preferred baseline risk models (all-cause mortality and hospitalisation)

	All-cause mortality (Weibull model)			All-cause hospitalisation (negative binomial model)		
Variable	Coefficient	Hazard ratio[a]	P-value	Coefficient	Hazard ratio[b]	P-value
Age (per year), time-dependent covariate	0.03	1.02	<0.001	0.02	1.00	0.004
Male gender	0.24	1.24	0.003	N/A	N/A	N/A
NYHA III	0.62	1.74	<0.001	0.74	2.10	<0.001
NYHA IV	1.30	3.20	<0.001	1.48	4.41	<0.001
Ischaemic aetiology	0.37	1.39	<0.001	0.09	1.09	0.031
QRS duration <120ms	-0.20	0.84	0.002	N/A	N/A	N/A
QRS duration ≥120ms and <150ms	N/A	N/A	N/A	0.20	1.22	<0.001
QRS duration ≥150ms	N/A	N/A	N/A	0.06	1.06	<0.001
LVEF>20% and <=25%	-0.26	0.79	0.001	N/A	N/A	N/A
LVEF>25% and <=30%	-0.34	0.74	<0.001	N/A	N/A	N/A
LVEF>30%	-0.65	0.56	<0.001	N/A	N/A	N/A
log(scale)	10.09	N/A	<0.001	N/A	N/A	N/A
log(shape)	0.12	N/A	<0.001	N/A	N/A	N/A
Constant	N/A	N/A	N/A	-2.73	N/A	N/A

a) Hazard ratio = exp(coefficient/shape); b) hazard ratio = exp(coefficient). N/A = not applicable

Table S9: Negative Binomial Regression coefficients used to predict baseline utility

Covariable	Coefficient	Hazard ratio[a]	p-value
NYHA = III	0.4667	1.595	<0.001
NYHA = IV*	0.7721	2.164	0.117
Age	-0.0061	0.994	0.003
Ischaemic aetiology	0.1427	1.153	0.001
Gender= Male	-0.2296	0.794	<0.001
Constant	3.5271	N/A	N/A

a) Hazard ratio =exp(coefficient);

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Appendix 5: Long term survival extrapolation and lifetime hospitalisation counts

Table S10: Predicted overall survival and lifetime hospitalisation event estimates (Medical Therapy, where included as a treatment option)

	Predicted overall survival							
Pt. group	0 yrs	2 yrs	4 yrs	6 yrs	8 yrs	10 yrs	Median	Hospitalisation count (lifetime)
Individuals without LBBB morphology								
NYHA I, QRS duration<120ms[a]	100.0%	87.5%	74.5%	62.0%	51.3%	42.0%	8.96	1.58
NYHA I, QRS duration≥120ms and <150ms[a]	100.0%	82.0%	64.6%	49.3%	37.5%	28.0%	6.37	1.44
NYHA I, QRS duration≥150ms[a]	100.0%	80.8%	62.7%	46.9%	35.0%	25.7%	6.06	1.19
NYHA II, QRS duration<120ms	100.0%	89.3%	77.9%	66.8%	57.0%	48.3%	10.61	1.78
NYHA II, QRS duration≥120ms and <150ms	100.0%	83.4%	67.1%	52.5%	40.8%	31.4%	7.00	1.54
NYHA II, QRS duration≥150ms	100.0%	82.4%	65.4%	50.4%	38.7%	29.4%	6.66	1.28
NYHA III, QRS duration<120ms	100.0%	78.3%	59.0%	43.2%	31.9%	23.4%	5.78	2.14
NYHA III, QRS duration≥120ms and <150ms	100.0%	69.8%	46.3%	29.7%	19.3%	12.6%	4.08	1.91
NYHA III, QRS duration≥150ms	100.0%	66.3%	41.5%	25.0%	15.4%	9.5%	3.58	1.49
NYHA IV, QRS duration<120ms	100.0%	52.0%	25.3%	11.7%	5.5%	2.6%	2.32	1.94
NYHA IV, QRS duration≥120ms and <150ms	100.0%	45.5%	19.9%	8.7%	4.1%	2.0%	2.02	2.03
NYHA IV, QRS duration≥150ms	100.0%	42.6%	17.0%	6.5%	2.6%	1.0%	1.82	1.59
Individuals with LBBB morphology								
NYHA I, QRS duration≥120ms and <150ms[a]	100.0%	83.4%	67.2%	52.7%	41.2%	31.9%	7.23	1.58
NYHA I, QRS duration≥150ms[a]	100.0%	82.1%	64.8%	49.6%	37.8%	28.5%	6.56	1.27

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NYHA II, QRS duration≥120ms and <150ms	100.0%	84.8%	69.7%	55.9%	44.8%	35.5%	7.82	1.66
NYHA II, QRS duration≥150ms	100.0%	85.0%	70.2%	56.5%	45.4%	36.2%	7.90	1.45
NYHA III, QRS duration≥120ms and <150ms	100.0%	69.8%	46.6%	30.3%	20.1%	13.5%	4.19	1.94
NYHA III, QRS duration≥150ms	100.0%	70.3%	47.2%	30.8%	20.4%	13.6%	4.20	1.68
NYHA IV, QRS duration≥120ms and <150ms	100.0%	46.8%	21.1%	9.7%	5.0%	2.7%	2.16	2.10
NYHA IV, QRS duration≥150ms	100.0%	45.6%	20.1%	8.8%	4.2%	2.0%	2.03	1.73

a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Table S11: Predicted overall survival and lifetime hospitalisation event estimates (ICD, where included as a treatment option)

	Predicted overall survival							
Pt. group	0 yrs	2 yrs	4 yrs	6 yrs	8 yrs	10 yrs	Median	Hospitalisation count (lifetime)
Individuals without LBBB morphology								
NYHA I, QRS duration<120ms[a]	100.0%	90.5%	80.2%	69.9%	60.6%	51.8%	11.08	1.47
NYHA I, QRS duration≥120ms and <150ms[a]	100.0%	88.3%	76.1%	64.1%	53.8%	44.1%	9.25	1.52
NYHA I, QRS duration≥150ms[a]	100.0%	86.1%	71.9%	58.5%	47.4%	37.5%	8.06	1.19
NYHA II, QRS duration<120ms	100.0%	91.9%	83.0%	73.9%	65.6%	57.6%	12.83	1.63
NYHA II, QRS duration≥120ms and <150ms	100.0%	89.2%	77.7%	66.4%	56.5%	47.0%	9.90	1.59
NYHA II, QRS duration≥150ms	100.0%	87.4%	74.3%	61.8%	51.2%	41.6%	8.86	1.27
NYHA III, QRS duration<120ms	100.0%	83.1%	66.9%	52.7%	41.6%	32.4%	7.32	2.05
NYHA III, QRS duration≥120ms and <150ms	100.0%	79.4%	60.7%	45.2%	33.7%	24.5%	6.00	2.10
NYHA III, QRS duration≥150ms	100.0%	74.8%	53.4%	37.0%	25.8%	17.6%	4.89	1.55
Individuals with LBBB morphology								
NYHA I, QRS duration≥120ms and <150ms[a]	100.0%	88.2%	75.8%	63.8%	53.5%	44.1%	9.48	1.55
NYHA I, QRS duration≥150ms[a]	100.0%	86.0%	71.7%	58.3%	47.2%	37.5%	8.12	1.20
NYHA II, QRS duration≥120ms and <150ms	100.0%	89.0%	77.4%	66.0%	56.1%	46.9%	10.05	1.60
NYHA II, QRS duration≥150ms	100.0%	88.2%	75.9%	64.0%	53.9%	44.7%	9.60	1.33
NYHA III, QRS duration≥120ms and <150ms	100.0%	77.3%	57.5%	41.7%	30.5%	22.0%	5.61	1.98
NYHA III, QRS duration≥150ms	100.0%	75.3%	54.4%	38.3%	27.2%	19.1%	5.11	1.58

a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Table S12: Predicted overall survival and lifetime hospitalisation event estimates (CRT-P, where included as a treatment option)

	Predicted overall survival							
Pt. group	0 yrs	2 yrs	4 yrs	6 yrs	8 yrs	10 yrs	Median	Hospitalisation count (lifetime)
Individuals without LBBB morphology								
NYHA III, QRS duration≥120ms and <150ms	100.0%	71.4%	48.4%	31.7%	21.0%	13.9%	4.29	1.35
NYHA III, QRS duration≥150ms	100.0%	71.9%	49.0%	32.1%	21.2%	13.8%	4.31	1.19
NYHA IV, QRS duration≥120ms and <150ms	100.0%	48.5%	22.7%	10.7%	5.4%	2.8%	2.21	1.33
NYHA IV, QRS duration≥150ms	100.0%	50.9%	24.2%	11.1%	5.3%	2.4%	2.27	1.18
Individuals with LBBB morphology								
NYHA III, QRS duration≥120ms and <150ms	100.0%	74.9%	53.8%	37.7%	26.7%	18.7%	5.05	1.54
NYHA III, QRS duration≥150ms	100.0%	78.7%	59.6%	44.0%	32.6%	23.6%	5.82	1.50
NYHA IV, QRS duration≥120ms and <150ms	100.0%	54.8%	28.6%	14.8%	8.1%	4.6%	2.67	1.54
NYHA IV, QRS duration≥150ms	100.0%	58.7%	32.8%	17.9%	10.1%	5.6%	2.90	1.45

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Table S13: Predicted overall survival and lifetime hospitalisation event estimates (CRT-D, where included as a treatment option)

	Predicted overall survival							
Pt. group	0 yrs	2 yrs	4 yrs	6 yrs	8 yrs	10 yrs	Median	Hospitalisation count (lifetime)
Individuals without LBBB morphology								
NYHA I, QRS duration≥120ms and <150ms[a]	100.0%	87.0%	73.5%	60.6%	49.6%	39.7%	8.37	1.24
NYHA I, QRS duration≥150ms[a]	100.0%	87.7%	74.8%	62.2%	51.5%	41.5%	8.71	1.10
NYHA II, QRS duration≥120ms and <150ms	100.0%	88.1%	75.6%	63.4%	52.9%	43.3%	9.15	1.31
NYHA II, QRS duration≥150ms	100.0%	88.7%	76.8%	65.1%	54.8%	45.1%	9.48	1.16
NYHA III, QRS duration≥120ms and <150ms	100.0%	77.8%	58.0%	42.0%	30.5%	21.6%	5.52	1.72
NYHA III, QRS duration≥150ms	100.0%	77.5%	57.5%	41.2%	29.6%	20.6%	5.36	1.46
NYHA IV, QRS duration≥120ms and <150ms	100.0%	57.7%	31.7%	17.3%	9.8%	5.5%	2.86	1.95
NYHA IV, QRS duration≥150ms	100.0%	58.9%	32.5%	17.2%	9.3%	4.7%	2.81	1.68
Individuals with LBBB morphology								
NYHA I, QRS duration≥120ms and <150ms[a]	100.0%	89.5%	78.2%	67.1%	57.3%	47.9%	10.18	1.42
NYHA I, QRS duration≥150ms[a]	100.0%	89.9%	79.0%	68.0%	58.3%	48.6%	10.18	1.23
NYHA II, QRS duration≥120ms and <150ms	100.0%	90.5%	80.2%	69.9%	60.7%	51.6%	10.99	1.49
NYHA II, QRS duration≥150ms	100.0%	91.6%	82.5%	73.1%	64.6%	55.8%	11.85	1.35
NYHA III, QRS duration≥120ms and <150ms	100.0%	80.3%	62.2%	47.0%	35.7%	26.4%	6.32	1.90
NYHA III, QRS duration≥150ms	100.0%	82.8%	66.4%	51.9%	40.6%	30.8%	7.02	1.77
NYHA IV, QRS duration≥120ms and <150ms	100.0%	62.9%	37.6%	22.0%	13.3%	8.0%	3.37	2.21
NYHA IV, QRS duration≥150ms	100.0%	65.4%	40.8%	24.8%	15.4%	9.1%	3.56	2.02

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a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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Appendix 6: Results from additional economic sensitivity analyses

Table S14: Cost-effectiveness results generated using constant treatment effects

Pt. group	C-E Sequence				ICERs			
	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Individuals without LBBB morphology								
NYHA I, QRS duration<120ms[a]	MT	ICD	N/A	N/A	Referent	£17,799	N/A	N/A
NYHA I, QRS duration≥120ms and <150ms[a]	MT	CRTD	ICD	N/A	Referent	Dominated	£12,991	N/A
NYHA I, QRS duration≥150ms[a]	MT	ICD	CRTD	N/A	Referent	£17,390	£19,372	N/A
NYHA II, QRS duration<120ms	MT	ICD	N/A	N/A	Referent	£17,305	N/A	N/A
NYHA II, QRS duration≥120ms and <150ms	MT	CRTD	ICD	N/A	Referent	Dominated	£13,210	N/A
NYHA II, QRS duration≥150ms	MT	ICD	CRTD	N/A	Referent	£16,577	£20,796	N/A
NYHA III, QRS duration<120ms	MT	ICD	N/A	N/A	Referent	£24,187	N/A	N/A
NYHA III, QRS duration≥120ms and <150ms	MT	CRTP	ICD	CRTD	Referent	£17,350	Ext Dominated	£20,117
NYHA III, QRS duration≥150ms	MT	ICD	CRTP	CRTD	Referent	Dominated	£12,008	£20,692
NYHA IV, QRS duration<120ms	MT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
NYHA IV, QRS duration≥120ms and <150ms	MT	CRTP	CRTD	N/A	Referent	£21,805	£37,981	N/A
NYHA IV, QRS duration≥150ms	MT	CRTP	CRTD	N/A	Referent	£16,271	£33,035	N/A
Individuals with LBBB morphology								
NYHA I, QRS duration≥120ms and <150ms[a]	MT	ICD	CRTD	N/A	Referent	£16,438	£18,239	N/A
NYHA I, QRS duration≥150ms[a]	MT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,058	N/A
NYHA II, QRS duration≥120ms and <150ms	MT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,318	N/A

NYHA II, QRS duration≥150ms	MT	ICD	CRTD	N/A	Referent	Ext Dominated	£13,510	N/A
NYHA III, QRS duration≥120ms and <150ms	MT	ICD	CRTP	CRTD	Referent	Dominated	£12,071	£20,255
NYHA III, QRS duration≥150ms	MT	ICD	CRTP	CRTD	Referent	Dominated	£8,935	£22,075
NYHA IV, QRS duration≥120ms and <150ms	MT	CRTP	CRTD	N/A	Referent	£17,519	£33,833	N/A
NYHA IV, QRS duration≥150ms	MT	CRTP	CRTD	N/A	Referent	£13,733	£36,328	N/A

a) Results in NYHA I and IV patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.

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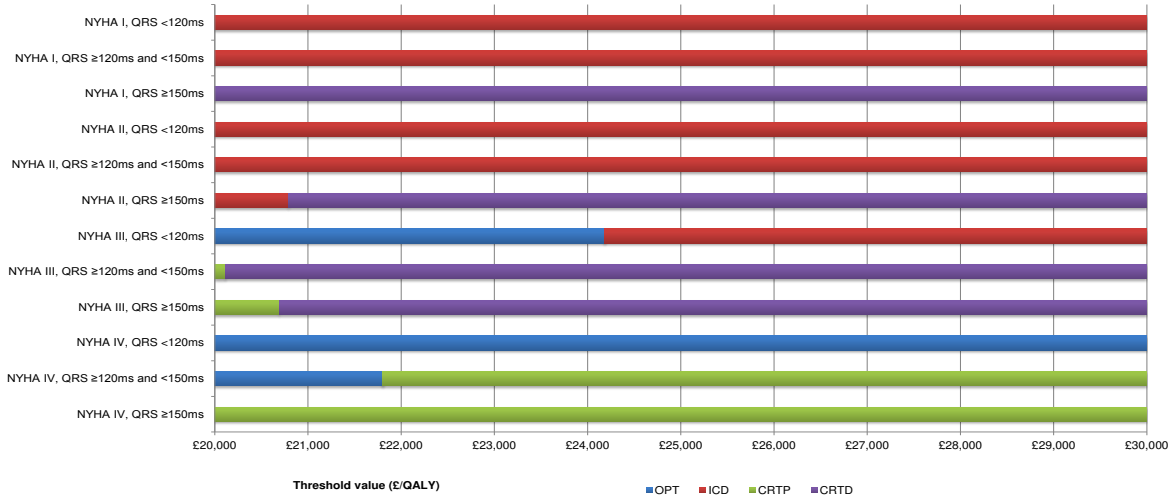
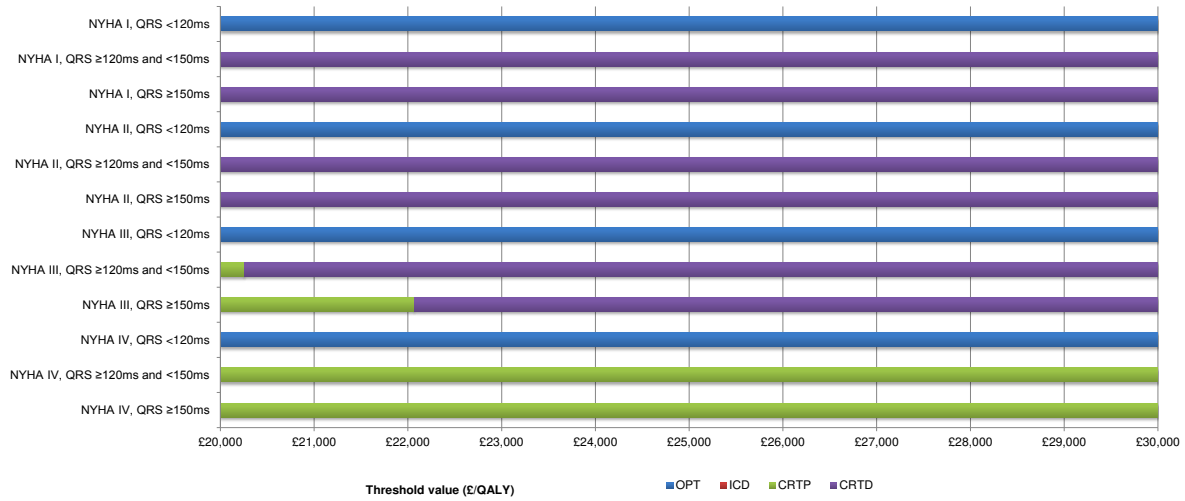
Figure S1: Graphic display of cost-effective option across cost-effectiveness threshold values in patients with LBBB morphology (sensitivity analyses – constant all-cause mortality and HRQoL treatment effects)



Panel a) patients without LBBB morphology



Panel b) patients with LBBB morphology

Legend: Results in NYHA I patients are based on relatively low patient numbers and may be subject to bias due to the nature of trial inclusion criteria for NYHA I patients. For further detail see main text.