Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation

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Scientific summary

Treatment of arrhythmias and HF with ICDs and CRT
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Scientific summary

Background

Management of people at increased risk of sudden cardiac death (SCD) as a result of ventricular arrhythmias and of people with heart failure (HF) due to left ventricular systolic dysfunction (LVSD) and cardiac dyssynchrony has continued to evolve. Implantable cardioverter defibrillators (ICDs), which can restore normal heart rhythm using pacing, cardioversion or defibrillation, and cardiac resynchronisation therapy (CRT), which resynchronises the contraction of the heart using biventricular pacing [CRT-pacer (CRT-P)] or combines the functionality of CRT-P and an ICD (known as CRT-defibrillator CRT-D), are used to manage these conditions. Given the considerable overlap in the conditions experienced by the different patient groups, some uncertainty remains as to which device(s) provide the most effective option(s) for their treatment.

Objectives

To assess the clinical effectiveness and cost-effectiveness of:

- ICDs in addition to optimal pharmacological therapy (OPT) for people who are at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT
- CRT-P or CRT-D in addition to OPT for people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT
- CRT-D in addition to OPT for people with both conditions.

Methods

Data sources

Electronic bibliographic databases including MEDLINE, EMBASE and The Cochrane Library were searched from inception to November 2012 for English-language articles. Bibliographies of included articles and manufacturers' submissions to the National Institute for Health and Care Excellence (NICE) were searched. Experts in the field were asked to identify additional published and unpublished references.

Study selection

Titles and abstracts were screened for eligibility by two reviewers independently. Inclusion criteria were applied to the full text of retrieved papers by one reviewer and checked independently by a second reviewer. Inclusion criteria were as follows:

- people at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT (studies comparing ICD with OPT)
- people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT (studies comparing CRT-P or CRT-D with each other or with OPT)
- people with both conditions described above (studies comparing CRT-D with ICD, CRT-P or OPT)
- outcome measures: mortality, adverse effects of treatment, health-related quality of life (HRQoL), symptoms and complications related to tachyarrhythmias and/or HF, HF hospitalisations, change in New York Heart Association (NYHA) class and change in left ventricular ejection fraction (LVEF)
- only randomised controlled trials (RCTs) or full economic evaluations were eligible.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved through discussion at each stage. The manufacturer's submission to NICE was reviewed.

Data synthesis

Studies were synthesised through a narrative review with full tabulation of results. Where appropriate, studies were combined in a meta-analysis.

Economic model

The model previously developed for the technology assessment of CRT for HF was adapted to estimate the cost-effectiveness of ICDs, CRT-P and CRT-D in the scoped populations. The Markov state transition model simulated disease progression in a cohort of patients who moved between distinct health states over their lifetime. Disease progression varied according to the characteristics of the population group and the care pathway that they follow. The key events modelled were hospitalisation because of HF or arrhythmia, transplant, surgical failure, death, perioperative complications of the implant procedure, routine device replacements, lead displacement, infections and device upgrades. Utility values for the several health states modelled were used to estimate the benefit of each intervention in terms of quality-adjusted life-years (QALYs). Resource use and cost estimation aimed to cost all relevant resources consumed in the care of patients in the three populations. The resources considered in the current model included medication, resources involved in device implantation, device-related complications and maintenance, hospitalisation because of HF or severe arrhythmia, and heart transplantation. Costs and benefits were discounted at 3.5% per annum. The perspective of the cost-effectiveness analysis was that of the NHS and Personal Social Services. Uncertainty was explored through deterministic and probabilistic sensitivity analysis.

Results

Clinical effectiveness

A total of 4556 references were identified, of which 26 RCTs were included in the review: 13 compared ICDs with medical therapy in people at risk of SCD as a result of ventricular arrhythmias; four compared CRT-P (and CRT-D in one RCT) with OPT in people at risk of HF because of LVSD and cardiac dyssynchrony; and nine compared CRT-D with ICD in people with both conditions.

People at risk of sudden cardiac death as a result of ventricular arrhythmias

Previous ventricular arrhythmia/cardiac arrest (secondary prevention)

Compared with antiarrhythmic drugs, ICDs reduced the risk of all-cause mortality [four RCTs; risk ratio (RR) 0.75, 95% confidence interval (CI) 0.61 to 0.93, $p = 0.01$]. One RCT found no significant differences in quality of life (QoL), whereas a second RCT found improvements with ICD but not in the control group. Prespecified subgroups did not differ significantly.

Recent myocardial infarction (within 6–41 days or ≤ 31 days)

Meta-analysis found no difference in all-cause mortality between the groups (two RCTs; RR 1.04, 95% CI 0.86 to 1.25, $p = 0.69$). QoL was not reported. No significant differences in all-cause mortality were found for 13 prespecified subgroups in one RCT.

Remote myocardial infarction (> 3 weeks or > 1 month previously)

Meta-analysis found a reduction in all-cause mortality with the use of ICDs (two RCTs; RR 0.57, 95% CI 0.33 to 0.97, $p = 0.04$). One RCT reporting hospitalisations found higher rates per 1000 months' follow-up among people receiving an ICD (11.3 vs. 9.4, $p = 0.09$), with higher HF hospitalisations (19.9% vs. 14.9%).

Differences in QoL measured using the Health Utilities Index 3 (HUI3) were not statistically significant between groups. All-cause mortality for 12 prespecified subgroups was similar.

Non-ischaemic or idiopathic dilated cardiomyopathy

Meta-analysis found no significant difference in all-cause mortality between the groups (three RCTs; RR 0.77, 95% CI 0.52 to 1.15, $p = 0.20$). Two trials reported no significant differences in QoL. One trial reported no statistically significant differences in six prespecified subgroup analyses for all-cause mortality. Meta-analysis of the three cardiomyopathy trials and the non-ischaemic congestive HF subgroup of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) found a statistically significant reduction in all-cause mortality with ICD therapy (RR 0.74, 95% CI 0.58 to 0.93, $p = 0.01$).

Scheduled for coronary artery bypass graft

One RCT found no difference in all-cause mortality between the groups (RR 1.08, 95% CI 0.85 to 1.38, $p = 0.53$).

Health-related quality of life was significantly better among people receiving OPT for some measures. There was no difference in all-cause mortality among 10 prespecified subgroups.

A broad population with mild to moderate ischaemic/non-ischaemic heart failure and a left ventricular ejection fraction of ≤ 35%

One three-arm trial compared ICDs, amiodarone and placebo. Compared with placebo, ICDs reduced the risk of all-cause mortality [hazard ratio (HR) 0.77, 97.5% CI 0.62 to 0.96, $p = 0.007$]. No significant difference was found in QoL. QoL was lower in people who had had an ICD shock within the previous month than in those who had not received a shock. There was no interaction of ICD therapy with the cause of congestive HF. Compared with placebo, ICDs reduced the risk of all-cause mortality in those in NYHA class II but not in NYHA class III.

Adverse events

Between 5% and 61% of people with an ICD experienced an adverse event, depending on the definition of adverse event and length of follow-up. Three trials reporting adverse event rates for the comparator treatment found rates between 12% and 55%. Lead-, electrode- or defibrillator generator-related problems affected 1.8–14% of people in five trials reporting this.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

Compared with OPT, CRT-P reduced the risk of all-cause mortality (four RCTs; RR 0.75, 95% CI 0.58 to 0.96, $p = 0.02$). An improvement in NYHA class (three RCTs; RR 1.68, 95% CI 1.52 to 1.86, $p < 0.00001$), LVEF (one RCT; $p < 0.001$), exercise capacity (three RCTs) and QoL [four RCTs; Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score mean difference (MD) –10.33, 95% CI –13.31 to –7.36, $p < 0.00001$] was also found with CRT-P. Prespecified subgroup analysis found that people with non-ischaemic heart disease had a greater change in LVEF, but there was little difference in the effect of CRT-P on the composite outcome for 16 subgroups.

One RCT found that CRT-D reduced the risk of all-cause mortality compared with OPT (HR 0.64, 95% CI 0.48 to 0.86, $p = 0.003$). Improvements in NYHA class (57% vs. 38%, $p < 0.001$), exercise capacity (6-minute walk distance 46 m vs. 1 m) and QoL (MLWHFQ score –26 vs. –12, $p < 0.001$) were also found with CRT-D at 6 months.

The rate of SCD was higher with CRT-P than with CRT-D (RR 2.72, 95% CI 1.58 to 4.68, $p = 0.0003$), but all-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p = 0.12$), HF hospitalisations (28% vs. 29%) and changes in NYHA class, exercise capacity and QoL were similar for CRT-P and CRT-D.

Adverse events

The rate of device-related deaths was between 0.2% and 0.8% for CRT-P (two trials) and 0.5% for CRT-D. The rate of moderate or severe adverse events related to the implantation procedure was 10% for CRT-P and 8% for CRT-D in one trial, with 13% and 9% of CRT-P and CRT-D implantations, respectively, unsuccessful. Moderate or severe adverse events from any cause were more common with CRT-D than with OPT (CRT-D 69%, CRT-P 66%, OPT 61%, CRT-D vs. OPT: $p = 0.03$; CRT-P vs. OPT: $p = 0.15$). Reported complications included lead displacements, infections and coronary sinus dissections.

People with both conditions

Compared with ICDs, CRT-D reduced the risk of all-cause mortality (eight RCTs; RR 0.84, 95% CI 0.73 to 0.96, $p = 0.01$) and HF hospitalisation (three RCTs; RR 0.75, 95% CI 0.64 to 0.88, $p = 0.0005$). No difference in the proportion of people experiencing at least one episode of ventricular tachycardia or ventricular fibrillation was found (four RCTs; RR 0.90, 95% CI 0.71 to 1.14, $p = 0.38$). An improvement in mean NYHA class (two RCTs; MD –0.19, 95% CI –0.34 to –0.05, $p = 0.008$) but not in the proportion of people who improved by one or more NYHA classes (three RCTs; RR 1.81, 95% CI 0.91 to 3.60, $p = 0.09$) was found with CRT-D. Improvements in LVEF (eight RCTs; MD 2.15, 95% CI 0.45 to 3.86, $p = 0.01$), exercise capacity and QoL (six RCTs; MLWHFQ score MD –6.9, 95% CI –10.4 to –3.4, $p = 0.0001$) were found with CRT-D compared with ICDs. Prespecified subgroup analyses found that longer QRS duration, women, left bundle branch block and non-ischaemic cardiomyopathy were associated with greater benefit from CRT-D for certain outcomes. One large RCT found significantly higher device- or implantation-related complications (13.3% vs. 6.8%, $p < 0.001$) and device-related hospitalisation (20% vs. 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p < 0.001$) with CRT-D than with ICDs.

Cost-effectiveness

A total of 1410 references were identified of which 51 economic evaluations were included in the review of cost-effectiveness (34 reported on ICDs, 15 reported on CRT and two reported on both ICDs and CRT). ICDs were reported to be cost-effective in almost half of the ICD studies. One relevant UK study reported a mean incremental cost-effectiveness ratio (ICER) for an average UK secondary prevention patient of £76,139 per QALY gained. Almost all CRT studies reported that CRT was cost-effective. One relevant UK study estimated an ICER of £16,735 per QALY gained for CRT-P compared with OPT and an ICER of £40,160 per QALY gained for CRT-D compared with CRT-P.

Six HRQoL studies were found. Two included people with an ICD; one found that the mean European Quality of Life-5 Dimensions (EQ-5D) score did not change with time after implant and the other reported no difference between EQ-5D scores of primary and secondary prevention patients and that QoL for ICD patients was similar to that of the general population. Four cohort studies reported EQ-5D scores in HF and the overall results showed decreased EQ-5D scores compared with scores in the general population, particularly in NYHA classes III and IV.

One joint manufacturer's submission was received from the Association of British Healthcare Industries (ABHI). The general approach taken in the manufacturer's submission seems reasonable although it is not clear whether or not uncertainty is properly assessed. Subgroups specified by ABHI do not directly address those scoped by NICE. Overall, the results show that for most subgroups there is at least one device with an ICER of < £30,000 per QALY gained, and in some cases a different device might have an ICER of < £20,000 per QALY gained.

Independent economic evaluation

People at risk of sudden cardiac death as a result of ventricular arrhythmias

The addition of ICD to OPT for the secondary prevention of SCD has an ICER of £19,479 per QALY gained compared with OPT alone. The probability of it being cost-effective at a willingness to pay (WTP) of £20,000 and £30,000 per QALY gained is 51% and 82% respectively. The ICER for the mixed-age cohort is slightly higher (£24,967 per QALY), as the ICER increased with age and 52% of these patients are

expected to be aged > 65 years. Subgroup analyses for ICD + OPT compared with OPT alone produced ICERs of £14,231 per QALY for people with remote myocardial infarction (MI), £29,756 per QALY for a broad population with mild to moderate HF and £26,028 per QALY for non-ischaemic cardiomyopathy. The parameters with the greatest impact on the ICER were the time horizon, the HR for all-cause mortality associated with the ICD + OPT arm, the risk of surgical death during ICD implantation and the lifetime of the device.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

The addition of CRT-P to OPT (in the initial stage of management of HF) resulted in an estimated ICER of £27,584 per QALY gained compared with initial management with OPT alone (allowing for the subsequent implants). Similarly, the initial implant of CRT-D alongside OPT resulted in an ICER of £27,899 per QALY gained compared with OPT alone. When comparing CRT-D + OPT with CRT-P + OPT, a slightly higher ICER was estimated for CRT-D + OPT (£28,420 per QALY gained). At a WTP of £20,000 per QALY gained, initial management with OPT alone followed by implantation of the clinically necessary device is the strategy with the highest probability of being cost-effective (83%). Above a WTP of £28,000 per QALY, the strategy with the highest probability of being cost-effective is CRT-D + OPT (38%). The incremental cost-effectiveness results for the comparisons seem to be sensitive mainly to device-related costs and to parameters that determine the incremental benefit of the devices for patients' survival, such as the RRs of SCD and HF death for CRT-P. The device lifetime of CRT-D also was particularly influential because of the incremental costs incurred when it became shorter. In a scenario assuming the upper limit estimates of device-related costs or lower estimates for the longevity of all devices, both CRT-P + OPT and CRT-D + OPT became non-cost-effective compared with initial management with OPT alone (followed by the subsequent upgrades).

People with both conditions

The most cost-effective strategy for people with both conditions at a WTP range of £20,000–30,000 per QALY is initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary). Both strategies with the initial implantation of CRT devices have ICERs of > £30,000 per QALY compared with OPT alone (CRT-D £35,193 per QALY; CRT-P £41,414 per QALY). Costs and QALYs for CRT-D and CRT-P are similar, as the effectiveness of CRT-P was assumed to be the same as for CRT-D. CRT-D + OPT has an ICER of £27,195 per QALY compared with ICD + OPT. At a WTP of £30,000 per QALY, OPT alone, ICD + OPT, CRT-D + OPT and CRT-P + OPT have a 44%, 31%, 15% and 10% probability of being cost-effective respectively. CRT-D + OPT becomes the intervention with the highest probability of being cost-effective above a WTP of £42,000 per QALY. Assuming the same HF progression as used in the model for people with HF and no ICD indication gives an ICER of £27,396 per QALY for CRT-D compared with OPT. The cost-effectiveness results for the comparison of CRT-D + OPT with ICD + OPT were fairly robust to the variation of input parameters. The most influential parameters were the RR of all-cause mortality for ICDs and the lifetime of the CRT-D and ICD devices.

Discussion

A de novo economic model was developed for the current appraisal following recognised guidelines, and systematic searches were conducted to identify the data inputs for the model. The independent model was adapted from the model structure used in the previous appraisal of CRT for HF [NICE technology appraisal (TA)120], providing a consistent approach and enabling comparability.

Despite following recognised guidance on developing economic models, the evaluation has some limitations. These include the use of structural assumptions about the risks and timing of reimplantation of devices and treatment options following occurrence of a major event from previous models; the extrapolation of trial survival estimates over time; and assumptions around parameter values when evidence was not available for specific patient groups, particularly for CRT-P in people with both

conditions. When limitations have arisen in the evaluation, these have been identified in the report. Assumptions made or data identified from alternative sources have been checked by seeking clinical advice and the effects of parameters thought to be influential to the results have been assessed through sensitivity analyses.

In general, the independent models were relatively robust to changes in the assumptions and data parameter values. Those parameters with the greatest impact on the cost-effectiveness results were the time horizon, the HR for all-cause mortality associated with the devices, and the lifetime of the devices.

Conclusions

Implantable cardiac defibrillators reduced all-cause mortality in people at increased risk of SCD, defined in trials as those with previous ventricular arrhythmias/cardiac arrest, remote MI, non-ischaemic cardiomyopathy (depending on data included) or ischaemic/non-ischaemic HF and LVEF $\leq 35\%$, but not in people scheduled for coronary artery bypass grafting or with recent MI. The addition of ICD to OPT was cost-effective at a WTP threshold of £30,000 for the scenarios modelled, and in some cases at a WTP threshold of £20,000, in patients at risk of SCD. CRT-P and CRT-D reduced all-cause mortality and HF hospitalisations and improved other outcomes in people with HF as a result of LVSD and cardiac dyssynchrony when compared with OPT. The rate of SCD was lower with CRT-D than with CRT-P, but other outcomes, including all-cause mortality, were similar. Both CRT-P and CRT-D had an ICER of $<$ £30,000 per QALY gained compared with OPT, as did the comparison between CRT-D and CRT-P in people with HF as a result of LVSD and cardiac dyssynchrony. In people with both conditions, CRT-D reduced the risk of all-cause mortality and HF hospitalisation, and improved other outcomes, compared with ICD. The ICER for the comparison of CRT-D + OPT with ICD + OPT but not with initial management with OPT alone was $<$ £30,000 per QALY (unless no difference in all-cause mortality was assumed). The costs and QALYs for CRT-D and CRT-P were similar.

A RCT comparing CRT-D and CRT-P in people with HF due to LVSD and cardiac dyssynchrony is required, for both those with and those without an ICD indication. A trial is needed of the benefits of ICD in non-ischaemic cardiomyopathy in the absence of dyssynchrony.

Study registration

This study is registered as PROSPERO number CRD42012002062.

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