NATIONAL INSTITUTE FOR HEALTH
AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)

Response from:

British Heart Rhythm Society

(formerly Heart Rhythm UK)

Introduction

The British Heart Rhythm Society (BHRS, formerly Heart Rhythm UK) is pleased to have the opportunity to comment on the Appraisal Consultation Document for implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120), published in January 2014.

We recognise the complexity of combining two sets of technology appraisal guidance into a single unified document. We applaud the careful analysis of clinical and cost effectiveness data and the work of the Southampton and ABHI groups in analysing the clinical trial results. This has produced innovative data which shed new light on efficacy in sub-groups which have been difficult to study in individual trials.

In particular, we are pleased that the committee has agreed with BHRS's assessments regarding left ventricular function assessment, non-ischaemic cardiomyopathy, non-sustained ventricular tachycardia, induction of ventricular arrhythmias, atrial fibrillation, echocardiographic dys-synchrony, and the utility of left bundle branch block in patients with QRS durations between 120 and 149ms.

No change has been proposed to secondary prevention guidance and this is appropriate.

The proposed guidance can be summarised in the following table:

LVEF ≤35%	NYHA I	NYHA II	NYHA III	NYHA IV
QRS <120ms	OPT	OPT	OPT	OPT
QRS 120-149ms without LBBB	ICD	ICD	ICD	CRT-P
QRS 120-149ms with LBBB	ICD	ICD	CRT-P or D	CRT-P
QRS ≥150ms without LBBB	CRT-D	CRT-D	CRT-P or D	CRT-P
QRS ≥150ms with LBBB	CRT-D	CRT-D	CRT-P	CRT-P

We would welcome the use of a similar table in the final appraisal documents for clarity.

Whilst we recognise that these proposals significantly improve on previous guidance, much more closely reflecting the current published trial data, meta-analyses and international guidance, we have major concerns in four patient categories: people with severe left ventricular impairment (LVEF ≤35%) and QRS <120ms; people with severe left ventricular impairment (LVEF ≤35%), QRS 120-149ms with LBBB and NYHA I or II heart failure symptoms; and people with severe left ventricular impairment (LVEF ≤35%), QRS ≥150ms with LBBB and NYHA III heart failure symptoms. We also question the selection of ICD therapy over CRT-D in patients with NYHA III symptoms and QRS 120-149ms without LBBB.

1) LVEF ≤35%, QRS <120ms NYHA I-III

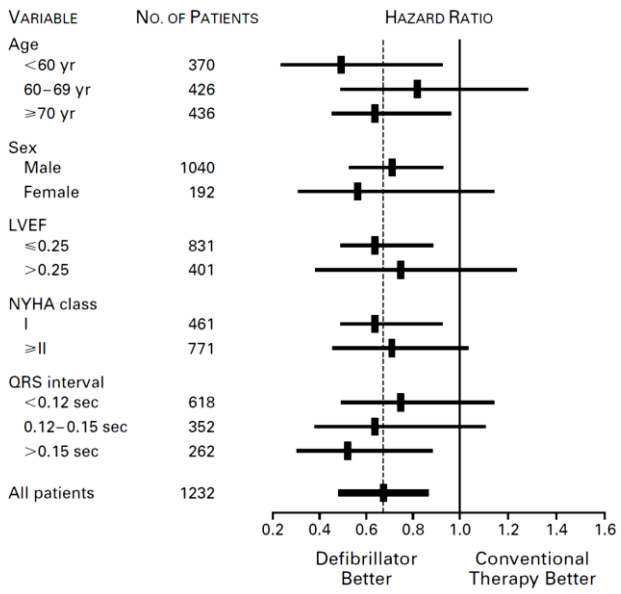
We recognise that QRS duration is critical in the selection of patients who benefit from CRT and that in the meta-analyses used in the appraisal, QRS duration is associated with baseline risk and treatment effect. However, QRS duration has never been used as an inclusion criterion for an ICD trial, and we are concerned that there is significant heterogeneity between patients with QRS <120ms, and that many are at high-risk of sudden cardiac death.

Data from the ABHI network meta-analysis published previously has shown highly favourable hazard ratios in all sub-groups other than women over 60-years-old:

Gender	Age	QRS	ICD vs. OMT
Female	<60	<120	0.82 (0.60, 1.13)
	>=60	<120	1.01 (0.76 , 1.36)
Male	<60	<120	0.62 (0.48 , 0.79)
	>=60	<120	0.76 (0.62 , 0.94)

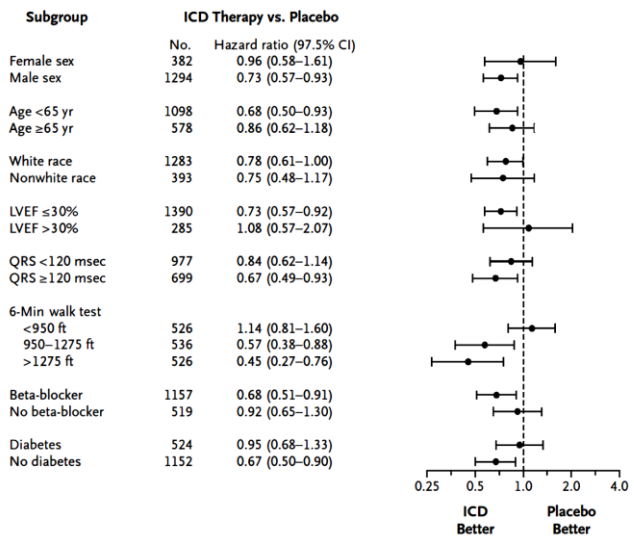
In the light of these data, BHRS requested the ABHI network meta-analysis group to provide further details on ICER calculations within these subgroups. These show ICERs for men under 60-years of £16,572 in NYHA I, £17,317 in NYHA II and £19,378 in NYHA III. The committee has recognised (section 4.3.9) "that some patient characteristics, such as age, sex, QRS duration and LBBB, were predictors of benefit from the different devices (effect modifiers)" and we are very concerned at the prospect of denying ICD therapy to groups of patients who derive significant clinical benefit.

As stated in the original BHRS submission, sub-set analysis of the MADIT II data was used in previous NICE guidance to restrict ICD therapy to those with QRS duration >120ms and LVEF ≤30%. However, there were no statistically significant differences in the effect of ICD therapy on survival when patients were stratified by QRS duration.



This Forest plot also demonstrates a greater benefit from ICD therapy in those <60 years.

Sub-set analyses of SCD-HeFT, do show a lower hazard ratio for patients with QRS ≥120ms than those <120ms but the relative risk reduction in those with normal QRS duration is 16% at 5 years:



This also demonstrates the greater benefit from ICD therapy in males and those <65 years.

International guidance supports the implantation of ICDs in patients with QRS <120ms:

a) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (Epstein *et al.* Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American ACC/AHA/HRS 2008. *J Am Coll Cardiol* 2008;**51**:e1-e62 http://content.onlinejacc.org/cgi/content/full/51/21/e1):

CLASS I

4. **ICD therapy is indicated in patients with LVEF less than or equal to 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III. *(Level of Evidence: A)*** (16,333)
5. **ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III. *(Level of Evidence: B)*** (16,333,369,379)
6. **ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30%, and are in NYHA functional Class I. *(Level of Evidence: A)*** (16,332)
7. **ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiological study. *(Level of Evidence: B)*** (16,327,329)

CLASS IIa

2. **ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. *(Level of Evidence: C)***
3. **ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD. *(Level of Evidence: C)***
4. **ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD. *(Level of Evidence: C)***

6. **ICD implantation is reasonable for non hospitalized patients awaiting transplantation. *(Level of Evidence: C)***

b) European Society of Cardiology

Current ESC guidance (Guidance on the diagnosis and treatment of acute and chronic heart failure 2012, McMurray *et al. European Heart Journal* 2012;**33**:1787-1847) states:

Primary prevention An ICD is recommended in a patient with symptomatic HF (NYHA class II–III) and an EF ≤35% despite ≥3 months of treatment with optimal pharmacological therapy, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death			
(i) Ischaemic aetiology and >40 days after acute myocardial infarction	I	A	148, 149
(ii) Non-ischaemic aetiology	I	B	149

c) UK

Current NICE guidance (Technology Appraisal 95 Implantable cardioverter defibrillators for arrhythmias, January 2006) states that ICD implantation is recommended for patients:

A history of previous (more than four weeks) myocardial infarction (MI) and:

either

- Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure), and
- Non-sustained VT on Holter (24 hour electrocardiogram [ECG]) monitoring, and
- Inducible VT on electrophysiological (EP) testing

or

- Left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure),

and

- QRS duration of equal to or more than 120ms

Supported by trial data and meta-analyses, we BHRS that the absence of non-sustained ventricular tachycardia or inducible VT on electrophysiology testing does not identify a low-risk group. The current appraisal consultation document does not recommend ICD therapy for any of these patients who are currently receiving this therapy.

It should be noted that the majority of patients with QRS <120ms require only single chamber ICDs. These have a lower cost and greater battery longevity than the mean figures quoted in the ACD and would therefore be expected to be reflected in lower ICERs.

BHRS would like to reassure the committee that although ICD shocks can cause distress, ICDs are not designed to be a primarily symptomatic treatment. When patients understand that the alternative to a shock would usually be sudden death, they are very accepting of this treatment and actively choose to continue it.

We urge the committee to reconsider the recommendation in this category of patients in whom the ICERs for ICD therapy are £25,714 to £29,309 as there is no other appropriate treatment to reduce their risk of sudden death.

2) LVEF ≤35%, QRS 120-149ms

The table below shoes ICERs using the committee's preferred model of a constant mortality treatment effect for 5 years followed by tapering over 20 years, taken from the original submission. Treatments with ICERs <£30,000 are shown in bold, the treatment recommended in the ACD is shown in red:

LVEF ≤35%	NYHA I	NYHA II	NYHA III	NYHA IV
QRS <120ms	CRT-P n/a **ICD £25,714** CRT-D n/a	CRT-P n/a **ICD £26,181** CRT-D n/a	CRT-P n/a **ICD £29,309** CRT-D n/a	CRT-P n/a ICD n/a CRT-D n/a
QRS 120-149ms without LBBB	CRT-P n/a **ICD £16,253** CRT-D Dominated	CRT-P n/a **ICD £16,813** CRT-D Dominated	**CRT-P £20,421** ICD Ext Dominated (£24K) **CRT-D £24,311**	**CRT-P £22,702** ICD n/a CRT-D £40,899
QRS 120-149ms with LBBB	CRT-P n/a **ICD £21,985** **CRT-D £23,080**	CRT-P n/a ICD Ext Dominated (£23K) **CRT-D £22,049**	**CRT-P £14,489** ICD Dominated **CRT-D £26,192**	**CRT-P £18,817** ICD n/a CRT-D £38,202
QRS ≥150ms without LBBB	CRT-P n/a **ICD £22,366** **CRT-D £23,168**	CRT-P n/a **ICD £25,267** **CRT-D £21,888**	**CRT-P £14,203** ICD Dominated **CRT-D £26,586**	**CRT-P £17,330** ICD n/a CRT-D £36,934
QRS ≥150ms with LBBB	CRT-P n/a ICD Ext Dominated **CRT-D £18,615**	CRT-P n/a ICD Ext Dominated **CRT-D £18,879**	**CRT-P £10,769** ICD Dominated CRT-D £30,548	**CRT-P £14,666** ICD n/a CRT-D £42,039

BHRS has concerns in 3 categories:

1) It is unclear why the guidance recommends ICD rather than CRT-D in patients with QRS 120-149ms without LBBB and NYHA III symptoms when it is extended dominated and CRT-D has an ICER of £24,311.

2) It is unclear why the guidance recommends ICD rather than CRT-D in patients with QRS 120-149ms with LBBB and NYHA I symptoms when the ICER for CRT-D is £23,080, below that

accepted in for patients similar ECG characteristics and NYHA III symptoms.

3) It is unclear why ICD implantation is recommended for patients with QRS 120-149ms with LBBB and NYHA II symptoms when this is extended dominated by CRT-D with an ICER of £22,049.

In section 4.3.17, the committee considered evidence from two trials (RethinQ, *N Engl J Med* 2007;**357**:2461-71, and EchoCRT, *N Engl J Med* 2013;369:1395-1405) and a meta-analysis (Cleland *et al. Eur Heart J* 2013;**34**:3547-3556) in which an absence of benefit from CRT was found in patients with narrow QRS and "was concerned that the subgroups with a QRS duration between 120 and 149ms were heterogeneous, containing some patients in whom CRT may be inappropriate".

RethinQ was a trial of CRT in 172 patients with an LVEF less than 35%, NYHA class III heart failure symptoms, caused by either ischemic or non-ischemic cardiomyopathy and a QRS duration of less than 130ms. A trend to benefit from CRT was seen, with statistically significant improvements in peak oxygen consumption in the pre-specified subgroup with QRS ≥120ms (p=0.02), and NYHA class in patients with both QRS ≥120ms (p=0.01) and QRS <120ms (p=0.04):

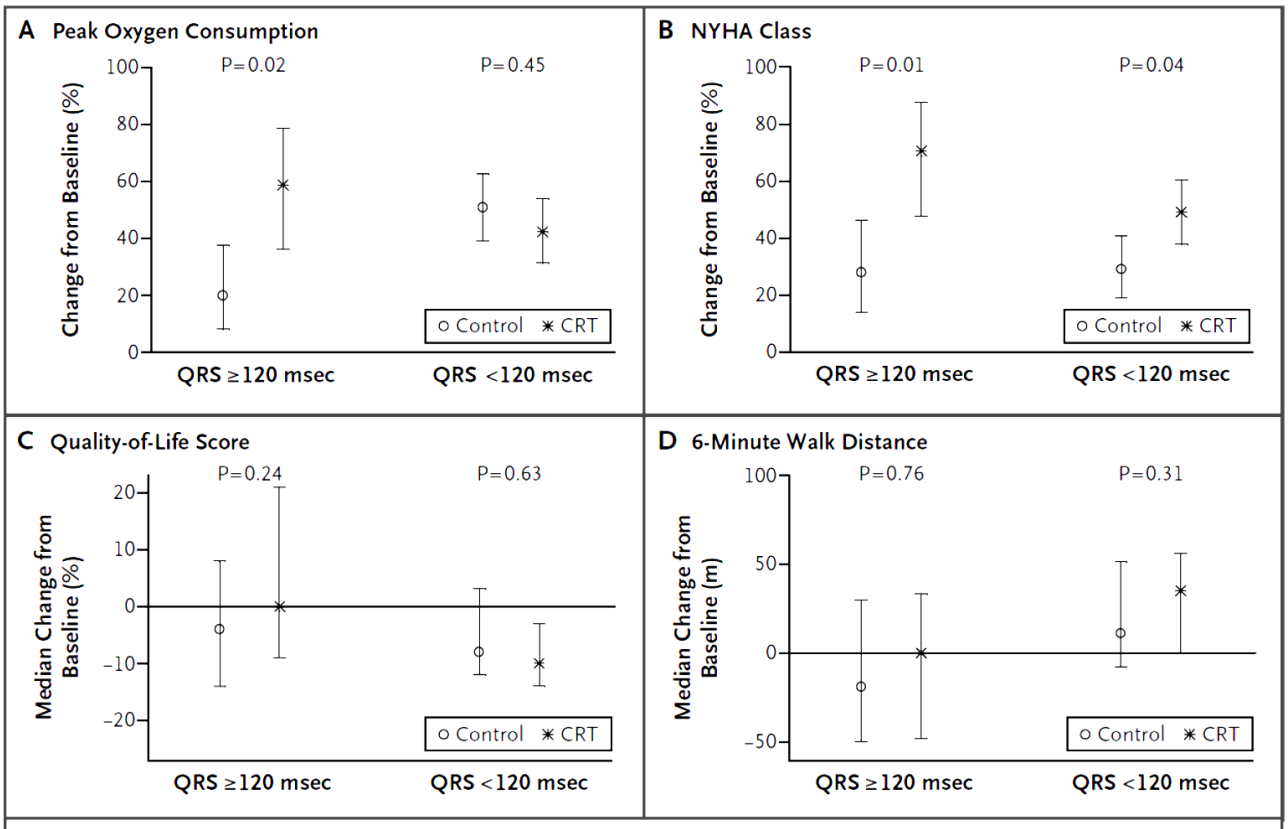


Figure 2. Subgroup Analysis According to the QRS Interval at 6 Months.

For the peak oxygen consumption, the primary end point was an increase of at least 1 ml per kilogram of body weight per minute from baseline (Panel A). For New York Heart Association (NYHA) class, shown are the proportions of patients whose condition improved by at least 1 class from baseline (Panel B). For the quality-of-life score (Panel C) and 6-minute walk distance (Panel D), shown are the median changes from baseline. In the CRT group, the QRS interval was 120 msec or more in 17 patients and less than 120 msec in 59 patients. In the control group, the QRS interval was 120 msec or more in 25 patients and less than 120 msec in 55 patients. P values are for the comparison between groups, and I bars indicate 95% confidence intervals.

However, there was no statistically significant change in the primary end point of the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months.

EchoCRT was a software randomised trial of CRT in 809 patients with NYHA class III or IV heart failure, LVEF ≤ 35%, QRS duration of < 130 ms, and echocardiographic evidence of left ventricular dyssynchrony. It concluded that CRT did not reduce the rate of death or hospitalization for heart failure in this group:

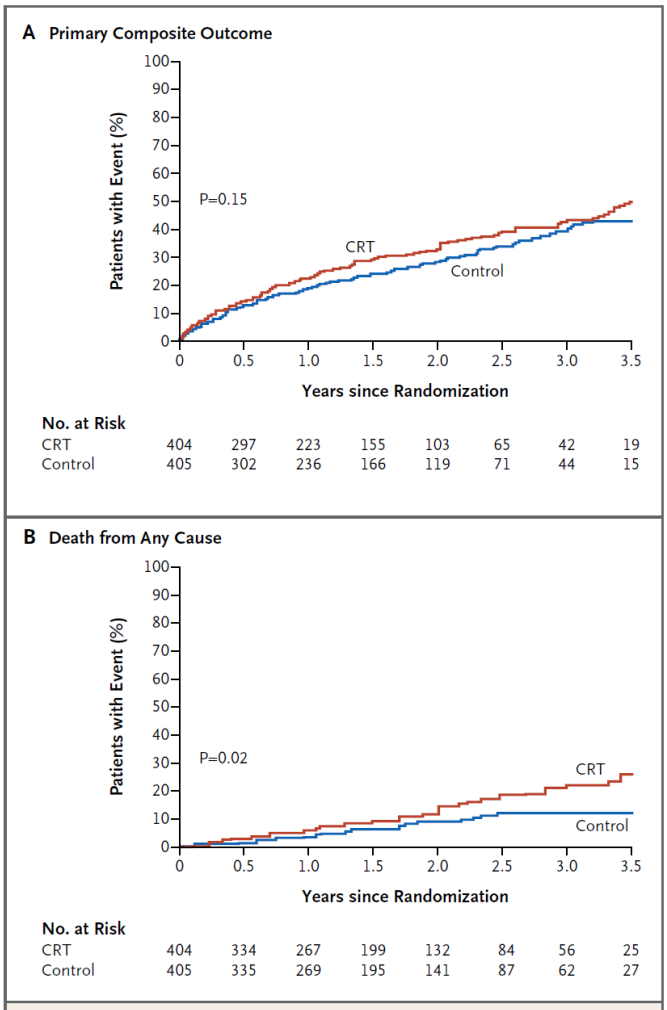


Figure 2. Kaplan–Meier Estimates for Primary-Outcome Events.
Panel A shows the Kaplan–Meier curves for the primary composite outcome of death from any cause or hospitalization for heart failure. Panel B shows the Kaplan–Meier curves for death from any cause.

It must be noted that the mean QRS duration of the patients in this trial was only 105ms, well below the selection criterion proposed in this guidance. Only 55 patients with QRS 120 to 129ms received CRT. Furthermore, on subset analysis of QRS duration, the only group for which the confidence intervals do not cross unity, was mortality in patients with QRS <120ms:

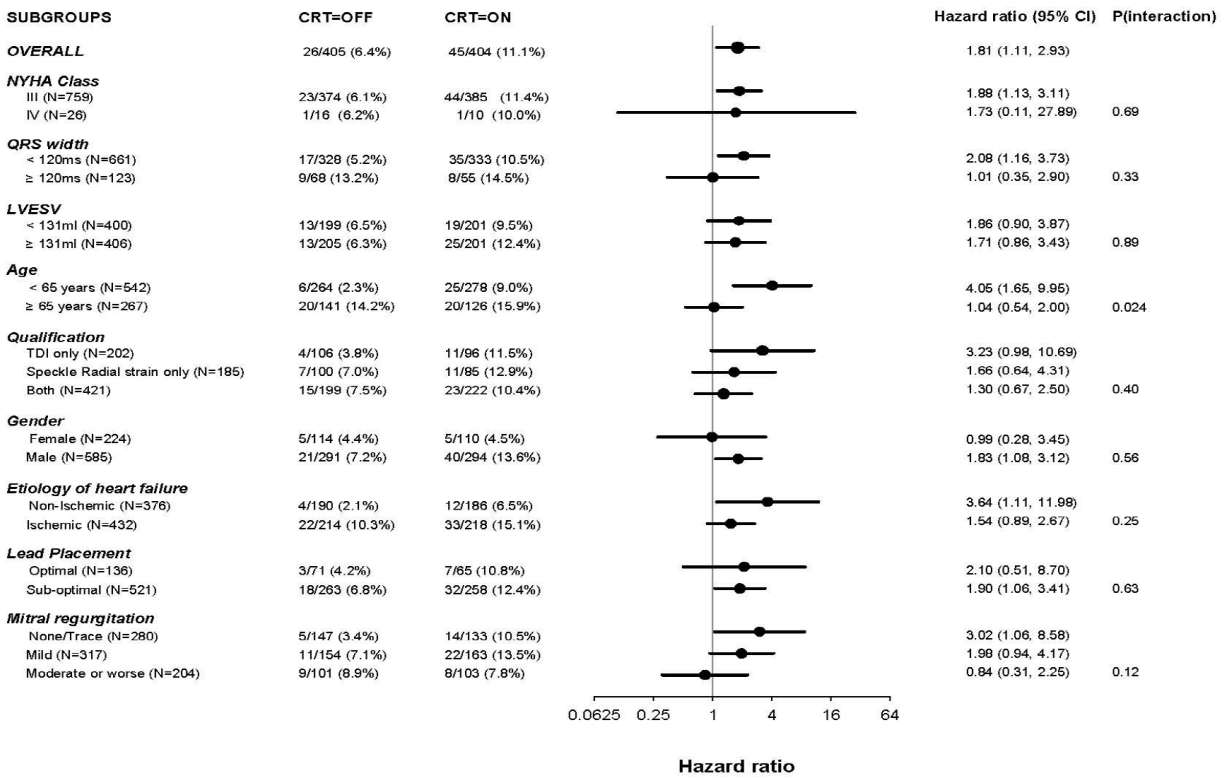
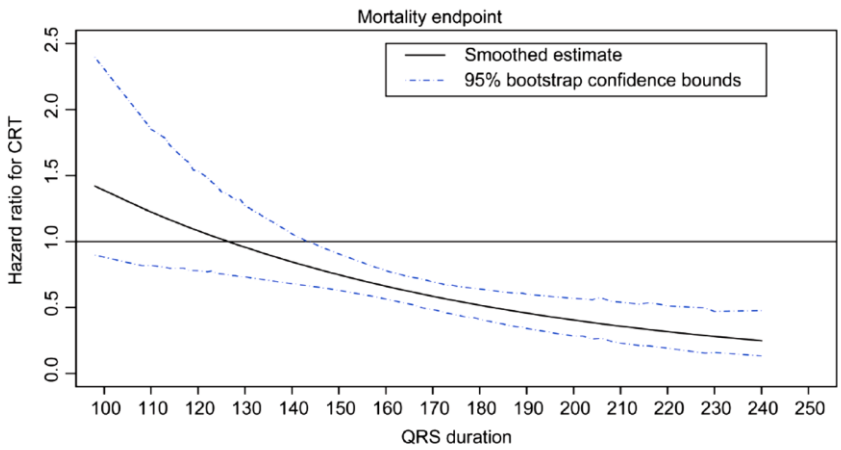


Figure S1c: Display of hazard ratios and 95% confidence intervals for CRT=ON relative to CRT=OFF for each pre-specified subgroup, with tabulation of corresponding numbers of subjects with all-cause mortality endpoint(percentage), hazard ratio and P-value for the interaction between the effect of CRT=ON relative to CRT=OFF across the subgroup categories.

Unfortunately, LBBB was not reported in this trial so the effect of CRT in pateints with QRS 120-129ms with LBBB cannot be determined.

The network meta-analysis published by Cleland *et al.* (*Eur Heart J* 2013;**34**:3547-3556) used data from 5 of the trials included in the individual patient data network meta-analysis adopted in this appriasal. The authors concluded that QRS duration was a powerful predictor of the effects of CRT on morbidity and mortality in patients with symptomatic HF and left ventricular systolic dysfunction. Patients who did not have LBBB appeared to have less benefit from CRT, especially in the composite outcome, but differences were not statistically significant.

Their model predicts mortality benefit from CRT in patients with QRS of approximately ≥ 126ms:



With the confidence intervals shown, and the trend to increased benefit in those with LBBB, these findings are consistent with the BHRS recommendation for CRT in patients with QRS 120-129ms and LBBB and the ICERs of £22,049 and £23,080.

BHRS would like to reassure the committee that there is no clinical concern about an adverse effect of CRT in patients with QRS 120-149ms and LBBB and would urge reconsideration of this recommendation.

3) LVEF ≤35%, QRS ≥150ms with LBBB, NYHA III

BHRS has serious concerns about the risk of sudden cardiac death in patients with LVEF ≤35%, NYHA III, QRS duration ≥150ms and LBBB. It is counter-intuitive to implant a CRT-P device rather than CRT-D in patients with these characteristics when patients in lower risk categories – the absence of LBBB and/or milder symptoms – are recommended to undergo CRT-D implantation. Whilst a CRT-P device will improve patient symptoms, it cannot prevent sudden cardiac death due to ventricular arrhythmias, and SCD this remains the commonest cause of death in this group of NYHA III patients.

BHRS would like to ask the committee to reconsider CRT-D treatment in this patient group with an ICER of just over £30,000.

4) Other points

BHRS would like to ask the committee to consider including the following points in its final guidance:

a) **Congenital heart disease**
For secondary prevention, the guidance should state that ICD implantation is indicted for “high risk” patients who have undergone surgical repair of congenital heart disease.

b) **Patient choice**
While a patient may have a recognised cost-effective indication for an ICD and/or a CRT device, they may have carefully considered reasons why they do not want to undergo such a procedure. The advantages and disadvantages of the treatment options must be clearly and honestly discussed and, as far as possible, individualised for that patient in order for them to come to a fully informed decision. Patient literature and decision aids should be developed to help in this discussion and decision making. The patient’s wishes must be respected.

c) **End of life care**
Defibrillators can be deactivated by simple non-invasive re-programming, and this is appropriate in a patient receiving terminal care for heart failure cancer or any other reason. Deactivation of defibrillator therapy will prevent the patient receiving painful and futile shocks at the end of their life. It is both legal and ethical to deactivate implanted devices after full discussion and agreement with a competent patient. Advice is provided in a British Heart Foundation booklet written by Dr James Beattie in 2009, Implantable cardioverter defibrillators in patients who are reaching the end of life” which is available from the BHF website (http://publications.bhf.org.uk/publications.aspx M105 ICDs end of life booklet).

Deactivation of CRT and/or bradycardia pacing is not required in this situation as pacing stimulation is asymptomatic. ICD therapy can be deactivated with affecting pacing. The depletion of a device battery should always allow reassessment of the continuing need for device therapy.

d) **National data collection**

National audit data collected by the national pacemaker and ICD database (www.devicesurvey.com) has demonstrated significant disparity in ICD and CRT implantation rates across the UK which cannot be explained by disease prevalence. The cause of this apparent inequality of access is unknown and requires further research. We suggest that NICE guidance should require each implanting centre to submit complete and timely audit data to the national database with a minimum data set including aetiology, NYHA functional class, left ventricular ejection fraction, QRS duration, history of ventricular arrhythmias (primary or secondary prevention) and complication rates. Expected implant rates for ICD and CRT have been very helpful in planning services and we would welcome revised rates in the new guidance.

e) **Reassessment**

When a patient is assessed and found not to fulfil NICE guidance criteria for device implantation, we recommend reassessment at annual review or when there is a clinical event or other change in symptoms or treatment.

f) **Implantation and follow-up**

The implantation of ICD and CRT devices is complex and can be time consuming. The complication rates are significantly higher than for bradycardia pacemakers. Device follow-up is also complex and time consuming with a requirement for individualisation of programming to optimise response and minimise the risk of inappropriate therapy. This includes the requirement for optimisation of programming in CRT devices with echocardiographic assessments, particularly in those who do not initially improve following implantation. In addition, patients with indications for ICD and CRT are complex and most have heart failure and other co-morbidity. They require frequent and expert clinical review to optimise symptoms and prevent decompensation and sudden death. Because of the effects of their underlying disease and treatment, many patients require psychological assessment and support. Implant and follow-up centres also need robust databases and protocols to deal with device complications and advisories with 24-hour cover for emergencies. It is BHRS's view that to maintain clinical the cost-effectiveness seen in the clinical trials, these devices should be implanted by high-volume operators in high-volume centres.

g) Other key points

1) All patients should receive optimal pharmacological and other therapies.
2) All patients with cardiovascular disease should be fully assessed in order to identify patients who would benefit from device therapy.
3) Patients who are found not to have a device indication should be reassessed annually or sooner if there is a change in their clinical status.
4) The advantages and disadvantages of device therapy should be discussed with all patients to allow them to come to a fully informed decision.
5) Patients with a high risk cardiac condition and a history of syncope are at similar risk of sudden cardiac death as those resuscitated from cardiac arrest and benefit from ICD implantation.

6) There are no large randomised controlled trials of primary prevention ICD therapy in patients with rare high risk cardiac conditions. The best available contemporary evidence of risk factors should be used to guide therapy.
7) Patients with QRS prolongation caused by necessary right ventricular pacing benefit from up-grade to a CRT device.
8) Patients with a bradycardia pacing indication and impaired ventricular function benefit from CRT.
9) The benefit of CRT shown in patients in atrial fibrillation is similar to sinus rhythm providing a high proportion of beats are biventricularly paced. This may require pharmacological treatment or ablation.

5) BHRS recommendations

1) All patients should undergo appropriate diagnostic tests to establish the aetiology and optimal management of their heart condition. It is essential to identify patients with conditions which can be cured with ablation therapy such as fascicular tachycardia or right ventricular outflow tract tachycardia.
2) All patients should receive optimal pharmacological therapy for their condition.
3) Patients should undergo revascularisation when indicated (NICE clinical guideline 126 – Management of Stable Angina. July 2011. http://guidance.nice.org.uk/CG126).
4) All patients should be assessed for relative and absolute contraindications to device therapy and co-morbidity which increases the risk of treatment or reduces its efficacy. These include myocardial infarction or revascularisation within 4 weeks unless the patient has had a secondary prevention ICD indication. This should be explained to the patient and weighed in decision making.
5) All patients should have their condition and its management options discussed with them to make a fully informed decision.
6) If a decision is made not to implant a device, this should be reviewed at least annually or when there is a significant change in the patient's condition.

Based on the currently available data, BHRS recommends that in the absence of a fully reversible cause (including an arrhythmia which can be prevented by ablation therapy), patients on optimal pharmacological therapy, with expectation of life expectancy of ≥1 year and with a quality of life acceptable to the patient:

Patients with LVEF ≤35% (regardless of aetiology) should routinely be considered for a device based on their symptoms (NYHA functional class) and QRS duration:

	NYHA I	NYHA II	NYHA III	ambulant NYHA IV
QRS <120ms	ICD	ICD	ICD	OPT
120-149 no LBBB	ICD	ICD	CRT-D	CRT-D
120-149 + LBBB	CRT-D	CRT-D	CRT-D	CRT-D
≥150ms	CRT-D	CRT-D	CRT-D	CRT-D

CRT-P (pacemaker) implantation should be offered in place of CRT-D (defibrillator) when ICD therapy is contraindicated or declined by the patient.

1) **Patients with LVEF >35%** (without NYHA IV symptoms):
   - with spontaneous sustained ventricular arrhythmias
     or
   - with inherited conditions with high risk features for sudden cardiac death according to the best available evidence

     should routinely be considered for: ICD

2) ICD implantation should not be performed within 4 weeks of a myocardial infarction or revascularisation unless the patient has a secondary prevention indication.