ORIGINAL ARTICLE

Cardiac resynchronisation therapy: pacemaker versus internal cardioverter-defibrillator in patients with impaired left ventricular function

Khang-Li Looi, Parag R Gajendragadkar, Fakhar Z Khan, Maros Elsik, David A Begley, Simon P Fynn, Andrew A Grace, Patrick M Heck, Munmohan Virdee, Sharad Agarwal

Papworth Hospital NHS Foundation Trust, Cambridge, UK

Correspondence to

Dr Khang-Li Looi, Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge CB23 3RE, UK; khangli@hotmail.com

Received 14 January 2014 Revised 12 February 2014 Accepted 3 March 2014

ABSTRACT

Objective Studies have shown beneficial effects of cardiac resynchronisation therapy (CRT) on mortality among patients with heart failure. However the incremental benefits in survival from CRT with a defibrillator (CRT-D) are unclear. The choice of appropriate device remains unanswered.

Method This is a single-centre observational study in a tertiary cardiac centre. Patients (n=500) implanted with a CRT device with pacing alone (CRT-P) (n=354) and CRT-D (n=146) were followed for at least 2 years (mean 29 months, SD 14 months). The primary end point was all-cause mortality.

Results A total of 116 deaths (23.2%) were recorded: 88 (24.8%) and 28 (19.2%), in the CRT-P and CRT-D groups, respectively. At 1 year there was a trend favouring CRT-D (HR 0.54, 95% CI 0.27 to 1.07, p=0.08) but this was attenuated by the 2nd year and became insignificant at the end of follow-up (HR 0.76, 95% CI 0.50 to 1.170, p=0.21). There was no survival benefit from having an internal cardioverter-defibrillator if patients were deemed non-responders to CRT. 27% of the CRT-P patients with ischaemic cardiomyopathy met indications for potential internal cardioverter-defibrillator implantation for primary prevention. These were older patients with poorer baseline function in comparison with CRT-D patients with devices for primary prevention. Once these differences were adjusted for, there was no difference in outcome between the groups.

Conclusions CRT-D did not offer additional survival advantage over CRT-P at longer-term follow-up, as the clinical benefit of a defibrillator attenuated with time. Further work is needed to define which subset of patients benefit from CRT-D.

INTRODUCTION

Cardiac resynchronisation therapy (CRT) has become an acceptable treatment modality for patients with medically refractory congestive heart failure (CHF). The clinical effects of long-term CRT have been proven to reduce mortality and hospitalisation from heart failure, resulting in clinically important improvements in exercise capacity and health related quality of life (QOL). 1–3 Patients may receive a CRT device with a defibrillator (CRT-D) or CRT with pacing alone (CRT-P).

The 2013 European Society of Cardiology guideline suggests that CRT is recommended in patients with CHF with LVEF ≤35% who remain in New York Heart Association (NYHA) functional

classes II, III and ambulatory IV; despite adequate medical treatment.4 It is also recommended that when an internal cardioverter-defibrillator (ICD) is planned for either primary or secondary prevention of sudden cardiac death (SCD), CRT is recommended when indicated. In the UK, the National Institute for Health and Care Excellence (NICE) recommended CRT with a pacing device as a treatment option for people with CHF fulfilling similar criteria on optimal pharmacological treatment.5 However, they suggest CRT-D may be considered for people who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD. Many patients may be eligible for both treatments, but it does not necessarily follow that such patients would obtain additional benefit from the combined treatment over one treatment alone, particularly in the longer

A meta-analysis found that CRT-D was associated with significant reductions in all-cause mortality as compared with an ICD alone. The risks of lead problems and coronary dissection were significantly higher in patients who received CRT-D which remained a concern. A recent systematic review showed some benefits of CRT-D over CRT-P in the all-cause death rate after 1-year follow-up. However, the crucial question regarding the choice of appropriate device in the longer term remains unanswered and deciding which patients may benefit from the added defibrillator device is challenging.

This study aimed to assess the long-term outcome of patients with either CRT-D or CRT-P in routine clinical practice and to identify any potential risk factors that would identify the patient population most likely to benefit from CRT-D.

METHODS

This study was a single-centre, retrospective observational study with prospective follow-up. A total of 500 consecutive patients implanted with either CRT-D or CRT-P at a tertiary referral centre (Papworth Hospital, Papworth, UK) from June 2006 to June 2010 were included. Initial choice of device (CRT-P vs CRT-D) was based on NICE guidance but then modified (as needed) after discussion between implanting physician and individual patients, taking into account their preferences. The devices were implanted using standard protocols after written consent was obtained. All the patients

To cite: Looi K-L, Gajendragadkar PR, Khan FZ, et al. Heart Published Online First: [please include Day Month Year] doi:10.1136/heartjnl-2014-305537

Arrhythmias and sudden death

were followed up in the pacing and general clinics. Patient information and data were retrospectively retrieved and analysed at the end of the follow-up period. Response to CRT was defined as improvement in NYHA functional class. The primary end point of the study was all-cause mortality.

Statistical analysis

We estimated a sample size of 140 per arm (280 total) would be needed to provide 80% power (p<0.05, two sided) to detect a 50% change in the hazard ratio (HR) between groups (CRT-D and CRT-P), assuming a median survival of 36 months and a follow-up of 30 months.⁸

Continuous variables are presented as mean \pm SD, and categorical data as counts or percentages. Analysis and comparisons of continuous data were performed using ANOVA, while the χ^2 test was used to compare categorical data. Fisher's exact test was used if χ^2 assumptions were not met.

Survival was estimated using Kaplan-Meier analyses. Cox proportional hazards models were used to explore univariate and multivariate predictors of events. Initial exploratory covariates of age, gender, atrial fibrillation, aetiology of heart failure, diabetes, hypertension, QRS morphology, QRS duration, LVEF, serum sodium and serum creatine were used. Multivariate models for mortality included terms with p value of <0.1 at univariate analysis along with type of device. Interaction terms between device choice and covariates were used to identify predictive factors by assessing whether there was a significant difference in the HR for death between subgroups. A two-sided probability level of <0.05 was considered statistically significant. All calculations were performed using SPSS V.20.0 (IBM Software, USA).

RESULTS

A total of 500 consecutive patients were enrolled. Overall mean age was 69±10 years with 78% being men. Mean follow-up was for 29±14 months. CRT-D was implanted in 146 patients (29.2%), while the remaining 354 patients (70.8%) received CRT-P. The mean LVEF was 25±7.5%. The baseline characteristics of the two groups are shown in table 1. Compared with the patients who received CRT-P, those who had CRT-D implanted were younger, more likely to be men and have ischaemic cardiomyopathy, and with milder symptoms. They also received more amiodarone compared with those who had CRT-P.

CRT-P versus CRT-D

The mean duration of follow-up was 887±416 days in the CRT-P group and 876±441 days in the CRT-D group (95% CI for difference: -103 to 81 days, p=0.82). There was a significant functional improvement in NYHA class, with only 29.3% having class III / IV symptoms at last follow-up compared with 92.3% previously. Overall, there were a total of 116 deaths (23.2%): 88 (24.8%) in the CRT-P group and 28 (19.2%) in the CRT-D group. The mean time to death from implantation was 513±420 days overall, 499±435 days in the CRT-P group and 554±374 days in the CRT-D group (95% CI for difference: -136 to 218 days, p=0.54).

Although not significant, at 1 year there was a trend to benefit in the CRT-D group (HR for CRT-D: 0.54, 95% CI 0.27 to 1.07, p=0.08). At follow-up of 2 years, the survival benefit afforded by CRT-D was attenuated and insignificant (HR for CRT-D 0.71, 95% CI 0.43 to 1.17, p=0.18) and this continued until the end of all follow-up (HR for CRT-D: 0.76, 95% CI 0.50 to 1.17, p=0.21, figure 1). Adjusting for baseline

Table 1 Baseline characteristics of CRT-P and CRT-D patients

Variable	CRT-P (n=354)	CRT-D (n=146)	p Value
Mean age—years±SD	70±9.9	67±9.3	0.002*
Male (%)	252 (72.6)	133 (91.1)	<0.001*
Ischaemic heart disease (%)	168 (48.3)	96 (65.8)	0.001*
Hypertension (%)	25 (7.1)	10 (6.8)	0.92
Diabetes mellitus (%)	57 (16.1)	20 (13.7)	0.48
History of AF (%)	71 (20.0)	21 (14.4)	0.21
AVN ablation (%)	27 (7.6)	2 (1.4)	0.003*
LVEF—%±SD	25.3±7.7	23.9±7.1	0.06
NYHA class III/IV (%)	333 (94.1)	128 (87.7)	0.019*
QRS duration—ms±SD	159±25.4	161±30	0.50
Use of an ACEI/ARB (%)	321 (90.1)	134 (91.2)	0.40
Use of a β blocker (%)	244 (69.5)	110 (76.9)	0.10
Use of mineralocorticoid antagonists (%)	216 (62.6)	84 (56.4)	0.23
Use of diuretics (%)	317 (92.2)	133 (89.3)	0.21
Use of digitalis (%)	62 (18)	24 (16.1)	0.80
Use of amiodarone (%)	34 (9.7)	25 (17.5)	0.016*
Use of anticoagulation (%)	93 (27.6)	36 (25.2)	0.74
Baseline biochemistry and haemato	logy		
Haemoglobin—g/dL	13.1±1.6	13.5±1.5	0.005*
Sodium—mmol/L	136±7.9	137±3.3	0.27
Urea—mmol/L	10.8±8.6	9.9±5.4	0.23
Creatine—µmol/L	128±48.5	131±43.8	0.47
Albumin—g/L	38±4.6	38±4.4	0.24
ALT—U/L	27±16	35±43	0.12
ALP—U/L	95±50	96±48	0.84

^{*}Two-sided p<0.05

ACEI/ARB, ACE inhibitor or angiotensin receptor blocker; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AVN, atrioventricular node; CRT-D, cardiac resynchronisation therapy with a defibrillator device; CRT-P, cardiac resynchronisation therapy with biventricular pacing; NYHA, New York Heart Association.

differences, the HR for CRT-D remained insignificant at all time points.

Responders versus non-responders

In the CRT-D and CRT-P groups, the response rates were 68.3% and 73.4%, respectively. There were no differences in the baseline characteristics between responders and non-responders other than slightly more frequent amiodarone use in the non-responders. At 1 year and at 2 year follow-ups, non-responders had a higher mortality (HR for death at 1 year 3.85, 95% CI 1.370 to 10.81, p=0.011 and HR for death at 2 years 2.06, 95% CI 1.02 to 4.18, p=0.04). Overall follow-up, there was no difference in the survival between the groups (HR for death for non-responders 1.32, 95% CI 0.73 to 2.39, p=0.36).

Stratifying by device showed that among people receiving CRT-P, non-responders did worse at 1 year (HR for death 3.31, 95% CI 1.01 to 10.86, p=0.048) and at 2 years (HR for death 2.21, 95% CI 1.01 to 4.88, p=0.049) but not overall. No mortality differences were found between responders and non-responders in the CRT-D group. Comparing the survival of non-responders alone by device (CRT-P vs CRT-D) revealed no survival differences at any time point.

Factors predicting survival

Table 2 shows results of the univariate and multivariate survival analyses. Younger age, dilated cardiomyopathy, hypertension,

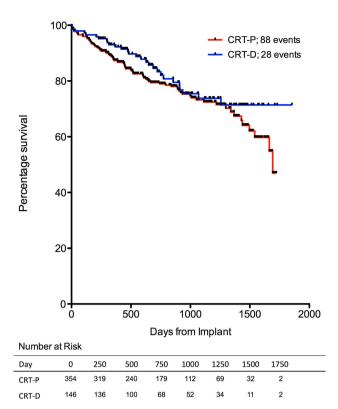


Figure 1 Kaplan-Meier survival curve for all-cause mortality across the whole study stratified by device type. CRT-P, cardiac resynchronisation therapy with pacing; CRT-D, cardiac resynchronisation therapy with a defibrillator.

higher sodium, lower creatine, use of ACE inhibitors or angiotensin receptor blockers, and the use of β -blockers, all predicted survival. In multivariate analysis, younger age, female gender, hypertension, higher serum sodium, lower creatine and β blocker use were significant predictors of survival. There were no differences in univariate and multivariate factors predicting survival when stratified separately by CRT-P and CRT-D.

NICE guidance for ICD implantation

Of the 146 patients that had CRT-D 49% were for primary prevention and 51% for secondary prevention indications. Virtually all patients (99.3%) with an ICD met NICE guidelines for its implantation. There was no survival difference between those who had CRT-D for either primary or secondary prevention reasons. There was also no survival difference between those with ischaemic or non-ischaemic cardiomyopathy for primary or secondary indications for ICD.

Among the 354 patients who received CRT-P, 95 patients (27%) strictly met primary prevention indications for ICD according to NICE guidance. The baseline characteristics of these patients and those who received CRT-D for primary prevention are shown in table 3. Compared with those who received CRT-D, this group of patients were generally older with higher NYHA functional class and poorer baseline status. As expected, there was higher number of deaths in the CRT-P group (HR for death 1.88, 95% CI 1.15 to 3.08, p=0.01). However, once baseline variables were controlled for, there was no difference in mortality between the groups (HR for CRT-P 1.31, 95% CI 0.41 to 4.17, p=0.65).

DISCUSSION

Our single-centre observational study suggests that a potential survival benefit of CRT-D over CRT-P at 1 year was not significant after longer-term follow-up. Response to CRT predicted survival, but non-responders did not survive longer if they had a CRT-D over a CRT-P device. Multivariate analysis of survival suggested that older men with hyponatraemia and renal dysfunction had the poorest survival, independent of other risk factors, including presence or absence of an ICD. The presence of hypertension suggests good cardiac output and therefore this could account for the improved survival in the multivariate analysis. In our cohort, patients who did not receive an ICD for primary prevention despite meeting NICE guidance for implantation, had a poorer prognosis than those receiving an ICD, but the difference was explained by poorer baseline functional

		Univariate	Universita			Multivariate	
Predictors	HR	95% CI	p Value	HR	95% CI	p Value	
Age	1.03	1.01 to 1.05	0.003*	1.03	1.00 to 1.05	0.03*	
Age >75 years old	1.23	0.82 to 1.85	0.32				
Male gender	1.62	0.98 to 2.68	0.06	2.09	1.18 to 3.71	0.012*	
Atrial fibrillation	1.40	0.92 to 2.14	0.12				
Ischaemic (vs dilated) cardiomyopathy	1.46	1.01 to 2.12	0.048*	1.14	0.76 to 1.72	0.52	
Diabetes mellitus	0.86	0.50 to 1.48	0.58				
Hypertension	0.33	0.12 to 0.91	0.032*	0.31	0.12 to 0.86	0.02*	
Left bundle branch block	0.65	0.38 to 1.11	0.12				
QRS width	0.99	0.99 to 1.00	0.61				
Preprocedure LVEF	0.98	0.96 to 1.00	0.11				
Sodium	0.98	0.97 to 0.99	<0.001*	0.90	0.86 to 0.94	<0.001*	
Creatine	1.01	1.01 to 1.02	<0.001*	1.004	1.007 to 1.009	0.02*	
ACEI/ARB use	0.50	0.29 to 0.88	0.016*	0.65	0.35 to 1.20	0.17	
β blocker use	0.63	0.43 to 0.92	0.015*	0.61	0.41 to 0.91	0.014*	
Spironolactone use	0.72	0.48 to 1.08	0.11				
CRT-D (vs CRT-P)	0.76	0.50 to 1.17	0.21	0.76	0.48 to 1.12	0.23	

^{*}Two-sided p<0.05

ACEI/ARB, ACE inhibitor or angiotensin receptor blocker; CRT-D, cardiac resynchronisation therapy with a defibrillator device; CRT-P, cardiac resynchronisation therapy with biventricular pacing; HR, hazard ratio.

Table 3 Baseline characteristics of CRT-P patients who met primary prevention indications for ICD, and those who received CRT-D for primary prevention

Variable	CRT-P (n=95)	CRT-D (n=74)	p Value
Mean age—years±SD	74±8.1	66±8.6	<0.001*
Male (%)	78 (82.1)	66 (89.2)	0.20
Ischaemic heart disease (%)	95 (100)	46 (62.2)	<0.001*
Hypertension (%)	5 (5.3)	3 (4.1)	0.76
Diabetes mellitus (%)	21 (22.1)	8 (10.8)	0.06
History of AF (%)	13 (13.7)	7 (9.5)	0.40
LVEF—%±SD	22.2±5.5	23.4±6.1	0.18
NYHA class III (%)	95 (100)	55 (74.3)	0.001*
QRS duration—ms±SD	160±25	156±28	0.24
Use of ACEI/ARB (%)	84 (88.4)	74 (98.7)	0.02*
Use of β blocker (%)	69 (72.6)	59 (79.7)	0.34
Use of mineralocorticoid antagonist (%)	57 (60)	42 (56.8)	0.29
Use of diuretics (%)	91 (95.8)	66 (89.2)	0.05
Use of digitalis (%)	17 (17.9)	12 (16.2)	0.75
Use of amiodarone (%)	5 (5.3)	8 (10.8)	0.19
Use of anticoagulation (%)	16 (16.8)	16 (21.6)	0.45
Baseline biochemistry and haematolog	gy		
Haemoglobin—g/dL	13.0±1.4	13.6±1.5	0.02*
Sodium—mmol/L	137±3.4	137±2.9	0.80
Urea—mmol/L	11.4±6.4	9.7±5.1	0.06
Creatinine—µmol/L	138±51.2	125±42.4	0.09
Albumin—g/L	37±4.9	39±3.7	0.03*
ALT—U/L	27±16.1	26±14.8	0.94
ALP—U/L	93±45.2	95.0±56.7	0.82

^{*}Two-sided n<0.05

ACEI/ARB, ACE inhibitor or angiotensin receptor blocker; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AVN, atrioventricular node; CRT-D, cardiac resynchronisation therapy with a defibrillator device; CRT-P, cardiac resynchronisation therapy with biventricular pacing; ICD, internal cardioverter defibrillator; NYHA, New York Heart Association.

ICDs in patients with heart failure

ICD implantation has escalated over the past 10 years. Observational data from early drug trials in patients with HF suggested that they had a high risk of SCD. 10 11 The Sudden Cardiac Death in Heart Failure trial was the first to show that ICD reduced all-cause mortality in patients with ischaemic and non-ischaemic cardiomyopathy. 12 In the COMPANION (Comparison of Medical Therapy, Pacing and defibrillation in Heart Failure) trial, all-cause mortality and all-cause hospitalisation were reduced by CRT-D and CRT-P compared with medical therapy.² Although there was some suggested superiority of CRT-D due to the short follow-up, a post hoc analysis subsequently showed no significant survival differences between the CRT-D and CRT-P arms. 13 One of the most important mechanisms of action for the benefit of CRT is reverse remodelling, which takes time to evolve.¹⁴ Given enough time, one may expect a significant reduction in mortality with CRT-P implanted patients and there is currently no robust evidence that the potential early benefit conferred by an ICD is durable. 15-17

Studies have demonstrated that in patients with CHF who received either ICD or CRT-D for primary or secondary prevention, the most common cause of death was progressive heart failure. ¹⁸ ¹⁹ In the prospective study of Thijssen *et al* ¹⁹ that examined the modes of death in 2859 ICD and CRT-D patients

over a 14-year period, the annual mortality rate was 5%. The proportion of patients who died suddenly was low and comparable for primary and secondary ICD and CRT-D patients. The 8-year cumulative incidence of SCD was 2.1% (95% CI 0.3% to 4.0%) in primary prevention ICD patients, 3.2% (95% CI 1.6% to 4.8%) in secondary prevention ICD patients and 3.6% (95% CI 1.8% to 5.3%) in CRT-D patients (log rank p=0.026). A recent small study involving a subgroup of patients post myocardial infarction with severe LV dysfunction that have a negative electrophysiological study showing no inducible ventricular tachycardia can do without the protection of an ICD with low rates of arrhythmias or death.

In our study, the potential advantage of a CRT-D device over CRT-P was attenuated after 1 year. It suggests that in individuals with severe and worsening CHF due to systolic LV dysfunction, CHF complications other than ventricular tachyarrhythmias contribute importantly to duration of survival. Selected patients may be better served by CRT-P with more aggressive medical treatment enhancing QOL in the longer term. Although CRT-D is still the device of choice for reducing the mortality in the early years of implant, downgrading to a CRT-P at generator change may be a viable option.

CRT-P versus CRT-D: which device to implant?

Our multivariate analysis suggested that age, gender, blood pressure, serum sodium and serum creatine were important predictors of outcome. Comorbidities, such as myocardial infarction and renal failure play a pivotal role in the prognosis of a patient with CRT-D.²¹ Hyponatraemia has also been recognised as an independent predictor of outcome in patients with LV dysfunction and an ICD. Factors such as age, and underlying comorbidities should all be taken into account before the decision regarding the type of device to be implanted is made. Existing evidence has showed that the benefits of ICDs in the elderly as well as in women are not well established. 22-25 A recent large prospective registry of ICD patients showed that elderly patients are at increased risk of death compared with their younger counterparts, but the absolute mortality risk is modest when patients are carefully selected.²⁶ These results may serve as a guide for discussion when elderly ICD candidates are evaluated.

Just over a quarter of our CRT-P patients met NICE indications for implantation of an ICD for primary prevention. An ICD was not implanted on the basis of a discussion between the patient and the physician in charge of their care. As expected, this group of patients had poorer baseline status compared with those who received CRT-D, and thus, a higher number of deaths were observed. However, once baseline comorbidities were adjusted for; there was no survival difference between the two groups.

Studies have shown that as the severity of heart failure increases, the proportion of SCD compared with heart failure-related deaths decreases. ¹⁰ ¹¹ Newer guidance highlights the lack of data comparing CRT-D and CRT-P directly, and suggests that ICD therapy is favoured in younger patients with life expectancy estimated at greater than 1 year, who have milder symptoms and less comorbidity. ⁴ Our results add weight to these recommendations. Consideration of comorbidities and known predictors of mortality will help to identify patients who are most likely to derive relative benefit from different devices.

Cost benefit

A large cost-effectiveness meta-analysis comparing medical therapy, CRT-P and CRT-D estimated implantation of a new CRT-P system to cost just over £5000 (€6000; \$8250) and a

CRT-D system to cost over £17 000 (€20 400; \$27 200). It suggested that CRT-P was cost-effective at a threshold of £20 000 (€24 000; \$33 000) per quality adjusted life year, but that CRT-D was effective only at a threshold of £40 000 (€48 000; \$66 000) per quality adjusted life year. A Belgian cost-benefit analysis concluded that although there may be a survival benefit from CRT-D over CRT-P, the incremental clinical benefit appeared too marginal to warrant a threefold higher device price for CRT-D. Bldentifying the patients most likely to benefit from a CRT-D device is essential. The higher number of CRT-P implants in our study reflects the reimbursement situation in UK, and thus will be difficult to translate to countries like the USA or Germany, where the majority of the implanted devices are CRT-D.

Limitations

This is a single-centre retrospective study with prospective follow-up. Device prescription was not randomised and patients with poor functional status and limited expected survival were likely implanted preferentially with CRT-P. This opens the door for bias, although we did try to control for this statistically. In common with other non-randomised studies however, unrecognised differences within the groups may well have introduced bias. We did not define the mode of death in all patients or identify CRT-D associated complications (eg, inappropriate shocks). The lack of survival difference between CRT-D and CRT-P shown by our study may be confounded by underlying patients' characteristics. For example, the use of ACE inhibitors, angiotensin receptor blockers or ß blockers which had been shown to prevent worsening CHF and SCD may reduce the survival differences between the two groups.²⁹ However, 'all-cause mortality' has been used widely as an end point in CRT trials.

The main strengths of our study were the long-term follow-up of a mean of 29 months, and the representation of 'real-world' practice. We defined 'CRT responders' as those who underwent an improvement in NYHA functional class at the end of follow-up. The definition of response to CRT varies widely between studies. A recent analysis of the most-cited publications on CRT suggested that agreement between different methods defining CRT response was poor 75% of the time and strong only 4% of the time.³⁰ In a practical setting, the definition of

Key messages

What is already known about this subject?

Cardiac resynchronisation therapy (CRT) has been proven to reduce the risk of mortality and hospitalisation from heart failure in patients with either a CRT device with a defibrillator (CRT-D) or CRT with pacing alone (CRT-P).

What does this study add?

Implanting CRT-D devices in patients fulfilling internal cardioverter defibrillator implantation criteria requires clinical judgement in patients with multiple comorbidities.

How might this impact on clinical practice?

CRT-D confers early survival benefit but this was not maintained at longer-term follow up. Balancing patients' comorbidities and the potential for device related complications against the potential benefit from the defibrillator is recommended on a case-by-case basis.

CRT response should extend to measure patient outcomes; that is, improvement in symptoms, QOL and duration of life.

The issue of whether to implant CRT-P or CRT-D remains controversial, and a definitive randomised trial comparing these treatments may never be conducted. An observational study with prospective follow-up such as ours provides a useful perspective for both clinicians deciding on an individual patient basis, and for health policy decisions and funding.

CONCLUSION

In our real-world observational study of 500 patients with CHF, CRT-D did not offer an additional survival advantage over CRT-P at longer-term follow-up as the clinical benefit of a defibrillator apparently attenuated with time. Our results add to existing literature suggesting that CRT-D confers an early survival benefit, but this was lost in the longer term. Balancing patients' comorbidities and the potential for device related complications against the potential benefit from the defibrillator is recommended on a case-by-case basis.

Acknowledgements The authors thank Laura Pasea at the Centre for Applied Medical Statistics (CAMS), University of Cambridge for her valuable comments in the statistical analysis of the data.

Contributors FZK, ME, SA were involved in conception and design of the study. FZK, ME, K-LL and PRG were involved in data collection, analysis and interpretation. K-LL, PRG and SA contributed to the writing of the manuscript as well as jointly developing the structure and arguments for the paper. SA, MV, AAG, SPF, DAB and PMH made critical revisions. All authors reviewed and approved of the final manuscript.

Competing interests None.

Ethics approval Local hospital ethics board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42:1454–9.
- 2 Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
- 3 Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
- 4 Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–329.
- 5 National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 120. Cardiac resynchronisation therapy for the treatment of heart failure. May 2007.
- 6 Chen S, Ling Z, Kiuchi MG, et al. The efficacy and safety of cardiac resynchronization therapy combined with implantable cardioverter defibrillator for heart failure: a meta-analysis of 5674 patients. Europace 2013;15:992–1001.
- 7 Jiang M, He B, Zhang Q. Comparison of CRT and CRT-D in heart failure: systematic review of controlled trials. *Int J Cardiol* 2012;158:39–45.
- 8 Saxon LA, Bristow MR, Boehmer J, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Circulation 2006;114:2766–72.
- 9 Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982;38:163–70.
- 10 Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: will the solution be shocking? J Am Coll Cardiol 1997;30:1589–97.
- MERIT-HF Study G. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999:353:2001–7.
- Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
- 13 Lindenfeld J, Feldman AM, Saxon L, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York heart association class IV heart failure. Circulation 2007;115:204–12.

Arrhythmias and sudden death

- Sutton MG, Plappert T, Hilpisch KE, et al. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006;113:266–72.
- 15 Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 2006;27:1928–32.
- 16 Linde C, Abraham WT, Gold MR, 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. J Am Coll Cardiol 2008:52:1834–43.
- Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
- 18 Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009–17.
- Thijssen J, van Rees JB, Venlet J, et al. The mode of death in implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillator patients: results from routine clinical practice. Heart Rhythm 2012;9:1605–12.
- Zaman S, Narayan A, Thiagalingam A, et al. Long-term arrhythmia-free survival in patients with severe left ventricular dysfunction and no inducible ventricular tachycardia post myocardial infarction. Circulation 2014;129:848–54.
- 21 Theuns DA, Schaer BA, Soliman OI, et al. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: comorbidity burden as predictor of mortality. Europace 2011;13:62–9.
- Healey JS, Hallstrom AP, Kuck KH, et al. Role of the implantable defibrillator among elderly patients with a history of life-threatening ventricular arrhythmias. Eur Heart J 2007;28:1746–9.

- 23 Henyan NN, White CM, Gillespie EL, et al. The impact of gender on survival amongst patients with implantable cardioverter defibrillators for primary prevention against sudden cardiac death. J Intern Med 2006:260:467–73.
- 24 Ghanbari H, Dalloul G, Hasan R, et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:1500–6.
- 25 Santangeli P, Pelargonio G, Dello Russo A, et al. Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis. Heart Rhythm 2010;7:876–82.
- 26 Yung D, Birnie D, Dorian P, et al. Survival after implantable cardioverter-defibrillator implantation in the elderly. Circulation 2013;127:2383–92.
- 27 Fox M, Mealing S, Anderson R, et al. The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. Health Technol Assess 2007;11:248.
- Neyt M, Stroobandt S, Obyn C, et al. Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure: a lifetime Markov model. BMJ Open 2011;1:e000276.
- 29 McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.
- Fornwalt BK, Sprague WW, BeDell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation 2010;121:1985–91.



Cardiac resynchronisation therapy: pacemaker versus internal cardioverter-defibrillator in patients with impaired left ventricular function

Khang-Li Looi, Parag R Gajendragadkar, Fakhar Z Khan, Maros Elsik, David A Begley, Simon P Fynn, Andrew A Grace, Patrick M Heck, Munmohan Virdee and Sharad Agarwal

Heart published online April 1, 2014

Updated information and services can be found at:

http://heart.bmj.com/content/early/2014/04/01/heartjnl-2014-305537

These include:

References This article cites 29 articles, 13 of which you can access for free at:

http://heart.bmj.com/content/early/2014/04/01/heartjnl-2014-305537

#BIBL

Email alerting service Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

Drugs: cardiovascular system (8671) Epidemiology (3662)

Notes

To request permissions go to: http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to: http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to: http://group.bmj.com/subscribe/