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Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]

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Aims The CArdiac REsynchronization-Heart Failure study randomized patients with left ventricular ejection fraction $\leq$35%, markers of cardiac dyssynchrony, and persistent moderate or severe symptoms of heart failure despite pharmacological therapy, to implantation of a cardiac resynchronization therapy (CRT) device or not. The main study observed substantial benefits on morbidity and mortality during a mean follow-up of 29.4 months [median 29.6, interquartile range (IQR) 23.6–34.6]. Prior to study closure, an extension phase lasting a further 8 months (allowing time for data analysis and presentation) was declared during which cross-over was discouraged.

Methods and results This was an extension of the already reported open-label randomized trial described above. The primary outcome of the extension phase was all-cause mortality from the time of randomization to completion of the extension phase. The secondary outcome was mode of death. The mean follow-up was 37.4 months (median 37.6, IQR 31.5–42.5, range 26.1–52.6 months). There were 154 deaths (38.1%) in 404 patients assigned to medical therapy and 101 deaths (24.7%) in 409 patients assigned to CRT (hazard ratio 0.60, 95% CI 0.47–0.77, $P < 0.0001$) without evidence of heterogeneity in pre-specified subgroups. A reduction in the risk of death due to heart failure (64 vs. 38 deaths; hazard ratio 0.55, 95% CI 0.37–0.82, $P = 0.003$) and sudden death was observed (55 vs. 32; hazard ratio 0.54, 95% CI 0.35–0.84, $P = 0.005$).

Conclusion The benefits of CRT observed in the main trial persist or increase with longer follow-up. Reduction in mortality was due to fewer deaths both from worsening heart failure and from sudden death.

Introduction

International guidelines recommend cardiac resynchronization therapy (CRT), with or without a concomitant defibrillator function, for the treatment of patients with persistent moderate or severe symptoms of heart failure due to left ventricular (LV) systolic dysfunction if they have a prolonged QRS interval on the surface electrocardiogram suggesting cardiac dyssynchrony.[1,2] This recommendation is based on a series of trials,[3–7] culminating in the CArdiac REsynchronization-Heart Failure (CARE-HF) trial,[8] showing that CRT improves cardiac function, symptoms, quality of life, and prognosis. These benefits are additive to those of modern pharmacological therapy and similar to or greater in magnitude.[9] However, apart from CARE-HF, the duration of these trials was relatively short. The initial costs of CRT are substantial compared to pharmacological therapy and there is a morbidity associated with device implantation. However, current CRT devices are expected to deliver therapy continuously for about 6 years at low additional cost. Accordingly, it is important from both clinical and economic perspectives to demonstrate whether the benefits of CRT are sustained, or increase or decrease over time.

Prior to closure of the CARE-HF study and without knowledge of the results, believing that the study was not powered for mortality and realizing that there would be a delay between study closure and the ability to act on the results, because of the time required to check and analyse the data, the Steering Committee declared an extension

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phase to the main study lasting ~8 months. The aim of the extension study was to assess the longer-term effects of CRT on mortality and mode of death.

Methods

The patient characteristics, study methods, and results have been published in detail.[8,10–12] In brief, the study was a randomized, open-label study comparing CRT and control. Major inclusion criteria were an LV ejection fraction (EF) ≤35%, a QRS duration ≥150 ms or QRS 120–149 ms associated with echocardiographic criteria for dyssynchrony, and the persistence of New York Heart Association (NYHA) class III/IV symptoms despite the use of loop diuretics and neuroendocrine antagonists. Patients who were not in sinus rhythm were excluded. All analyses were conducted on an intention-to-treat basis. The protocol was approved by all relevant Ethics Committees, and patients provided written informed consent. Medtronic sponsored the study.

The data safety and monitoring board (DSMB), after conducting its third interim analysis in March 2004, indicated that they had no safety concerns but recommended, without stating the reason, that the Steering Committee should extend the trial until May 2005. The Steering Committee considered several interpretations of the recommendation, including the possibility that CRT was having a smaller than anticipated effect on the primary outcome and therefore the trial needed to accrue more events by longer follow-up. Alternatively, the Steering Committee considered the possibility that the primary concern of the DSMB was that the trial should provide evidence that the effects of CRT on mortality were convincingly neutral or positive. As there were few deaths compared with primary endpoint events, the confidence interval around all-cause mortality might be wide, creating uncertainty about the effects of CRT on mortality. The Steering Committee noted that both of the pre-defined stopping criteria, a minimum follow-up of 18 months and at least 300 patients reaching the primary outcome, would be met on 30 September 2004 and therefore closed the main study on that date. The original protocol allowed for an additional 6-month follow-up of patients after study close, as it was recognized that the study result might not be known immediately. However, patients were also asked to provide additional written informed consent for the extension phase. The Steering Committee was unable to recommend whether patients should receive a device or not until the analysis was completed and presented. During October to December 2004, outstanding data were collected and the database checked prior to 'data-lock' and unblinding. The Steering Committee was unaware of the outcome of the study until the end of January 2005. Presentation of the data was scheduled for March 2005 at the American College of Cardiology meeting, during which a simultaneous recommendation on further patient management was planned. Although knowledge of the results would be expected to lead to an increase in cross-over from assigned therapy, the Steering Committee considered that this would have little effect on the results before May 2005, as investigators would probably not be able to act immediately on the findings. As there was no scientific value in retaining the original primary endpoint in the extension phase, all-cause mortality until May 2005 was declared the primary endpoint.

Deaths were adjudicated from documents blinded to treatment assignment by an endpoints committee in an identical fashion to the main study. The likely cause of death was first classified as cardiovascular, non-cardiovascular, or unclassifiable. Cardiovascular deaths were further subclassified as due to worsening heart failure and as sudden or not sudden.

Statistical analysis

Analyses were pre-specified in a statistical analysis plan and were conducted according to the intention-to-treat principle. All subgroups were pre-specified. Tests were considered significant at the 2.5% level on an one-sided test. The primary outcome for the extension phase was all-cause mortality. No adjustments were made for multiple testing. Time-to-event was described using the Kaplan–Meier curves and analysed using Cox proportional hazards models, including baseline NYHA as a covariate and 95% confidence intervals. NYHA was included as a covariate as randomization was stratified on this characteristic. The assumption of constant proportional hazards was assessed using an explanatory time-dependent variable. We examined the potential heterogeneity of effect by subgroup using an interaction term in the Cox proportional hazards model. The study was designed by the Steering Committee. Analyses were conducted by NF and results interpreted independently of the sponsor, which did not have access to the study database.

Results

Key baseline features of patients enrolled in the study are shown in *Table 1*. A more detailed description has also been published.[8,12] The patients had moderate or severe symptoms of heart failure associated with marked reduction in LVEF, LV dilatation, and prolongation of the QRS interval. Patients were generally receiving therapy appropriate to their condition.

Survival status was known for all patients at the end of the main study and for all but one patient assigned to the control group at the end of the extension phase. Among the 409 patients assigned to CRT, 19 patients never received a device of whom six (31.6%) died during follow-up. One patient died while awaiting implantation, the investigator or patient decided not to proceed in four cases, and attempts at device implantation failed in 14 patients. Of the 390 patients who had a device implanted, 95 died (24.4%). Among the 404 patients assigned to medical therapy alone, 95 patients received a CRT device and had it activated during follow-up of whom 22 died (23.2%). Fifty patients had a CRT device implanted and activated during the course of the main study, four patients had a device implanted during the main study but only activated during the extension phase and a further 41 patients had a CRT device implanted and activated during the extension phase. Of 309 patients who were not known to have had a CRT device implanted by the end of the extension phase, 132 had died (42.7%). There were three emergency and seven elective heart transplants in the medical group and one emergency and 10 elective transplants in the CRT group during follow-up. All emergency transplant patients died within 7 days but none of the elective cases.

The mean follow-up by the end of the extension phase had increased from 29.4 months (range 18.0–44.7) to 37.4 months [median 37.6, interquartile range (IQR) 31.5–42.5, range 26.1–52.6 months]. There were 120 deaths in the main study and a further 34 in the extension phase leading to a total of 154 deaths (38.1 or 12.2% per annum) in 404 patients assigned to medical therapy. There were 82 deaths in the main study and a further 19 in the extension phase leading to a total of 101 deaths (24.7 or 7.9% per annum) in 409 patients assigned to CRT (hazard ratio 0.60, 95% CI 0.47–0.77, $P < 0.0001$) (*Figure 1*). Reductions in the risk of death due to heart failure (64 vs. 38 deaths or

Table 1 Baseline characteristics

	Medical therapy alone ($n = 404$)	CRT ($n = 409$)
Age (years), median (IQR)	66 (59–72)	67 (60–73)
Male (%)	293 (73%)	304 (74%)
NYHA class III (%)	377 (93%)	386 (94%)
Ischaemic heart disease (%)	144 (36%)	165 (40%)
Systolic BP (mmHg), median (IQR)	110 (100–125)	110 (100–125)
PR interval (ms), median (IQR) QRS duration	160 (152–180)	160 (152–180)
NT proBNP (pg/mL), median (IQR)	1806 (719–3949)	1920 (744–4288)
EF (%), median (IQR)	25 (22–29)	25 (21–29)
Interventricular mechanical delay (ms), median (IQR)	50 (30–66)	49 (32–67)
Mitral regurgitation area index, median (IQR)	23 (11–34)	21 (12–33)
ACE-inhibitors/ARB (%)	383 (95%)	387 (95%)
Beta-blockers (%)	288 (71%)	298 (73%)
Spironolactone (%)	238 (59%)	219 (54%)
High-dose loop diuretics (%)[a]	177 (44%)	175 (43%)
Digoxin (%)	181 (45%)	165 (40%)

GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure. To convert from pg/mL to pmol/L, divide by 8.457.
[a]≥80 mg furosemide, ≥2 mg bumetanide, or ≥20 mg torsemide.

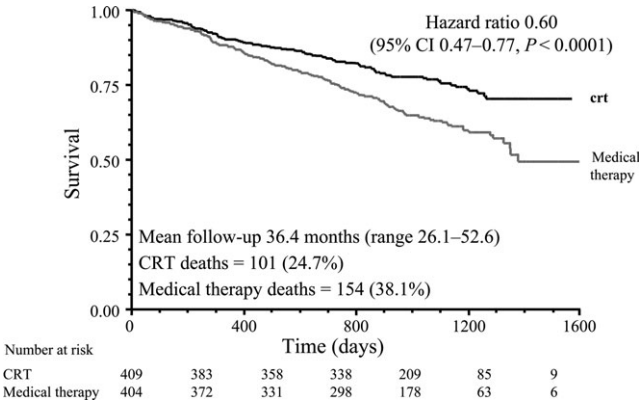

Figure 1 The Kaplan–Meier estimates of the time to all-cause mortality.

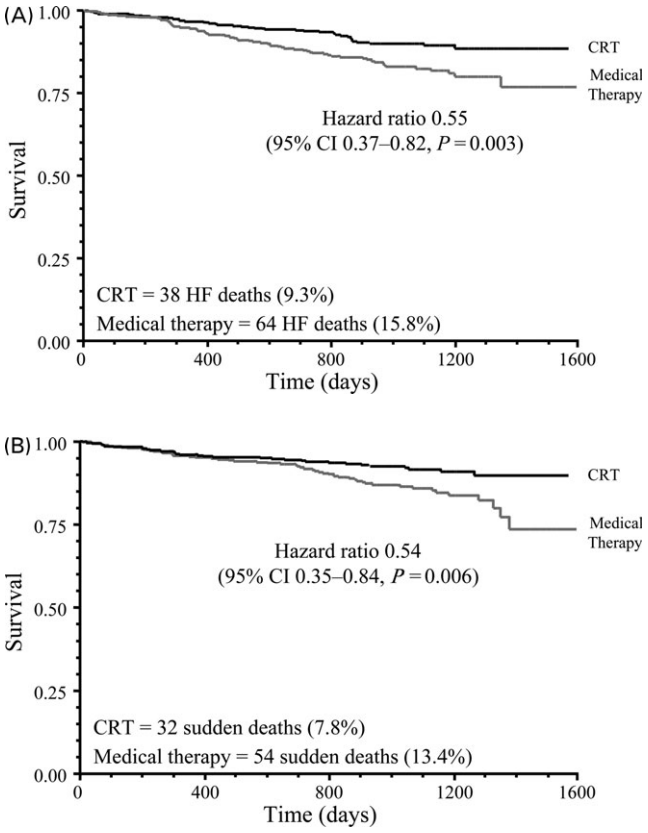

Figure 2 The Kaplan–Meier estimates of the time to death from worsening heart failure (*A*) or sudden death (*B*).

5.1 vs. 3.0% per annum; hazard ratio 0.55, 95% CI 0.37–0.82, $P = 0.003$) and sudden death were observed (54 vs. 32 or 4.3 vs 2.5% per annum; hazard ratio 0.54, 95% CI 0.35–0.84, $P = 0.005$) (*Figure 2A* and *B*). Of 19 sudden deaths in the extension phase, 16 occurred in the control group. The hazard ratio remained constant throughout the duration of the trial, for overall mortality, and for death due to heart failure or sudden death. Mortality at 3 years was 35.1% in the medical group and 23.6% in the CRT group. A subgroup analysis was conducted using variables pre-specified for the main study and extension phase that showed no heterogeneity of effect (*Figure 3*).

Discussion

The extension phase of CARE-HF suggests that, in patients with heart failure due to cardiac dyssynchrony, the reduction in mortality due to implantation of a CRT device is maintained in relative terms and increases in absolute magnitude with longer follow-up. The average annual mortality despite intensive medical therapy including ACE-inhibitors, beta-blockers, and aldosterone antagonists

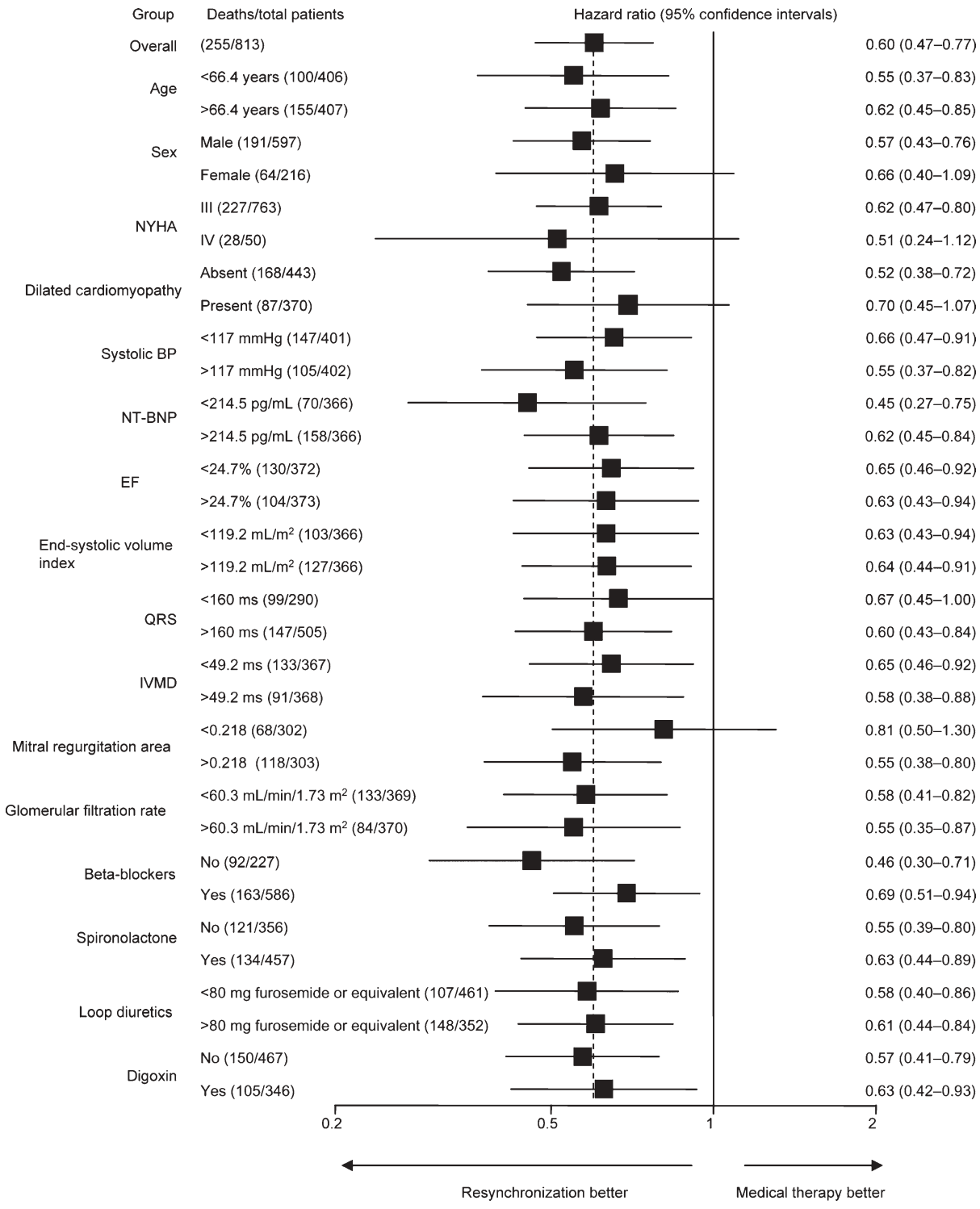

Figure 3 Effect of cardiac resynchronization on all-cause mortality in subgroups pre-defined by the main study analysis. Hazard ratios and 95% CIs are shown. The subgroups of age, systolic blood pressure, mitral-regurgitation area, interventricular mechanical delay, EF, end-systolic volume index, and glomerular filtration rate are divided according to the median value in the study population. All analyses were stratified according to the NYHA class, except the subgroup analysis of NYHA class. To convert values for N-terminal pro-brain natriuretic peptide (NT-BNP) to picomoles per litre, divide by 8.457. For some data (QRS width, for instance), many patients had results at the median value, and this led to some inequality in the sizes of the subgroups. Because of missing baseline data, not all subgroup numbers total 813.

was 11.7% over the first 3 years which was reduced to 7.9% by CRT. The reduction in mortality was similar in all pre-specified subgroups, including subgroups of patients with ventricular dysfunction due to ischaemic and non-ischaemic causes. Calculations based on survival analysis suggest that one more patient would be alive at 2 years for every 13 patients and at 3 years for every nine patients in whom a device implantation is attempted. This may be an underestimate of the real magnitude of benefit with CRT, as the annual mortality rate of patients assigned to

pharmacological therapy alone who never received a CRT device was 12.6%.

The original CARE-HF report suggested that most of the reduction in mortality was due to a decline in deaths due to worsening heart failure.[8] This is consistent with the concept that CRT leads to improved cardiac function and efficiency, which translates into an improvement in symptoms and outcome. However, improved cardiac function would also be expected to reduce the incidence of serious arrhythmias leading to a reduction in sudden death.[13] Although there was no difference in overall mortality between CRT alone and CRT with a defibrillator in the COMPANION study,[14] the trend to fewer early deaths in COMPANION was attributed by some to a greater reduction in sudden deaths due to the defibrillator. There is a theoretical risk of inducing arrhythmias with multi-site pacing, although we observed no evidence of an increased early hazard of sudden death with CRT in the CARE-HF trial. The extension data show that CRT alone can reduce sudden death. During the extension phase, sudden death occurred more commonly than death due to worsening heart failure. Only three of the 19 late sudden deaths were in the CRT group. In the COMPANION study, the mortality with CRT alone vs. a CRT defibrillator was similar after 2 years of follow-up.[14] These two pieces of information could be interpreted as evidence that the ability of CRT to reduce sudden death is delayed and potentially dependent on improvements in cardiac function and beneficial ventricular remodelling. However, the proportional hazards of both sudden death and death from worsening heart failure were constant throughout the CARE-HF trial and extension and therefore do not support the notion of a time-dependent increase in the effect of CRT on sudden death. Most deaths among patients with advanced heart failure are due to worsening of their condition but the rate of sudden death is also high. The rate of sudden deaths is lower in patients with less severe heart failure but the proportion of deaths is higher because fewer patients die of progressive heart failure. Accordingly, CRT might also be expected to reduce the rate but increase the proportion of deaths that are sudden. The failure to observe an increase in the proportion of patients assigned to CRT who died suddenly might reflect an additional anti-arrhythmic effect of CRT but could also reflect the fact that about 30% of patients remained in NYHA class III or IV despite treatment.

Despite CRT, 32 patients (7.8%) died suddenly during the entire period of follow-up and some of these deaths might have been prevented had the patients been implanted with a device that included a defibrillator function. Assuming that the combination of CRT and a defibrillator could prevent half of sudden deaths, a study of 1600 patients per group followed for $\sim$3 years would have 90% power to detect a 3.8% absolute reduction in all-cause mortality with combined therapy compared with CRT alone.

In conclusion, the prognostic benefits of CRT are maintained or increased with longer-term follow-up and are due to reductions in sudden death and death due to worsening heart failure in roughly equal proportion.

Conflict of interest: The study was funded by Medtronic. Authors were funded to attend meetings and to undertake work related to the trial. NF received funds to provide statistical analyses and JGFC and LT to provide core-laboratory services. All members of the Steering Committee have received honoraria for speaking on aspects of heart failure at meetings funded by companies in the pharmaceutical and device industries. All have participated in other studies or research projects funded by industry.

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