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Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial

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Cardiac resynchronization therapy;
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Aims The cardiac resynchronization therapy in heart failure trial (CARE-HF) demonstrated that cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with heart failure and cardiac dyssynchrony. The aim of this study was to develop a prognostic model to evaluate the relationship between prospectively defined patient characteristics and treatment on the trial primary outcome of death from any cause or unplanned hospitalization for a major cardiovascular event.
Methods and results A total of 813 patients were enrolled in the CARE-HF study and were followed for a mean of 29.4 months. A Cox Proportional Hazards Model was fitted to identify predictors of the primary outcome and any predictors that modified the effect of CRT. Ischaemic aetiology, more severe mitral regurgitation and increased N-terminal pro-brain natriuretic peptide, were associated with an increased risk of death or unplanned cardiovascular hospitalization irrespective of cardiac resynchronization [Hazard ratio (HR) 1.89, 95% CI 1.45–2.46, HR 1.71, 95% CI 1.38–2.12 and HR 1.31, 95% CI 1.17–1.47, respectively] and increasing systolic blood pressure with a decreasing risk of an event (HR 0.99, 95% CI 0.98–1.00). The benefits of cardiac resynchronization were modified by systolic blood pressure and interventricular mechanical delay (IVMD). Patients with increasing systolic blood pressure appear to receive reduced benefit from CRT (HR 1.02, 95% CI 1.00–1.03), whereas those patients with more severe IVMD appear to benefit more from treatment (HR 0.99, 95% CI 0.98–1.00).
Conclusion Patients with echocardiographic evidence of more severe cardiac dyssynchrony and low systolic blood pressure obtain greater benefit from CRT, although benefits were substantial across the range of subjects included in the trial.

Introduction

Heart failure is a common and serious condition with a complex and varied pathophysiology.[1] A substantial minority of patients with heart failure due to left ventricular (LV) systolic dysfunction have prolonged QRS and amongst these patients there is a high prevalence of cardiac dyssynchrony, which leads to a decline in cardiac efficiency through diverse mechanisms.[2–4] For patients with heart failure due to cardiac dyssynchrony who have persistent moderate or severe symptoms despite standard pharmacological therapy, cardiac resynchronization therapy (CRT) improves cardiac function leading to an improvement in well-being and a reduction in morbidity and mortality.[5–8]

The cardiac resynchronization therapy in heart failure trial (CARE-HF) is one of the largest randomized studies of CRT, has a longer duration of follow-up than any other, and has a robust primary clinical endpoint.[7] These attributes make it a valuable resource for the investigation of those factors that predict the likelihood that a patient will or will not respond to CRT. The aim of this analysis was to evaluate the relationship between prospectively defined clinical, echocardiographic and neurohormonal variables, collected at baseline during the CARE-HF trial, on overall outcome in all patients and on the response to CRT.

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Table 1 Baseline characteristics of the patients

	Control			Treatment		
	n	Median	(IQR)	*n*	Median	(IQR)
Age (years)	403	66	(59–72)	409	67	(60–73)
Aetiology (ischaemic)	144			165		
Systolic blood pressure (mmHg)	399	110	(100–125)	404	110	(100–125)
Glomerular filtration rate (mL/min/1.73 m^2)	372	61	(46–73)	367	60	(46–73)
N-terminal pro-brain natriuretic peptide (pg/ml)	370	1806	(719–3949)	362	1920	(744–4288)
Use of beta-blockers (Y/N)	298			288		
QRS width (ms)	394	160	(152–180)	401	160	(152–180)
Interventricular mechanical delay (ms)	370	50	(30–66)	365	49	(32–67)
End-systolic volume index (mL/m^2)	376	117	(94–147)	356	121	(92–151)
Ejection fraction ($\leq$35%)	378	25	(22–29)	367	25	(21–29)
Mitral regurgitation[a]	303	23	(11–34)	302	21	(12–33)

IQR, interquartile range.
[a]Mitral regurgitation defined as area of colour flow Doppler regurgitant jet divided by area of left atrium in systole, both in square centimetre.

Methods

Data source

We used individual patient data collected during the CARE-HF trial. The design and results of the CARE-HF study have been reported previously.[7,9] In brief, the CARE-HF trial enrolled 813 patients recruited from 82 centres across Europe. Eligible patients were at least 18 years of age, had evidence of heart failure for at least 6 weeks, and were in New York Heart Association class III or IV despite receipt of standard pharmacologic therapy, with a LV ejection fraction (EF) of $<$35%, a LV end-diastolic dimension of $\geq$30 mm (indexed to height), and a QRS interval of $>$120 ms on the electrocardiogram. Patients with a QRS interval of 120–149 ms were required to meet two of three additional criteria for dyssynchrony: an aortic pre-ejection delay of more than 140 ms, an interventricular mechanical delay (IVMD) of $>$40 ms, or delayed activation of the posterolateral LV wall. The IVMD was calculated as the time difference between the onset of forward flow in the LV (APET) and RV (PPET) outflow tracts: IVMD = APET − PPET.[10] A total of 409 patients were randomized to CRT and medical therapy, whereas 404 received medical therapy alone. The primary outcome was the time to death from any cause or an unplanned hospitalization for a major cardiovascular event. Patients were followed up for a mean of 29.4 months.

Statistical analysis

Model specification and validity

A number of potentially important clinical, echocardiographic, and neurohormonal variables collected at baseline were specified *a priori* for evaluation in a prognostic model. These were mitral regurgitation (MR), end-systolic volume index, aetiology (ischaemic and non-ischaemic disease), EF, use of beta-blockers, age, QRS width (QRS), supine systolic blood pressure (SBP), glomerular filtration rate, N-terminal pro-brain natriuretic peptide, as determined by Roche Assay (NT-pro-BNP), and IVMD.[11–13] MR was defined as area of colour flow Doppler regurgitant jet divided by area of left atrium in systole, both in square centimetre.

We fitted Cox Proportional Hazards models to identify predictors of risk of death from any cause or an unplanned hospitalization for a major cardiovascular event (main effects) and to identify any predictors modified by cardiac resynchronization.[14,15]

Our modelling strategy was based upon the approach suggested by Harrell that attempts to avoid the problem of over-fitting the model.[16–19] Over-fitting may occur when *P*, the total number of predictor degrees of freedom used to fit the model, is large in comparison to *N*, where *N* is the number of uncensored event times, or for a binary outcome the number of patients in the smaller (less frequent) primary outcome category. In this study, there where 383 patients with uncensored event times. *P* can be interpreted as the number of regression coefficients estimated in fitting a model, for this study $P = 9$. If $N/P < 10$, this may indicate over fitting, we have $383/9 > 10$, this does not indicate over fitting is present. In order to evaluate whether any of the variables had a non-linear relationship with outcome, we assessed transformations of each variable using the natural logarithm and cubic spline.[20–24] The Akaike Information Criteria were used to determine the most appropriate transformation.[25] The validity of any transformations was further assessed by examining plots of the cumulative Martingale residuals vs. the transformed variable.[26,27] The proportional hazards assumption was also assessed. Statistically significant variables identified from univariate analyses were combined in a single Cox Proportional Hazard model using a forward stepwise selection to obtain the final model, the entry criteria for the forward selection procedure was 0.05, meaning a variable has to be significant at the 0.05 level before it can enter the model. All analyses were performed in SAS v 9.1 using the PHREG procedure and the RCS macro.[28] The RCS macro[28] was used to fit cubic splines with four knots for the continuous variables, with the knot positions specified PHREG, was then used tp genearate a model from which it was possible to determine whether the cubic spline was an appropriate transformation for the particular variable concerned. All analyses were undertaken according to the intention to treat principle.[29]

To validate the final model two further steps were taken. First, a bootstrap revalidation process was used to estimate the degree of over-fitting from the model fitting process.[17] The design library in the statistical package R was used to undertake this validation.[30] Second, we used multiple imputation using the SAS procedures MI, and MIANALYSE, to examine the effect of missing data on the final model.[31]

Estimation of absolute risk

Estimates of the survival function $S(t)$ and the absolute risk $(1-S(t))$ were produced using the SAS procedure PHREG. Estimation of absolute risk using real patient data provides clinically relevant estimates of risk. Risk estimates were derived on the basis of the maximum follow-up in the CARE-HF, which was 44.7 months, although including censorship patients were only followed for 29.4 months. Thus

Table 2 Potential predictors of risk: results of univariate analyses

	Hazard ratio	95% CI	*P*-value
Mitral regurgitation[a]			
Log_e(MR)	2.14	1.68–2.71	<0.0001
CRT	1.85	0.59–5.08	0.2938
CRT * log_e(MR)	0.72	0.50–1.02	0.0670
Interventricular mechanical delay (*ms*)			
IVMD	0.99	0.99–1.00	0.0028
CRT	0.92	0.62–1.36	0.6784
CRT * IVMD	0.99	0.99–1.00	0.0473
End-systolic volume index (mL/m^2)			
Log_e(ESVI)	1.52	1.08–2.14	0.0175
CRT	0.62	0.04–9.88	0.7354
CRT * log_e(ESVI)	1.00	0.56–1.77	0.9978
Glomeruler filtration rate ($ml/min/1.73\ m^2$)			
GFR	0.99	0.98–0.99	0.0005
CRT	0.74	0.38–1.48	0.3964
CRT * GFR	1.00	0.99–1.01	0.5811
Systolic blood pressure (*mmHg*)			
SBP	0.99	0.98–1.00	0.0011
CRT	0.14	0.03–0.63	0.0097
CRT * SBP	1.01	1.00–1.03	0.0491
Ejection fraction (%)			
Log_e(EF)	0.38	0.22–0.66	0.0006
CRT	0.38	0.02–5.44	0.4298
CRT * log_e(EF)	1.24	0.51–3.03	0.6341
N-terminal pro-brain natriuretic peptide (*pg/mL*)			
Log_e(NT-pro-BNP)	1.47	1.31–1.66	<0.0001
CRT	0.33	0.08–1.37	0.1275
CRT * log_e(NT-pro-BNP)	1.08	0.91–1.29	0.3833
Age (*years*)			
Age	1.02	1.01–1.04	0.0011
CRT	0.87	0.21–3.6	0.8416
CRT * Age	1.00	0.97–1.02	0.6400
Aetiology (*ischaemic*) (*yes/no*)			
Ischaemic	1.68	1.29–2.19	0.0001
CRT	0.48	0.35–0.66	<0.0001
CRT * ischaemic	1.49	0.99–2.26	0.0583

[a]Mitral regurgitation represents the results of fitting single Cox Proportional Hazards model, a patients chance of experiencing the primary event being assumed to be dependent on mitral regurgitation and also the presence or absence of CRT.

The term CRT * log(MR) is a treatment modifier, this means that the beneficial effect of CRT may be reduced or increased depending on the patients level of mitral regurgitation. Mitral regurgitation is a significant predictor of outcome, $P < 0.0001$, however, the *P*-value for CRT * log(MR) > 0.05 so mitral regurgitation does not significantly change the benefit a patient may receive from CRT.

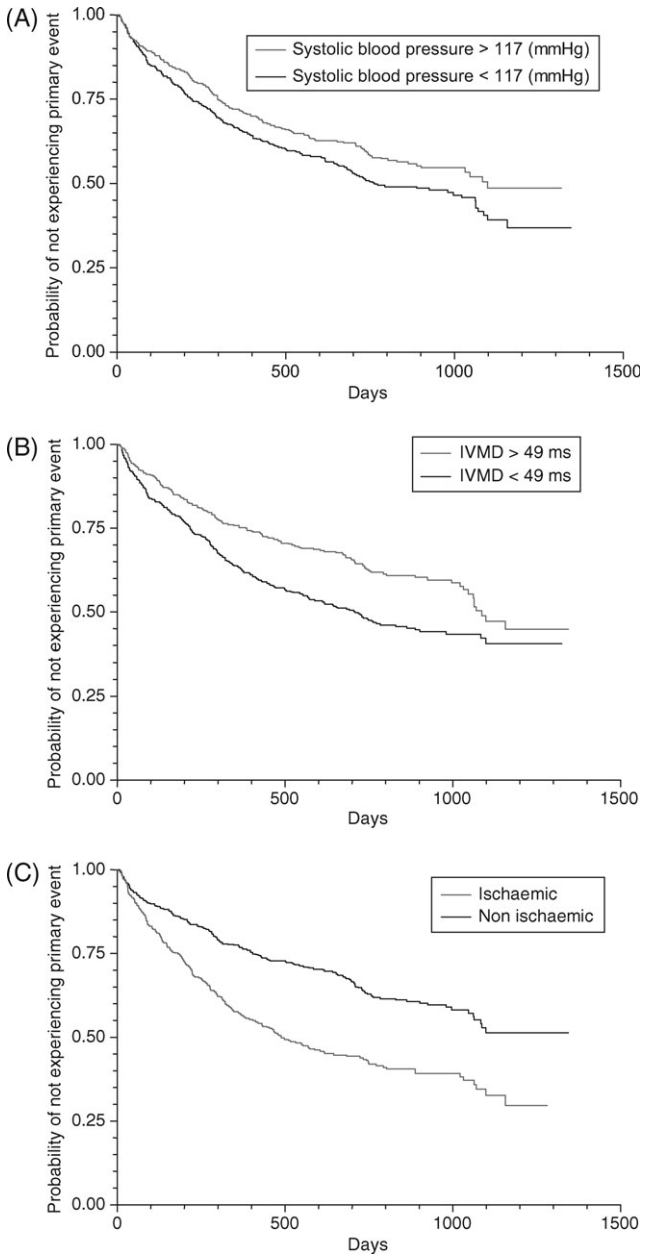
Table 3 Predictors of outcome and response to CRT (Cox Proportional Hazards analysis)

	Transformation	Hazard ratio	95% CI	*P*-value
Predictors of overall outcome				
Mitral regurgitation[a]	Log_e	1.71	1.38–2.12	<0.0001
N-terminal pro-brain[a] natriuretic peptide (pg/ml)	Log_e	1.31	1.17–1.47	<0.0001
Systolic blood pressure (mmHg)	Linear	0.99	0.98–1.00	0.0698
Interventricular mechanical delay (ms)	Linear	1.00	0.99–1.01	0.7617
Aetiology (ischaemic) (yes/no)	No transformation	1.89	1.45–2.46	<0.0001
CRT (yes/no)	No transformation	0.15	0.03–0.87	0.0347[c]
Predictors of response to CRT				
Systolic blood pressure (mmHg)[b]	CRT * SBP	1.02	1.00–1.03	0.0183
Interventricular mechanical delay (ms)[b]	CRT * IVMD	0.99	0.98–1.00	0.0084

[a]Mitral regurgitation and N-terminal pro-brain natriuretic peptide have been identified as statistically significant predictors of outcome.

[b]The terms CRT * SBP and CRT * IVMD represent modifiers of response to CRT, i.e. both systolic blood pressure and interventricular mechanical delay may modify the beneficial effect of CRT. The *P*-values for CRT * SBP and CRT * IVMD are both <0.05, indicating that systolic blood pressure and interventricular mechanical delay are statistically significant. Note that individually systolic blood pressure nor interventricular mechanical delay are statistically significant, in other words they are not predictors of outcome.

[c]The *P*-value for CRT is relatively large (0.0347) due to the inclusion of the CRT modifiers in the model.



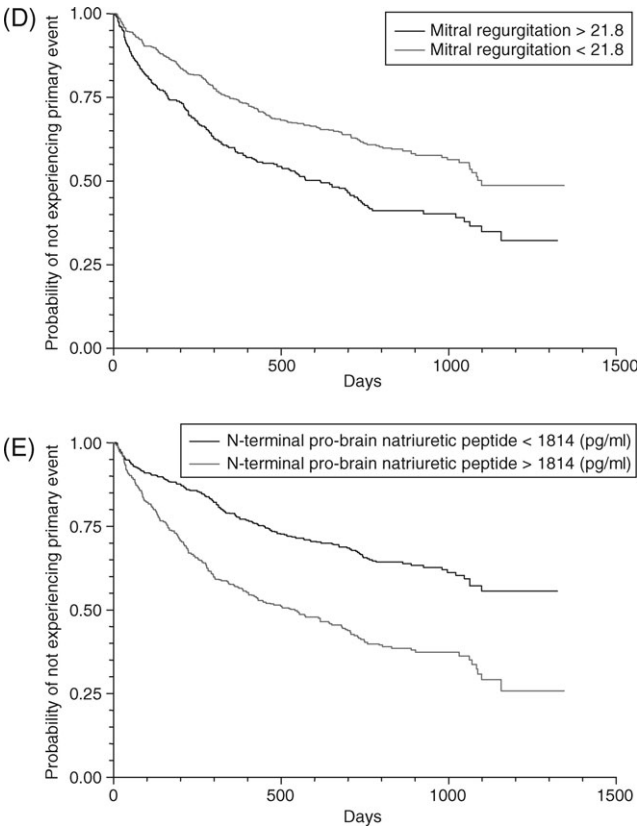


Figure 1 (*A*) Time to first primary event by systolic blood pressure. (*B*) Time to first primary event by interventricular mechanical delay. (*C*) Time to first primary event by aetiology (ischaemia). (*D*) Time to first primary event by mitral regurgitation. (*E*) Time to first primary event by N-terminal pro-brain natriuretic peptide (pg/ml).

predicted event rates are considerably higher than those actually observed in the trial.

This work is the first prognostic model derived from a morbidity/mortality trial of CRT, and so the principal aim of the analysis was to identify potential treatment modifiers using robust methods and not to develop a definitive prognostic tool that will require further validation using new data from an appropriate large randomized trial or epidemiological study.

Calculation of risk scores

The coefficients of the final model can be used to generate a risk score for an individual patient.

Figure 1 Continued.

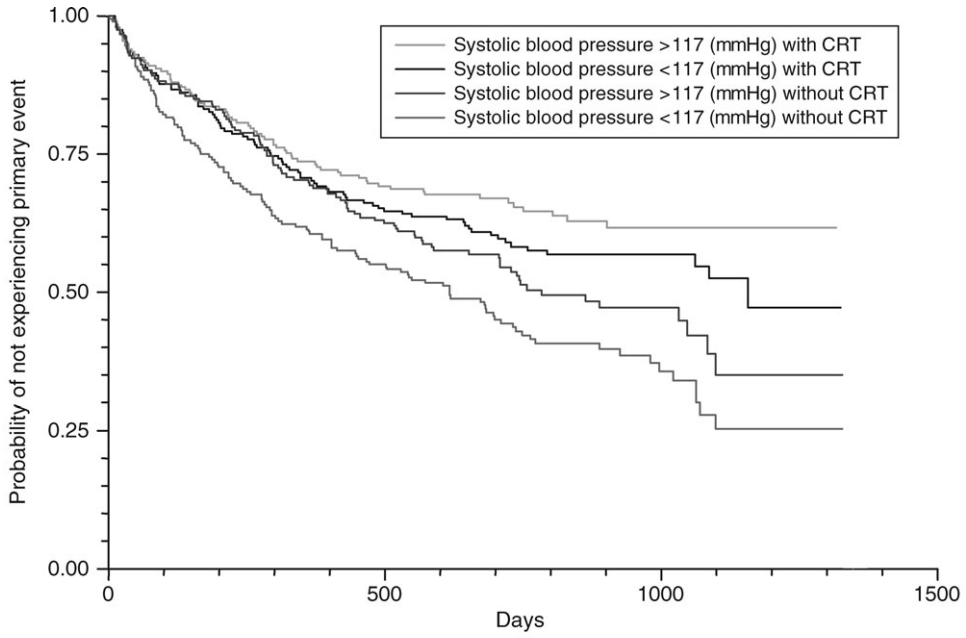
Results

The baseline characteristics of patients from the CARE-HF trial are shown in *Table 1*.

These data are consistent with the patients having, on average, moderate to severe LV systolic dysfunction, dilatation and dyssynchrony with a low arterial pressure, and renal dysfunction. About 40% of patients had ischaemic heart disease.

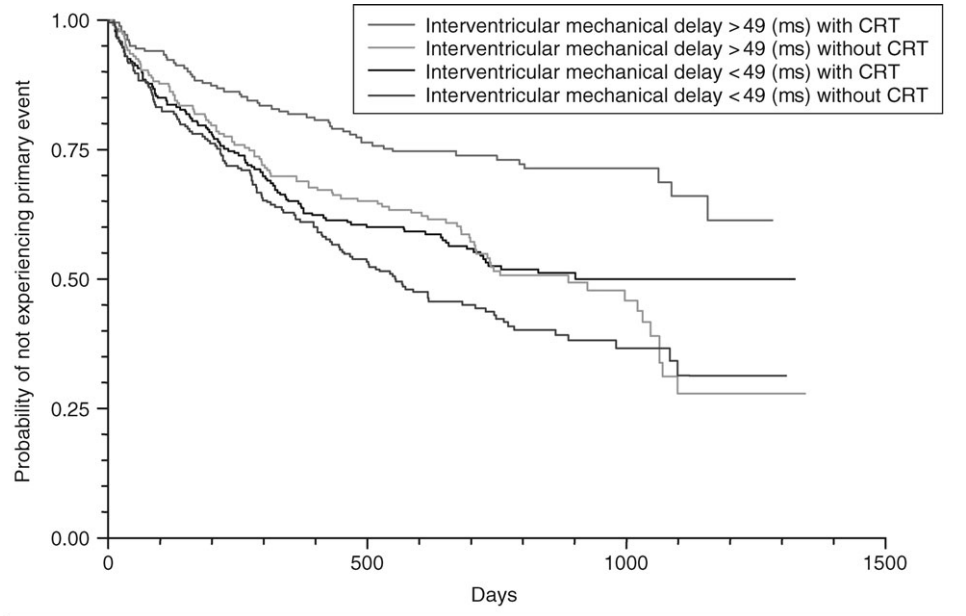
Univariate analyses were used to identify those variables that were significant predictors of outcome (irrespective of treatment allocation) and those variables shown to predict response to CRT (indicated by the CRT * variable interaction term) (*Table 2*). The most appropriate transformation of each variable is indicated (for example a logarithmic transformation led to the best model fit for MR). The remaining variables (beta-blocker use and QRS width) were not significantly associated with outcome and did not predict response to CRT.

Those variables identified to be significantly ($P < 0.05$) associated with the primary composite outcome, time to death from any cause, or an unplanned hospitalization for a major cardiovascular event were entered in a multivariate Cox Proportional Hazards model (*Table 3*). Ischeamic aetiology, more severe MR, and increased NT-pro-BNP were all independent predictors of an increased risk of death or unplanned cardiovascular hospitalization irrespective of cardiac resynchronization [Hazard ratio (HR) 1.89, 95% CI 1.45–2.46, HR 1.71, 95% CI 1.38–2.12 and HR 1.31, 95% CI 1.17–1.47, respectively] and increasing SBP with a



Number at risk systolic blood pressure (SBP)				
SBP	1 month	3 months	6 months	12 months
<117 (mmHg) without CRT	198	173	154	125
<117 (mmHg) with CRT	193	179	166	141
>117 (mmHg) without CRT	186	171	161	133
>117 (mmHg) with CRT	191	181	167	147

Figure 2 Time to first primary event by systolic blood pressure (mmHg) and cardiac resynchronization therapy.



Number at risk interventricular mechanical delay (IVMD)				
IVMD	1 month	3 months	6 months	12 months
<49 ms without CRT	202	179	164	130
<49 ms with CRT	213	194	179	145
>49 ms without CRT	181	165	151	128
>49 ms with CRT	176	169	159	147

Figure 3 Time to first primary event by interventricular mechanical delay (ms) and cardiac resynchronization therapy.

decreasing risk of an event (HR 0.99, 95% CI 0.98–1.00) (*Figure 1A–E*). Note, in *Figure 1A*, 117 mmHg is the median value of SBP for the combined data, i.e. the median for the treatment and control groups combined.

Only two variables, IVMD and SBP predicted response to CRT, with modest statistical precision (*Figures 2* and *3*). Patients with increasing SBP appear to receive reduced benefit from CRT (HR 1.02, 95% CI 1.00–1.03), whereas those patients with more severe IVMD appear to benefit more from treatment (HR 0.99, 95% CI 0.98–1.00).

Absolute risk estimation

The effect of SBP and IVMD on the absolute risk of a patient experiencing death from any cause or an unplanned hospitalization for a major cardiovascular event in the presence and absence of CRT or ischaemic heart disease are shown in *Tables 4* and *5*, respectively. In both examples, mitral regurgitation, NT-pro-BNP, and IVMD were held constant at the median values (see *Table 1*).

The estimated absolute risk of experiencing death or an unplanned hospitalization for cardiovascular cause for a non-ischaemic patient with a SBP of 117 mmHg (the median for the whole dataset) on medical therapy (but not CRT) was 0.97 over the entire trial duration (*Table 4*). Treatment of such a patient with CRT reduces the estimated absolute risk to 0.41. The presence of ischaemia led to an increase in absolute risk to 0.63 and 0.99 in the presence and absence of CRT, respectively. The absolute risk of experiencing event increased with increasing SBP, this is due to the fact that although SBP alone is associated with a decrease in risk, the statistical interaction between SBP and CRT is associated with a small increase in risk.

The absolute risk for a patient with IVMD of 49 ms vs. a patient with IVMD of 66 ms in the presence and absence of ischaemia and CRT is shown in *Table 5*. Increasing the IVMD from 49 to 66 ms leads to reductions in the absolute risk of experiencing an event.

Table 4 Estimated absolute risk of an event for patients with different systolic blood pressures (117–130 mmHg) with and without cardiac resynchronisation therapy and in the presence and absence of ischaemic heart disease

Patient	Systolic blood pressure (mmHg)	Aetiology (ischaemic)	Cardiac resynchronisation therapy	Absolute risk
1	117	No	Yes	0.41
2	117	No	No	0.97
3	117	Yes	Yes	0.63
4	117	Yes	No	0.99
5	130	No	Yes	0.44
6	130	No	No	0.98
7	130	Yes	Yes	0.67
8	130	Yes	No	0.99

Mitral regurgitation, N-terminal pro-brain natriuretic peptide and interventricular mechanical delay were held constant (median values).

Risk score

A quick and convenient way of estimating risk for an individual patient is to substitute patient characteristics in the Cox model. An example showing how the risk score is calculated is given in the appendix (*Figures 4* and *5*).

Model validation and multiple imputation

The bootstrap validation of the final fitted model indicated only modest over-fitting, around 3.4%. However the model was somewhat sensitive to multiple imputation, where when fitting the final model, the interaction between CRT and SBP was no longer statistically significantly predictive. All other variables remained in the model.

Discussion

The CARE-HF trial demonstrated that CRT exerts a substantial reduction in morbidity and mortality with little evidence of heterogeneity in pre-defined subgroups.[7] This more detailed analysis provides evidence that IVMD and to a lesser extent SBP predict patients' response to CRT. These finding must be treated with a degree of caution as the model is exploratory and the interactions between CRT and either IVMD or SBP were not particularly strong. However, the observed interaction between IVMD and the effects of CRT are consistent with the view that IVMD is a more precise physiological marker of cardiac dyssynchrony, the problem that CRT is designed to treat, than any other variable analysed. IVMD could therefore potentially be used as an inclusion criterion in future randomized controlled trials examining the effects of CRT in patient populations not included in CARE-HF, such as patients with less severe symptoms or with shorter QRS intervals. Whether IVMD should now be used in preference or in addition to QRS

Table 5 Estimated absolute risk of an event for patients with varying interventricular mechanical delay (49–66 ms) with and without cardiac resynchronisation therapy and in the presence and absence of ischaemia

Patient	Interventricular mechanical delay (ms)	Aetiology (ischaemic)	Cardiac resynchronisation therapy	Absolute risk
1	49	No	Yes	0.39
2	49	No	No	0.96
3	49	Yes	Yes	0.60
4	49	Yes	No	0.99
5	66	No	Yes	0.33
6	66	No	No	0.93
7	66	Yes	Yes	0.53
8	66	Yes	No	0.99

Mitral regurgitation, N-terminal pro-brain natriuretic peptide and systolic blood pressure were held constant (median values).

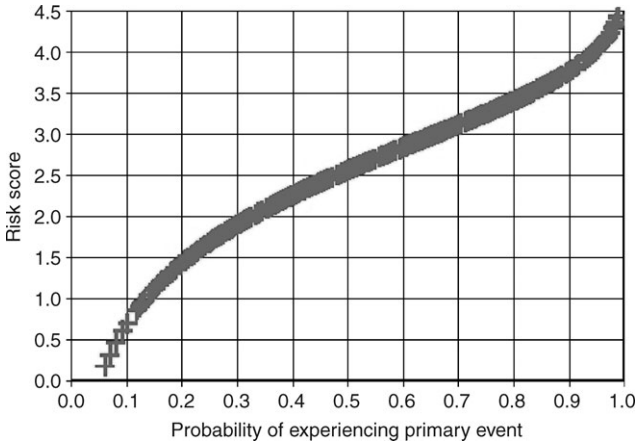


Figure 4 Risk score vs. probability of primary event at end of follow-up period.

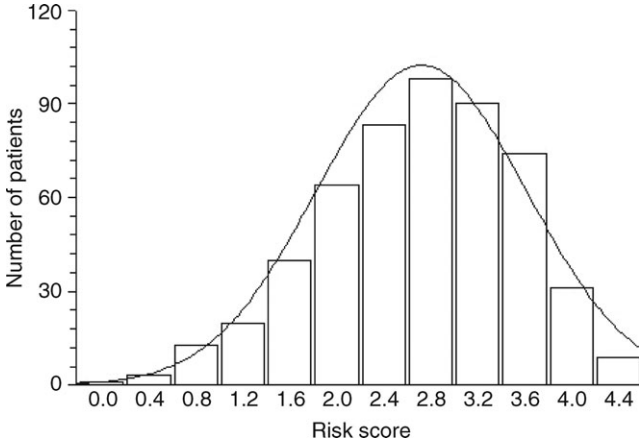


Figure 5 Histogram of risk score for patients at end of follow-up period.

duration to identify whether a patient should receive CRT is a matter for the individual clinician to decide and for future research. It is of great importance to note that IVMD is the best predictor of response to CRT in a population having large volumes, low EF, and broad QRS. We cannot state that IVMD is a better predictor of response to CRT in other populations.[32]

The estimated absolute risk of experiencing a primary outcome event may seem surprisingly high in some cases (absolute risk of 0.99 as shown in *Tables 4* and *5*). However, patients recruited to the study had severe heart failure (NYHA class III–IV) and therefore had an inherently high risk of experiencing the primary outcome during the study follow-up (which ranged from 18 to 44.7 months). The hazard functions from the model are based upon prediction of event rates across the maximum follow-up from the study, which had reached 55% in the control group in mean 29.4 months of follow-up. In order to estimate the absolute risk of an event with changing SBP and IVMD, the remaining clinical predictors were held constant. It is important to note that since these are also strong clinical predictors of outcome changing these values from the median has a large impact on the estimates of absolute risk. For example, in a non-ischaemic patient not receiving CRT with a SBP of 117 mmHg, use of lower interquartile range values for mitral regurgitation and NT-pro-BNP results in an estimate of absolute risk of approximately 0.84, an absolute reduction of around 13%.

The plasma concentration of NT-pro-BNP was a strong predictor of clinical outcome. Other competing measures of ventricular dysfunction were eliminated from the multivariate model. CRT reduces the severity of mitral regurgitation and plasma concentrations of NT-pro-BNP, and the two phenomena may be related. Any interaction between mitral regurgitation and NT-pro-BNP may be weak due to the occurrence of mitral regurgitation being related to the mechanical consequences of pacing, whereas release of NT-pro-BNP is associated with regional ventricular load and its later biological consequences (ventricular remodelling). It is perhaps not surprising that what they indicate differs on outcome. Despite this interaction between mitral regurgitation and NT-pro-BNP, which might be expected to eliminate one or other from the prognostic model, each provided independent prognostic information. The only other factor that provided important prognostic information was the aetiology of LV dysfunction. Patients with IHD did worse. This may be due to coronary events having an important additional effect on outcome, superimposed on the background severity of ventricular dysfunction as measured by NT-pro-BNP. Therapy, apart from CRT, did not predict outcome but this could reflect the high uptake of treatment with beta-blockers at baseline and changes during the course of the study.

There are a number of limitations to this analysis. In about 25% of patients, the core laboratory did not obtain a valid measure of mitral regurgitation. However, there were few missing data for other variables. Multiple imputations did indicate that the model was somewhat sensitive to missing data, with the interaction between CRT and SBP no longer featuring in the final model when the imputed datasets were used.

We analysed data according to the intention to treat principle.[29] Over 95% of patients assigned to CRT received a device before they reached a primary endpoint but resynchronization will have been sub-optimal either due to poor lead placement or failure to obtain adequate capture in some patients. Only 5% of patients received a CRT device before they reached a primary outcome event in the control group. These factors would be expected to reduce the strength of the interaction between baseline IVMD and the effect of CRT. Validation of the model using an independent data set would be valuable. The fact that the primary outcome is a composite measure may also be considered a limitation, but the rate of mortality in the trial was insufficient for us to examine the potential influence of the variables under investigation.

Conclusion

CRT has substantial clinical benefits in a broad range of patients with evidence of cardiac dyssynchrony, poor LV systolic function, and persistent symptoms despite pharmacological therapy. This analysis provides further evidence that a measure of cardiac dyssynchrony rather than the QRS interval on the ECG is currently the best marker of dyssynchrony. However, the predicted benefits from the model indicate that CRT appears worthwhile across the range of patients included in the CARE-HF trial.

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Appendix: calculation of risk score for patients within the CARE-HF trial

Methods

Risk score for patient with mitral regurgitation of 38.1, NT-pro-BNP of 2858 pg/ml, systolic blood pressure of 100 mmHg, IVMD of 13.8 ms, ischaemia, and in receipt of CRT would be calculated as follows:

$$\text{Risk score} = 0.5379 \log_e(\text{MR}) + 0.2717 \log_e(\text{NT-pro-BNP}) - 0.0087(\text{SBP}) + 0.0010(\text{IVMD}) + 0.6340(\text{ischaemic}) + 0.0172(\text{CRT} * \text{SBP}) - 0.0131(\text{CRT} * \text{IVMD}) - 1.8740(\text{CRT}).$$

Result

$$\text{Risk score} = 0.5379 \log_e(38.1) + 0.2717 \log_e(2858) - 0.0087(100) + 0.0010(13.8) + 0.6340(\text{ischaemic}) + 0.0172(1 * 100) - 0.0131(1 * 13.8) - 1.8740(1) = 2.93.$$

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