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The effect of QRS duration on cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial

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Aims In EchoCRT, a randomized trial evaluating the effect of cardiac resynchronization therapy (CRT) in patients with a QRS duration of <130 ms and echocardiographic evidence of left ventricular dyssynchrony, the primary outcome occurred more frequently in the CRT when compared with the control group. According to current heart failure guidelines, CRT is recommended in patients with a QRS duration of ≥120 ms. However, there is some ambiguity from clinical trial data regarding the benefit of patients with a QRS duration of 120–130 ms.

Methods and results The main EchoCRT trial was prematurely terminated due to futility. For the current subgroup analysis we compared data for CRT-ON vs. -OFF in patients with QRS < 120 ($n = 661$) and QRS 120–130 ms ($n = 139$). On uni- and multivariable analyses, no significant interaction was observed between the two groups and randomized treatment for the primary or any of the secondary endpoints. On multivariable analysis, a higher risk for the primary endpoint was observed in patients with a QRS duration of 120–130 ms randomized to CRT-ON vs. CRT-OFF (hazard ratio 2.18, 95% CI 1.02–4.65; $P = 0.044$). However, no statistically significant interaction, compared with patients with QRS < 120 ms randomized to CRT-ON vs. CRT-OFF, was noted (P-interaction = 0.160).

Conclusions In this pre-specified subgroup analysis of EchoCRT, no benefit of CRT was evident in patients with a QRS duration of 120–130 ms. These data further question the usefulness of CRT in this patient population.

Keywords Cardiac resynchronization therapy • Narrow QRS • QRS duration

Introduction

In view of the reduction in morbidity and mortality observed in large clinical trials, cardiac resynchronization therapy (CRT) has become an important element of modern day heart failure therapy. Current guidelines recommend CRT implantation for patients with symptomatic chronic heart failure (CHF), a severely reduced left ventricular ejection fraction (EF ≤ 35%) and a QRS complex ≥120 ms, based on published landmark studies.[1–4] While patients with left bundle branch block (LBBB) have a class I indication for

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CRT, class IIa and IIb indications are given to patients with non-LBBB and a QRS duration ≥150 and 120–150 ms, respectively. Although inclusion criteria of previous landmark trials usually allowed patients with a QRS duration ≥120 ms to enter the trial, the majority of individuals had longer QRS durations (≥150 ms). Indeed, recent meta-analyses have questioned the benefit of CRT in patients with shorter QRS duration, i.e. a QRS duration of <130–150 ms.[5,6] As such, there is some ambiguity regarding the optimal cut-off QRS duration for CRT and, specifically, whether patients at lower end of current recommendations (i.e. with a QRS duration of 120–130 ms) truly benefit from CRT.

EchoCRT was a randomized trial evaluating the effect of CRT in patients with a QRS duration of <130 ms and echocardiographic evidence of left ventricular dyssynchrony as previously described (ClinicalTrials.gov Identifier: NCT00683696).[7] The trial was terminated early due to futility. Moreover, a significant relative increase in all-cause mortality of 81% was observed in the CRT-ON vs. -OFF group. As a result of EchoCRT, current guidelines recommend against the use of CRT in patients with a QRS duration of ≤120 ms.[4] Whether the lack of benefit for CRT applies to the entire EchoCRT cohort, or whether patients with a longer QRS duration (i.e. 120–130 ms) may derive a benefit from CRT, is presently elusive. This is of clinical importance as these patients are currently indicated to receive CRT, albeit with conflicting results as stated. The current pre-specified subgroup analysis was therefore conducted to assess whether QRS duration has an impact on clinical outcome in patients enrolled in EchoCRT.

Methods

Study design and conduct

The EchoCRT study was an investigator-initiated, international, multicentre, randomized, clinical trial. The outcome results of the main trial have previously been reported, including the complete study protocol.[7] In brief, the trial was designed by the executive committee and sponsored by Biotronik, with a support for echocardiographic training and software provided by GE Healthcare. All study results were independently analysed at the Robertson Centre for Biostatistics at the University of Glasgow. Patients were eligible if they had New York Heart Association (NYHA) class III or IV heart failure; a left ventricular ejection fraction of 35% or less; a standard indication for an implantable cardioverter-defibrillator (ICD); optimized medical heart failure therapy; a QRS duration of <130 ms; a left ventricular end-diastolic diameter of 55 mm or more; and echocardiographic evidence of left ventricular dyssynchrony as previously defined.[7] A 12-lead electrocardiogram obtained using a standard electrocardiograph at a speed of 25 mm/s was used to confirm QRS duration eligibility criteria at baseline, prior to implant. The 12-lead electrocardiogram was submitted to the ECG Core Laboratory for independent confirmation. QRS durations as measured by the independent corelab were used for the current analysis. As for the main publication,[7] our current analysis comprised *all* patients included in EchoCRT (with screening QRS measurements performed by the including centre). In 16 of the included patients, a QRS of ≥130 ms was measured by the independent core lab. Eliminating these 16 patients from the analyses resulted in overall consistent results with the reported outcomes of the entire cohort.

After implantation of a Biotronik Lumax HF-T CRT-D system, patients were randomly assigned in a 1:1 ratio to have CRT capability turned on (the CRT group) or to have CRT capability turned off (the control group). Device-implanting physicians were aware of the study-group assignments, but patients, heart failure physicians, and study personnel completing the follow-up assessments were unaware of the group assignments.

The study was conducted in accordance with the Declaration of Helsinki.

Endpoints

The primary efficacy outcome was the combination of death from any cause or first hospitalization for worsening heart failure.[7] The primary safety outcome was freedom from CRT-D-related complications at 6 months. The pre-specified secondary outcomes included all hospitalizations for worsening heart failure throughout the study; changes in NYHA classification after 6 months; changes in quality of life (QOL; as measured by the Minnesota Living with Heart Failure questionnaire after 6 months); a study-specific score based on the composite outcome of death, first hospitalization for worsening heart failure (up to 24 months), and change in the score on the Minnesota Living with Heart Failure questionnaire after 6 months; and all-cause mortality.[7]

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Baseline characteristics were compared with the use of two-sample *t*-tests and χ^2 (or Fisher's exact) tests for continuous and categorical variables, respectively. Hazard ratios (HRs) for CRT-ON and -OFF with 95% CIs were calculated with the Cox proportional hazards models for each QRS duration strata including the stratification factor of country in the model. Additionally, a multivariable Cox proportional hazards model was performed to account for differences across randomized treatment groups in baseline characteristics between QRS duration strata [country, age, gender, QOL score, systolic blood pressure (SBP), ischaemic cardiomyopathy, coronary artery bypass grafting, chronic kidney disease, left ventricular end-diastolic diameter (LVEDD), and qualification by tissue Doppler imaging (TDI), and/or radial dyssynchrony]. Interactions between QRS duration strata and treatment (CRT = ON and CRT = OFF) were tested for in Cox models that included QRS duration strata and treatment main effects and interaction terms. Time to event curves were estimated with the use of the Kaplan–Meier method.

Changes in NYHA class from baseline to 6 months were analysed as a binary outcome (improved condition vs. no change or deteriorated condition) with the use of a logistic-regression model with adjustment for country of recruitment. The change in total score on the Minnesota Living with Heart Failure questionnaire was analysed with the use of an analysis of co-variance with adjustment for the baseline total score and country of recruitment.

All tests were two sided with a $P < 0.05$ considered to be significant. SAS version 9.2 was used for all analysis.

Results

Baseline parameters at the time of trial entry are presented in *Table 1*. Compared with patients with QRS < 120 ms, patients with a QRS of 120–130 ms were older, more frequently males had larger end-diastolic left ventricular diameters, and more frequently had underlying ischaemic cardiomyopathy and chronic kidney disease.

333/661 patients (50%) and 65/139 (47%) of patients with QRS duration of ≤120 ms and QRS 120–130, respectively, were randomized to CRT-ON. There was no statistically significant interaction regarding

Table 1 Baseline characteristics

Variable	QRS < 120 (n = 661)	QRS 120–130 (n = 139)	P-value
Age (years)	57.2 (12.82)	61.8 (11.83)	<0.001
Males	466 (70.50%)	110 (79.14%)	0.039
Walking distance (m)	324.9 (121.21)	325.7 (114.40)	0.944
Quality-of-life score	52.3 (24.16)	45.4 (24.05)	0.002
NYHA classification			
I	3 (0.45%)	2 (1.44%)	*
II	14 (2.12%)	4 (2.88%)	
III	624 (94.40%)	128 (92.09%)	
IV	20 (3.03%)	5 (3.60%)	
BNP (pg/mL)[#]	249.0 (92.00, 540.00)	322.0 (120.00, 613.00)	0.288
NT-proBNP (pg/mL)[#]	1080.5 (427.00, 2447.0)	1232.0 (609.00, 1870.0)	0.505
Sitting SBP (mmHg)	118.2 (18.93)	122.0 (20.62)	0.035
Sitting DBP (mmHg)	72.8 (11.82)	72.8 (11.98)	0.952
BMI (kg/m^2)	30.8 (11.61)	31.3 (14.84)	0.656
Ischaemic cardiomyopathy	338 (51.21%)	89 (64.03%)	0.006
Myocardial infarction >3 months ago	252 (38.12%)	65 (46.76%)	0.058
PCI > 3 months ago	237 (35.85%)	49 (35.25%)	0.893
CABG > 3 months ago	114 (17.25%)	35 (25.18%)	0.029
Hypertension	427 (65.19%)	100 (72.46%)	0.100
Congenital heart disease	14 (2.15%)	2 (1.47%)	1.000
Prior ischaemic stroke or TIA	74 (11.28%)	19 (13.77%)	0.409
Diabetes	264 (40.12%)	52 (37.41%)	0.553
Chronic lung disease	118 (18.04%)	31 (22.30%)	0.243
Chronic kidney disease	80 (12.20%)	26 (18.84%)	0.037
LVEF biplane (%)	27.1 (5.59)	26.8 (5.40)	0.657
LV end-diastolic diameter (mm)	65.8 (7.32)	69.2 (8.09)	<0.001
Qualified by TDI and/or radial dyssynchrony			
TDI only	178 (26.97%)	22 (15.83%)	0.012
Radial strain only	152 (23.03%)	31 (22.30%)	
TDI and radial strain	330 (50.00%)	86 (61.87%)	
ACE inhibitor or ARB	627 (94.86%)	131 (94.24%)	0.769
Aldosterone antagonist	397 (60.06%)	83 (59.71%)	0.939
β-Blocker	640 (96.82%)	134 (96.40%)	0.800
Diuretic agent	571 (86.38%)	121 (87.05%)	0.835

For categorical variables, number and percentage are reported; for continuous variables, mean and SD are reported (except for BNP and NT-proBNP where median and inter-quartile range are presented).
SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischaemic attack; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; BMI, body mass index; NYHA, New York Heart Association; BNP, brain natriuretic peptide; LV, left ventricular; EF, ejection fraction; TDI, tissue Doppler imaging; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
[#]BNP: n = 329 and 62; NT-proBNP: n = 308 and 71.
*P-value is not reported due to small numbers.

the primary outcome for CRT-OFF vs. CRT-ON in patients with QRS < 120 ms when compared with QRS ≥ 120 ms (*Figures 1* and *2*). In unadjusted analysis, a higher cardiovascular mortality was observed in CRT-ON vs. -OFF in patients with QRS < 120 ms (P < 0.003), which was not observed in patients with QRS ≥ 120 ms (albeit without a significant interaction; P-interaction = 0.153; *Figure 2*).

On multivariable adjustment (*Figure 3*), an apparent increase in the primary endpoint as well as in recurrent CHF hospitalization was observed for patients with a QRS of ≥120 ms, but not with a QRS of <120 ms (which again, however, was not significant on interaction analysis). For 'cardiovascular mortality' and 'heart failure mortality' the absolute low number of events precluded adjusting for all baseline variables. We therefore performed a limited multivariable analysis, adjusting only for ischaemic cardiomyopathy, age, and LVEDD. The results were consistent with the univariable analyses for cardiovascular mortality (QRS < 120 ms: HR 2.85 (95% CI 1.37–5.90), P = 0.0049 vs. QRS ≥ 120 ms: HR 1.78 (95% CI 0.56–5.64), P = 0.33, P-interaction = 0.23) and heart failure mortality (QRS < 120 ms: HR 1.86 (95% CI 0.74–4.68), P = 0.19 vs. QRS ≥ 120 ms: HR 1.16 (0.12–11.08), P = 0.90; P-interaction = 0.40).

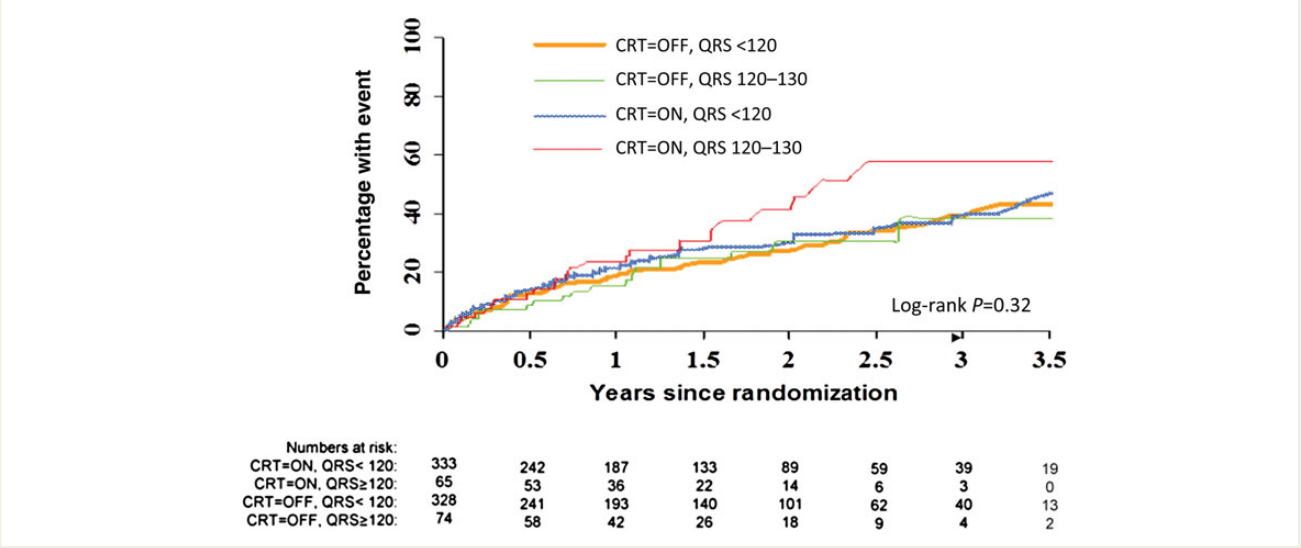

Figure 1 Kaplan–Meier estimates for primary outcome events, stratified by QRS duration. Kaplan–Meier curves for the primary composite outcome of death from any cause or hospitalization for heart failure in patients randomized to CRT-ON and -OFF, stratified by QRS duration.

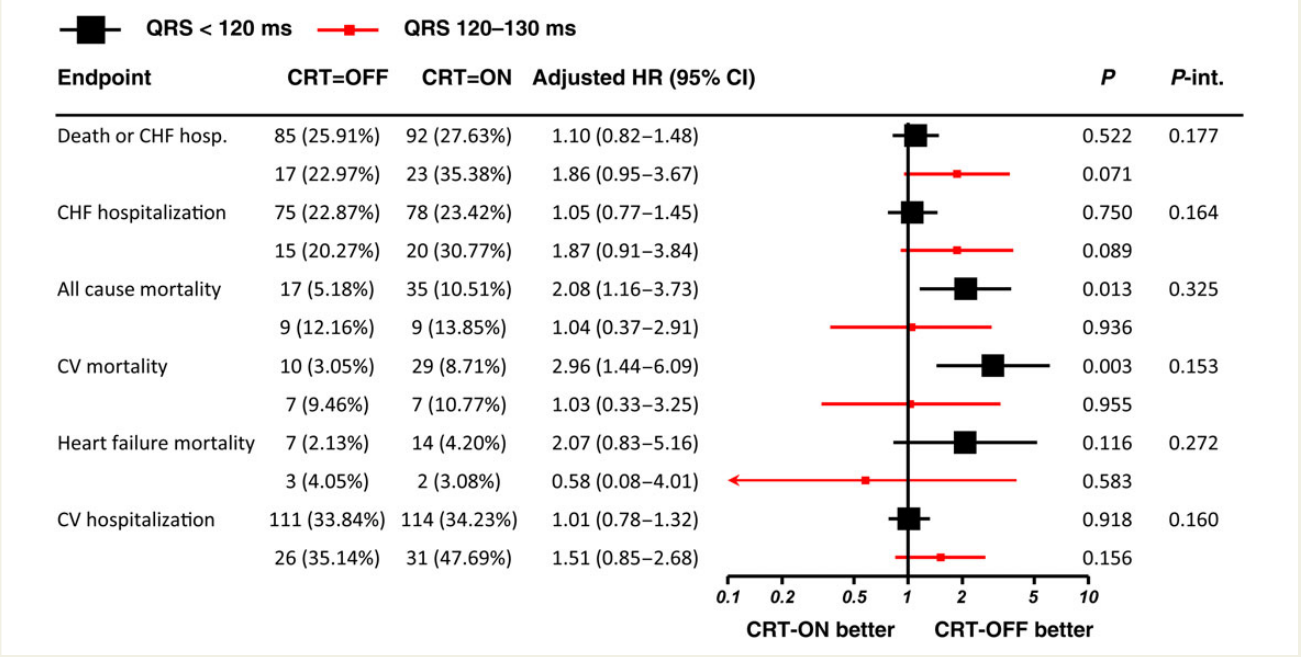

Figure 2 Endpoint results by QRS duration. Hazard ratio (95% confidence interval) adjusted for country and *P*-value from Wald test are presented. Data for QRS < 120 ms (black) and QRS 120–130 ms (red) are shown.

There was no difference in changes in Minnesota Living with Heart Failure, NYHA class, BNP/NT-proBNP, or 6 min walking distance from baseline to 6 months between the two groups (data not shown).

When results were analysed based on four groups of QRS duration (QRS < 100 ms ($n = 236$), QRS 100–109 ms ($n = 227$), QRS 110–119 ms ($n = 198$), and QRS ≥ 120 ms ($n = 139$)), a similar picture was observed (Supplemental material online, *Tables S1* and *S2*). Again, no statistically significant interaction was seen regarding the primary outcome for CRT-OFF vs. CRT-ON in patients with QRS < 120 ms when compared with QRS ≥ 120 ms. However, some numerical trends towards an increased hazard were observed for QRS ≥ 120 ms in uni- and multivariable analysis.

As in the overall study,[7] the primary safety endpoint of CRT-D-related complications were significantly more frequent in the CRT-ON when compared with the control group. This difference was similar in patients with QRS ≤ 120 ms and QRS 120–130 ms:

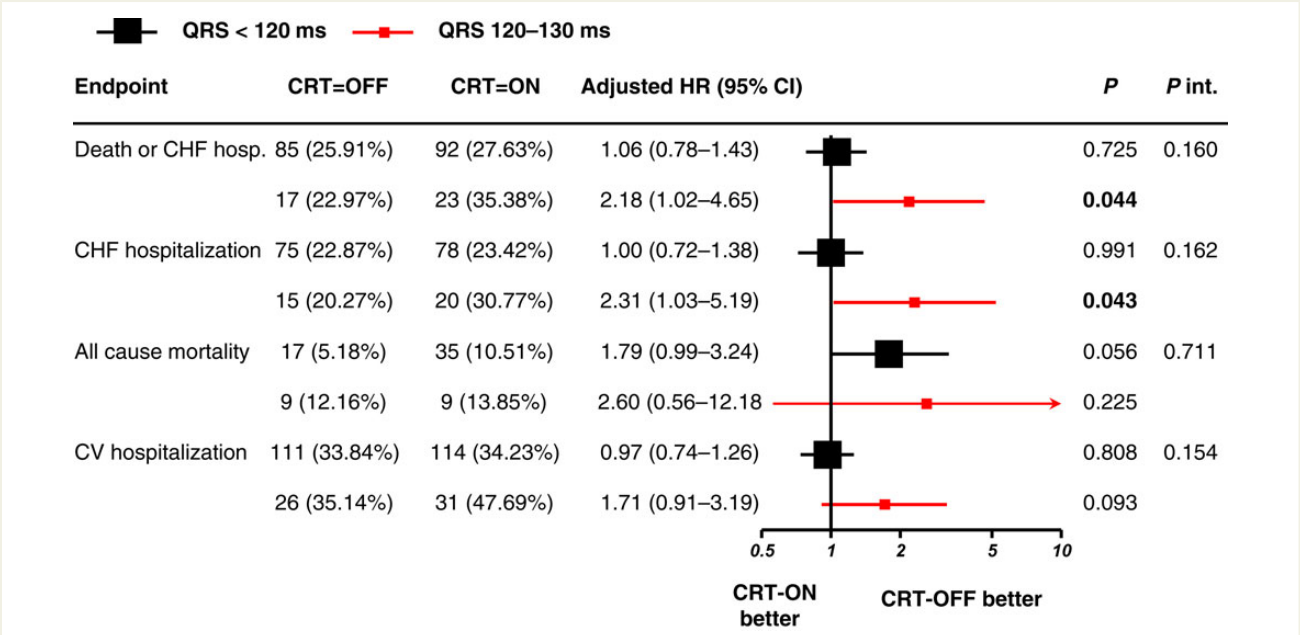

Figure 3 Endpoint results by QRS duration (fully adjusted models). Hazard ratio (95% confidence interval) adjusted for country, age, gender, quality-of-life score, systolic blood pressure, ischaemic cardiomyopathy, coronary artery bypass grafting, chronic kidney disease, left ventricular end-diastolic diameter, and qualification by tissue Doppler imaging and/or radial dyssynchrony are presented. *P*-value from Wald test. Data for QRS < 120 ms (black) and QRS 120–130 ms (red) are shown.

CRT-D system-related complications occurred in 47/333 (14.11%) and 24/328 (7.32%) patients with CRT-ON vs. CRT-OFF, respectively, in patients with QRS duration of ≤120 ms, and 8/65 (12.31%) and 5/74 (6.76%) patients with CRT-ON vs. CRT-OFF, respectively, in patients with QRS duration of 120–130 ms.

Discussion

Prior to EchoCRT, several small single-centre studies with soft endpoints had indicated a potential benefit of CRT in patients with a narrow QRS complex and echocardiographic evidence of dyssynchrony.[8–10] Moreover, several small pilot outcome trials failed to demonstrate consistent results,[11–13] underlining the necessity for EchoCRT, a large, endpoint-driven randomized clinical trial to adequately assess this issue. The EchoCRT trial was terminated early due to futility, indicating that CRT did not reduce the occurrence of first hospitalization for heart failure or death from any cause in this patient population.[7] Postulating a decreasing benefit of CRT with decreasing QRS duration, as indicated earlier, our current subgroup analysis investigated those individuals from EchoCRT most likely to respond to CRT, i.e. those with the longest QRS complex within the inclusion criteria. However, our results indicate that the primary outcome of EchoCRT is consistent in patients with different QRS durations. There was no signal for a benefit in any subgroup of QRS duration; particularly, patients with a QRS of 120–130 ms did not benefit when compared with patients with a shorter QRS duration.

Based on the inclusion criteria of published landmark trials, current guidelines recommend CRT for patients with symptomatic CHF, a severely reduced left ventricular ejection fraction (EF ≤ 35%) and a QRS complex ≥ 120 ms.[1–4] However, the majority of included individuals had longer QRS durations. Indeed, the median QRS duration in CARE-HF was 160 ms (interquartile range 152–180);[1] along the same line, 65% of patients included in MADIT-CRT had a QRS duration of ≥150 ms.[14] Several subgroup analyses have indicated a more pronounced benefit of CRT in patients with longer QRS duration. In MADIT-CRT, patients with QRS ≥ 150 ms showed a 52% reduction in the primary endpoint with CRT vs. ICD, while those with a QRS of <150 had no benefit from CRT (*P*-interaction = 0.001).[14] In a recent individual patient meta-analysis of CARE-HF, MIRACLE, MIRACLE-ICD, REVERSE, and RAFT, the effect of baseline QRS duration on the benefit of CRT when compared with no active device or with a defibrillator alone was investigated.[5] On multivariable analysis, only QRS duration predicted the magnitude of effect of CRT on outcomes. Further analyses indicated an increasing benefit of CRT on all-cause mortality and on the composite of first hospitalization for HF or death with increasing QRS duration, with a high probability of a benefit particularly in patients with QRS duration of ≥140 ms.[5] Hence, although currently indicated in these patients, the benefit of CRT on individuals at the lower end of the QRS spectrum is elusive at best. Our current subgroup analysis of EchoCRT confirms and extends these findings. Indeed, inclusion into EchoCRT was based not only on QRS duration but also on the presence of echocardiographic signs of dyssynchrony. Taken together with the aforementioned clinical trials, the lack of benefit even in this 'enriched' cohort strongly speaks against a relevant benefit of CRT in this patient population. As such, strong evidence is accumulating that patients in this range

of QRS duration may not be the optimal candidates for CRT and may possibly derive harm from it. Indeed, in our multivariable analysis, patients with a QRS duration of 120–130 ms showed an increased hazard for the combined primary endpoint (although this needs to be interpreted with caution in view of the negative interaction *P*-value and relatively small sample size). It is conceivable that limited power due to low number of events and premature termination of the trial contributed to the lack of statistical significance of some of the results, which may have turned out significant with a higher number of included patients and events.

Patients with left bundle branch block have been shown to have a higher probability to profit from CRT than those with non-specific intra-ventricular conduction disorder or right bundle branch block.[15] As a result, patients with LBBB have a class I indication for CRT (level of evidence A for QRS $\geq$ 150 ms and B for QRS 120–150 ms). In contrast, a class IIa indication is given to patients with non-LBBB and a QRS duration of $\geq$150 ms, while only a class IIb indication is given to patients with non-LBBB and a QRS of 120–150 ms (both level of evidence B). As EchoCRT was primarily performed in patients with a narrow QRS complex, presence or absence of bundle branch block (or bundle branch block 'pattern') was not assessed. In view of the trends observed in our current analysis, it appears unlikely that patients with a QRS duration of 120–130 ms and LBBB may have derived a substantial benefit from CRT.

Modern echocardiographic techniques including speckle tracking radial strain as well as TDI were used in EchoCRT,[7] which had been shown to be associated with beneficial outcomes in patients with a wide QRS complex.[16–18] It can only be speculated whether use of other, novel echocardiographic parameters of dyssynchrony would allow for better distinction of patients likely to respond to CRT. Several such parameters, including assessment of 'apical rocking', have recently been brought forward.[19,20] In the absence of an adequately powered randomized clinical trial, however, these findings should be viewed as hypothesis generating at best, and not as a base for clinical decisions regarding CRT implantation, particularly for patients with a narrow QRS complex. Experience from the past pilot studies cited above serves as a clear and present reminder that such hypotheses may eventually be proven wrong if assessed in an endpoint-driven clinical trial.

Since initiation of the EchoCRT trial, various studies have indicated an increased likelihood of benefit for CRT in patients in whom placement of the LV electrode was targeted to the site of latest mechanical or electrical activation of the left ventricle.[21] From our current data, it cannot be excluded that such a strategy may have resulted in a benefit of CRT in patients with a QRS duration of 120–130 ms or even shorter. Further endpoint-driven randomized trials are necessary to prove or dismiss the concept of targeted LV lead placement in this particular patient population.

Our data are consistent with other large-scale clinical trials and meta-analyses,[5,14] indicating a lack of benefit (and potential harm) for CRT in 'borderline' QRS duration of 120–130 ms. As a result, an adaptation of current clinical guidelines recommending CRT for patients presenting with a QRS complex $\geq$ 120 ms may be viewed as self-evident. Looked upon purely from a clinical trial point of view, this may be problematic as it implies adaptation of guidelines based on subgroup analyses rather than clinical trial inclusion criteria. However, data from several carefully and independently conducted randomized clinical trials all point into the same direction, indicating a solid base for a guideline adaptation. Interestingly, an ESC CRT Survey conducted in 2009 in 13 countries reported that 19% of patients receiving a CRT had a QRS duration of $<$130 and 9% had a QRS duration of $<$120 ms.[22] It should not be forgotten that CRT by itself may be associated with harm, which if not counterbalanced by clear clinical benefit may result in a worse outcome. Also in EchoCRT, the rate of adverse effects was substantially higher in patients randomized to CRT-ON, mainly driven by lead-related problems.[7] Other potentially harmful effects have been related to the additional risk of infection, as well as a potentially increase proarrhythmic effect due to an increase in transmural dispersion of repolarization.[23] As such, CRT implantation in non-suitable patients may not only result in a neutral effect due to lack of benefit, but may negatively affect clinical outcome.

Limitations

Although pre-specified, this subgroup analysis of EchoCRT should by definition be interpreted as hypothesis generating. Randomization was not stratified by QRS duration leaving the possibility of unmeasured residual confounding. As the trial's primary endpoint was negative, any subgroup analyses need to be interpreted with caution. Moreover, the trial was terminated prematurely, further reducing the statistical power of any subgroup analysis. The number of patients included with QRS 120–130 ms was too small to meaningfully perform further subgroup analyses; as such, it cannot be assessed with confidence if patients with a QRS of 120–130 ms and positive prognostic characteristics for response (women, non-ischaemic patients, etc.) may have profited from CRT.

Conclusion

In this pre-specified subgroup analysis of EchoCRT, no benefit of CRT was evident in patients with a QRS duration of 120–130 ms. Our data further question the usefulness of CRT in this specific patient population. Together with the consistent data from other large-scale randomized trials, these findings may have important implication for further guidance regarding the optimal QRS duration cut-off for CRT.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: J.S. reports consultant and/or speaker fees from Amgen, Astra-Zeneca, Bayer, Biotronik, Biosense Webster, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sankyo, Cook Medical, Medtronic, Novartis, Pfizer, Roche, Sanofi-Aventis, Sorin, and St. Jude Medical and is co-director of CorXL. He reports grant support through his institution from Bayer Healthcare, Biotronik, Daiichi-Sankyo, Medtronic, and St. Jude Medical. J.P.S. reports grants and personal fees from Biotronik, grants and personal fees from Boston Scientific, grants and personal fees from Medtronic, grants from St. Jude Medical, personal fees from Sorin Group, personal fees from CardioInsight, personal fees from Respicardia Inc. during the conduct of the study. W.T.A. reports grant

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