# Impact of QRS duration on left ventricular remodelling and survival in patients with chronic heart failure

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**Abstract**

Background In patients with chronic heart failure, QRS duration is a consistent predictor of poor outcomes. It has been suggested that for indicated patients, cardiac resynchronisation therapy (CRT) could come sooner in the treatment algorithm, perhaps in parallel with the attainment of optimal guideline-directed medical therapy (GDMT). We investigated differences in left ventricular (LV) remodelling in those with narrow QRS (NQRS) compared to wide QRS (WQRS) in the absence of CRT, whether an early CRT strategy resulted in unnecessary implants and the effect of early CRT on outcomes. Methods and results Our cohort consisted of 214 consecutive patients with LV ejection fraction (LVEF) [?]35% who underwent repeat echocardiography 1-year after enrolment. Of these, 116 patients had NQRS, and 98 had WQRS of whom 40 received CRT within 1-year and 58 did not. In the absence of CRT patients with WQRS had less LV reverse remodelling compared to those with NQRS, with differences in ΔLVEF (+9% vs 2 %, p<0.001), ΔLV end-diastolic diameter (-2mm vs -1mm, p=0.095) and ΔLV end-systolic diameter (-4.5mm vs -2mm, p=0.038). LVEF was more likely to improve by [?]10% if patients had NQRS or received CRT (p=0.08). Thirteen (24%) patients with WQRS achieved an LVEF >35% in the absence of CRT, however none achieved >50%. Conclusions A strictly linear approach to HF therapy might lead to delays to optimal treatment in those patients with the most to gain from CRT and the least to gain from GDMT.

**Title**

Impact of QRS duration on left ventricular remodelling and survival in patients with chronic heart failure

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**Abstract**

*Background*

In patients with chronic heart failure, QRS duration is a consistent predictor of poor outcomes. It has been suggested that for indicated patients, cardiac resynchronisation therapy (CRT) could come sooner in the treatment algorithm, perhaps in parallel with the attainment of optimal guideline-directed medical therapy (GDMT). We investigated differences in left ventricular (LV) remodelling in those with narrow QRS (NQRS) compared to wide QRS (WQRS) in the absence of CRT, whether an early CRT strategy resulted in unnecessary implants and the effect of early CRT on outcomes.

*Methods and results*

Our cohort consisted of 214 consecutive patients with LV ejection fraction (LVEF) [?]35% who underwent repeat echocardiography 1-year after enrolment. Of these, 116 patients had NQRS, and 98 had WQRS of whom 40 received CRT within 1-year and 58 did not. In the absence of CRT patients with WQRS had less LV reverse remodelling compared to those with NQRS, with differences in $\Delta$LVEF (+9% vs 2 %,$p$ <0.001), $\Delta$LV end-diastolic diameter (-2mm vs -1mm, p=0.095) and $\Delta$LV end-systolic diameter (-4.5mm vs -2mm, $p$ =0.038). LVEF was more likely to improve by [?]10% if patients had NQRS or received CRT ($p$ =0.08). Thirteen (24%) patients with WQRS achieved an LVEF >35% in the absence of CRT, however none achieved >50%.

*Conclusions*

A strictly linear approach to HF therapy might lead to delays to optimal treatment in those patients with the most to gain from CRT and the least to gain from GDMT.

**Key words:** Cardiac resynchronisation therapy, bi-ventricular pacing, heart failure, remodelling, pharmacotherapy.

**Abbreviations list**

HFrEF – heart failure with reduced ejection fraction

CRT – cardiac resynchronisation therapy

LV – left ventricle

GDMT – guideline-directed medical therapy

LVEF – left ventricular ejection fraction

LBBB – left bundle branch block

HF – heart failure

DCM – dilated cardiomyopathy

eGFR – estimated glomerular filtration rate

ECG - electrocardiogram

LVEDd – left ventricular end diastolic diameter

LVESd – left ventricular end systolic diameter

ACE – angiotensin converting enzyme

ARB – angiotensin II receptor blocker

MRA – mineralocorticoid receptor antagonist

ARNI – angiotensin receptor-neprilysin inhibitors

nQRS – narrow QRS

NYHA – New York Heart Association

PIONEER-HF – Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized for an Acute Heart Failure Episode

TRANSITION – post-discharge tReatment initiation with sacubitril/valsartan in heart failure patieNtS with reduced ejection-fracTion hospitalised for an acute decOmpensation eveNt

NEOLITH - New-Onset LBB-Associated Idiopathic Nonischaemic CardiomyopaTHy

GWTG-HF – Get With the Guidelines Heart Failure

REVERSE – Resynchronisation reVErses Remodelling in Systolic left vEntricular dysfunction

BLOCK-HF – Biventricular verses Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block

**Manuscript text**

**Introduction**

For patients with heart failure with reduced ejection fraction (HFrEF) receiving guideline-directed medical therapy (GDMT),[1,2] QRS duration is a consistent predictor of poor outcomes. In appropriately selected patients with QRS duration [?]120ms cardiac resynchronisation therapy (CRT) reduces hospitalisations,

improves symptoms and survival.[3] The optimal timing of CRT implantation is unknown, and is recommended to patients who remain symptomatic and have persistently impaired left ventricular (LV) function with an LV ejection fraction (LVEF) [?]35%.[4,5]

GDMT is recommended as an initial step based largely on the inclusion criteria of randomised controlled trials supporting the use of CRT.[6] It has been suggested that for indicated patients CRT should come sooner in the treatment algorithm, since and patients with wide QRS (WQRS) might experience an early prognostic benefit from CRT.[7] Additionally, most patients receiving CRT are not on optimal doses of GDMT when they are implanted.[8] The paradox is however that physicians delay implantation based on guidelines while the aforementioned issues would favour earlier implant during the attainment of optimal GDMT.

We aimed to test the hypotheses that 1) LV remodelling in response to GDMT is less in patients with WQRS compared to narrow QRS (NQRS) in the absence of CRT; 2) early CRT implantation, during the attainment of optimal medical therapy would not be associated with unnecessary implantation; and 3) whether early CRT is associated with improved outcomes over delayed implantation.

## Methods

*Participants*

As described in our earlier publications,[9-11] we conducted a prospective cohort study with the predefined aims of studying outcomes in ambulatory patients with HFrEF receiving state of the art therapy. Between July 2006 and January 2009 consecutive patients attending specialist cardiology clinics in 4 UK hospitals were approached to participate. In all, 628 patients provided informed, written consent and of these an unselected cohort of 408 patients prospectively underwent clinical and echocardiography assessment at baseline and after 1-year. For the present analysis we included ambulatory patients with stable clinical signs and symptoms of HF for 3 months, with LVEF [?]35% on transthoracic echocardiogram. Inclusion was not dependent on the aetiology of HF and included patients with ischaemic heart disease and non-ischaemic cardiomyopathies. We excluded patients with missing data and those who had CRT at enrolment.

*Variables and data sources*

At the time of enrolment baseline clinical and demographic variables were recorded for all patients. Aetiology of LV impairment was classified as either ischaemic heart disease or non-ischaemic cardiomyopathy. Medical history included diabetes mellitus, chronic kidney disease, stroke, chronic obstructive pulmonary disease, malignancy and hypertension. A venous blood sample was taken at enrolment and tested for serum haemoglobin, white blood cell count, platelets, estimated glomerular filtration rate (eGFR) and albumin. Rhythm, heart rate, PR interval, QRS duration and QRS morphology were determined by electrocardiogram (ECG) interpreted by a cardiologist (RMC, KKW or MTK). LBBB was defined as QRS [?]120ms, the absence of Q waves in leads I, V5 and V6, R wave in I, V5 and V6 and ST and T wave displacement opposite to the major deflection of the QRS complex. Cardiac imaging data consisted of LV end diastolic diameter (LVEDd), LV end systolic diameter (LVESd) and LVEF obtained by transthoracic echocardiogram interpreted by two British Society of Echocardiography accredited senior sonographers (JG, MP).

GDMT was prescribed at the discretion of the responsible cardiologist. Patients who did not have contraindications received either angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) as well as β-adrenoceptor antagonist (beta-blocker) and mineralocorticoid receptor antagonist (MRA) as indicated. Patients underwent physician and specialist nurse supervised up-titration of GDMT as heart rate and blood pressure allowed according to local protocol to achieve maximally tolerated doses. The study period pre-dated the availability of angiotensin receptor-neprilysin inhibitors (ARNI).

*Outcomes*

The primary outcome of the current analysis was LV remodelling between baseline and 1-year, measured by change in LVEF, LVEDd and LVESd between those with NQRS and WQRS divided by those who did or did not receive CRT prior to follow-up. Secondary outcomes were changes in dosage of GDMT and change

in symptoms reported according to New York Heart Association (NYHA) class. We performed an analysis of remodelling in those patients who did or did not receive early CRT, restricted to patients with LBBB. We also assessed the survival of patients with WQRS who did or did not receive CRT, and the survival benefit associated with reverse remodelling in those who achieved a ΔLVEF [?]10%, which has previous been shown to be a reliable marker of beneficial prognosis.[12] All patients were registered with the United Kingdom Office of Population Consensus and Surveys, which provided details of the time of death, follow-up censorship occurred in June 2018.

*Definitions*

NQRS was taken as <120ms and WQRS as [?]120ms. The first clinic attendance during the study period was the point of enrolment for the purposes of analysis. HF due to ischaemic heart disease was defined as either a previous myocardial infarction, coronary artery bypass grafting, coronary stenting at index presentation, evidence of inducible ischaemia on non-invasive imaging or scar suggesting infarction on cardiac magnetic resonance imaging. LVEF was measured by Simpson's biplane method where endocardial border definition allowed[13].

*Statistics*

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY). After testing for normality of distribution, continuous variables are expressed as mean ± standard error of mean or median (interquartile range) and discrete variables are presented as number (percentage). Groups were compared using Student's t-test or one-way analysis of variance for normally distributed continuous data, by Mann-Whitney U test or Kruskal-Wallis H-test for non-normally distributed continuous data and by Pearson $\chi^2$ tests for categorical data. Unadjusted survival was illustrated by Kaplan-Meier plots, and differences between groups defined by log-rank tests. In all analyses $p$ <0.05 was regarded as statistically significant.

*Ethical consideration*

Consecutive patients were approached by a cardiologist (RMC, KKW or MTK) in an ambulatory HF clinic and provided informed, written consent. The study was approved by the Leeds West Research Ethics Committee (07/Q1205/17) and conducted according of the principles expressed in the Declaration of Helsinki.

**Results**

*Patients*

The final dataset included 214 patients with LVEF[?]35% who did not have CRT at baseline, of whom 163 (76%) were male with an average age of 67 (57-76) years (figure 1). Of these, 116 patients had NQRS and 98 had WQRS, of which 40 received CRT implant within 1-year and 58 who did not. Of the 98 patients with WQRS, 61 (62%) had LBBB, and 37 (38%) had non-LBBB. In those who received CRT within 1-year the median time from enrolment to CRT implant was 123 days. Of the 58 patients without CRT at 1-year, 12 were subsequently implanted after a median of 568 days.

Patients were broadly similar at baseline, although those with WQRS who received CRT were on average older (Table 1). Patients who received CRT had worse renal function, and a greater baseline LVEDd and LVEDd compared to those who did not (table 2). The distribution of aetiology of HF and sinus rhythm were not different across groups. Patients who received early CRT were more likely to have LBBB (75%) compared to those who did not (54%) ($p$ =0.031).

*Prescription and up-titration of GDMT*

There were no significant differences in the dosing of GDMT between groups at baseline, a total of 184 (86%) patients were prescribed an ACE-inhibitor or ARB, 174 (82%) a beta-blocker, and 99 (47%) an MRA. Following supervised up-titration of GDMT between baseline and 1-year the change in dosing were not significantly different between groups except the greater increase in beta-blocker dosage in patients who

received CRT. We also observed an increase in the proportion of patients receiving beta-blockers (82% to 89%) and ACE-inhibitor or ARB (87% to 90%) between baseline and 1-year.

*Reverse remodelling in response to GDMT and CRT*

The change in clinical status between baseline and 1-year for patients with NQRS and WQRS with and without CRT are displayed in Table 3. In patients with WQRS in the absence of CRT, we observed less LV reverse remodelling compared to those with NQRS (figure 2) with significant differences in ΔLVEF (+9% vs 2 %, $p$ <0.001) ΔLVEDd (-2mm vs -1mm, p=0.095) and ΔLVESd (-4.5mm vs -2mm, $p$ =0.038). In patients with NQRS, echocardiography follow-up at 1-year demonstrated that 64 (62%) patients attained a LVEF of >35% compared with 13 (24%) patients with WQRS who did not receive CRT (p<0.001) and were therefore no longer indicated for CRT according to guidelines. Importantly, no patient with WQRS attained a LVEF of >50% in the absence of CRT, whilst 9 (16%) achieved an LVEF >40%. A total of 79 (40%) patients achieved a ΔLVEF of *[?]* 10% between baseline assessment and follow-up echocardiogram, of whom 51 (49%) had NQRS, 15 (41%) had WQRS and received CRT and 13 (24%) who had WQRS did not receive CRT ($p$ =0.08). In analysis restricted to patients with LBBB findings were similar. Recipients of CRT demonstrated improved cardiac function at 1-year compared to those without CRT, with greater improvement in LVEF (+8% vs +2%, $p$ =0.035) and trend to reverse remodelling as measured by LVEDd (-2.5mm vs 0mm, $p$ =0.32) and LVESd (-5mm vs -1mm, $p$ =0.21) (Supplementary table 1).

*Change in symptoms in response to GDMT and CRT*

Between baseline and follow-up symptoms improved in 83 (39%) patients, worsened in 29 (14%) and were unchanged in 102 (48%). Patients with NQRS or those with WQRS who received CRT were significantly more likely to experience and improvement symptoms and less likely to experience a deterioration compared to those with WQRS who did not receive CRT (table 3). The mean ΔNYHA class was significantly greater in those with NQRS or early CRT implant compared to those without CRT (p=0.008). In patients with WQRS who did not receive CRT, only 4 (10%) had improvement in symptoms and were NYHA class I at follow-up.

*Outcomes*

During a mean follow-up of 8.2 ± 3.4 years there were 125 (59%) deaths. Patients with effective remodelling (ΔLVEF of [?]10%) had a significant survival advantage compared to those who did not (p=0.004). In patients with WQRS who received early CRT (before 1-year) there was a significant survival advantage over a finite time compared to those with WQRS who did not ($p$ =0.001) (figure 3).

## Discussion

*Key findings*

The findings of this study were: 1) patients with NQRS had significantly greater reverse remodelling compared to those with WQRS not implanted with CRT; 2) patients with WQRS implanted with CRT had significantly greater reverse remodelling compared to those who were not; 3) these observations persisted in an analysis restricted to those with LBBB; and 4) those with an improvement in LVEF due to GDMT or CRT (or both) lived longer. Cumulatively these observations suggest that patients with WQRS are unlikely to archive this crucial treatment goal in the absence of CRT. Had we employed an early strategy in all, 13 (24%) patients with LVEF [?]35% at follow-up would have received CRT outside of the current guidelines [4].

*Role and timing of GDMT in patients with HFrEF*

There is a growing recognition that the timely initiation of GDMT early in the disease process might improve outcomes in HFrEF. Most recently this paradigm shift has been explored with sacubatril-valsartan. The Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized for an Acute Heart Failure Episode (PIONEER-HF) and TReatment initiation with sacubitril/valsartan in heart failure patieNtS with reduced ejection-fracTion hospitalised for an acute decOmpensation eveNt (TRANSITION) trials demonstrated the safety, improved treatment adherence, attainment of target doses

and, on post-hoc analysis, improvement in clinical outcomes when GDMT is initiated during HF hospitalisation [14-17]. In PARADIGM-HF and TRANSITION 29% and 34.4% of patients had *de novo* HF, and 52.1% and 24% were ACE-inhibitor/ARB naïve, respectively. *De novo* HF was an independent predictor of success of up-titration of sacubitril-valsartan, demonstrating the importance of up-front initiation of GDMT for patients with HFrEF.

*Response to GDMT in HFrEF with broad QRS*

GDMT can produce improvements in LV function but there is a growing recognition that LBBB can act as a primary cause of HFrEF in some with idiopathic cardiomyopathy [18-20], and that patients with LBBB often fail to remodel with GDMT. Intuitively it makes sense that a problem of electro-mechanical desynchrony is unlikely to be adequately treated with pharmacotherapy and would require an electrical solution. In one study of 361 patients with idiopathic DCM the only predictors of reverse remodelling with GDMT were higher systolic blood pressure and the absence of LBBB (odds ratio 2.47, $p$ =0.009)[1]. In the New-Onset LBBB-Associated Idiopathic Nonischaemic CardiomyopaTHy (NEOLITH) I study, many patients with DCM indicated for CRT failed to remodel despite GDMT, most remained candidates at subsequent review and many achieved a LVEF [?]50% following CRT implant [7]. To our knowledge, randomized controlled trials investigating the efficacy of GDMT in HFrEF have not performed analyses stratified by QRS duration and so the relative benefit of GDMT for patients with WQRS is unknown [21-26].

In the present analysis, attempts to up-titrate the dosage of GDMT were made systematically for all patients according to local protocol to achieve maximally tolerated dosages. The change in beta-blocker and ACE-inhibitor doses were similar between groups (with the exception of beta-blocker in recipients of CRT) but despite this, patients with WQRS remodelled less favourably in the absence of CRT. In addition, patients with WQRS who did not receive CRT were also significantly less likely to see an improvement in NYHA class between baseline and follow-up, with only 4 attaining Class I symptoms.

*Timing of cardiac resynchronisation therapy implantation*

The evidence base for CRT is strongest in patients with LBBB, which is independently associated with HF hospitalisation and death[27] although data also support the use of CRT in patients with non-LBBB WQRS ([?]150ms). In both groups, guidelines recommend CRT for those who remain symptomatic despite GDMT[4,5]. American guidelines recommend a period of 3-months of GDMT prior to implantation [5], and whilst European guidelines do not stipulate a time interval, the need for ongoing assessment inevitably results in delays to implantation and further follow-up and imaging costs[4]. These recommendations are based on the inclusion criteria or randomised controlled trials, which aimed to demonstrate the benefits of CRT*per se* rather than a combination of CRT and GDMT. In these trials GDMT was optimised prior to enrolment, and in some cases was not allowed to change during the study period.[6]

The timing of CRT implant might have implications for LV reverse remodelling and therefore long-term survival in patients indicated for device therapy [28,29]. The New-Onset LBBB-Associated Idiopathic Nonishcaemic CardiomyopaTHy (NEOLITH) II study was a retrospective analysis of 123 patients with DCM receiving CRT stratified by time from diagnosis of HFrEF to CRT implant. In adjusted analysis, early CRT implantation (within 9 months of diagnosis) was associated with greater chance of achieving a LVEF [?]35% [30]. In an analysis of 15,619 eligible HFrEF patients from the Get With the Guidelines Heart Failure (GWTG-HF) database, CRT during HF hospitalization was associated with reduced re-hospitalization and improved survival compared to delayed CRT implantation after discharge[31]. Information from both of these datasets is in parallel with our data which suggest that a delayed CRT strategy might be harmful.

*Risks and possible opportunities of early CRT implantation*

Patients with WQRS represent a group at high risk of hospitalisation, poor quality of life and death. The introduction of CRT into the treatment algorithm as a parallel to GDMT and the ability thereby to intervene more completely earlier in the disease process must be weighed against unnecessary implantation for patients who would have remodelled with GDMT alone. In addition, CRT often improves blood pressure and protects

against bradycardia making the parallel optimisation of GDMT alongside implantation a logical choice. The risks of CRT implant include pneumothorax, infection, haematoma, coronary sinus dissection, pericardial effusion and failure to place the LV lead, but significant complications are rare.

On the other hand, our results suggest that the potential for unnecessary implantation is relatively low and that delays to try and avoid this by waiting for remodelling might be detrimental to individuals and to society. The majority of patients indicated for CRT who did not receive early implant were still indicated at follow-up. 13 (24%) patients with WQRS who did not receive CRT attained an LVEF >35% and so were no longer indicated according to current guidelines [4,5] and 9 (16%) would have been implanted beyond the evidence base supporting the use of CRT [32]. However, there is no suggestion that implantation in these patients would be harmful. A pooled analysis of individual patient data from the Resynchronisation reVErses Remodelling in Systolic left vEntricular dysfunction (REVERSE) trial [32] and the Biventricular verses Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial [20] where inclusion criteria included LVEF [?]40% and [?]50% respectively, did not suggest a loss of effect or adverse safety signal in patients with less severely reduced LVEF [3]. Furthermore, in post hoc analysis of the Multicentre Automatic Defibrillator Implantation Trial with Cardiac Resynchronisation Therapy (MADIT-CRT) trial, core laboratory echocardiography assessment showed that the clinical benefit of CRT was evident regardless of the baseline LVEF. This was true even in the 38% of patients with LVEF >30% (range 30.1% to 45.3%) who were beyond the inclusion criteria and included both LBBB and non-LBBB QRS morphologies. Finally, the possible economic disadvantages of early CRT would be greatly mitigated by carefully targeted CRT-Defibrillator implantation [33].

*Strengths and limitations*

Our study presents real-world outcomes from a highly characterised HFrEF population from 4 UK hospitals, with long-term follow-up. We report data for patients with both LBBB and non-LBBB QRS morphologies and whilst this might have implications for patients with non-LBBB, in which there is conflicting evidence to support additional benefit from CRT, our aim was to reflect clinical practice and to be generalisable to all indicated patients. Furthermore, in analysis restricted to patients with LBBB, findings were similar, although non-significant for comparisons of LVEDd and LVESd.

This was a retrospective analysis with a small number of participants and our findings must be interpreted in light of this. An additional limitation is that patients who received early CRT were allocated based on physician or patient preference, and although groups were similar, there is the possibility of unmeasured confounders due to non-random allocation, which could only be accounted for by a randomised controlled trial. Also, it might be possible that some of the benefits from early CRT were because it facilitated the up-titration of beta-blockers due to protection from bradycardia.

The prescription of MRA at baseline enrolment was lower than would be expected in clinical practice, however these data reflect prescription following the first attendance at the specialist heart failure clinic and does not reflect further up-titration in subsequent consultations. This was an historic patient cohort predating the availability of ARNI which may have resulted in a less remodelling than would be seen in the modern era. However, there is as yet no published data clarifying heterogeneity of remodelling between patients with and without a WQRS receiving ARNI. Finally, our criteria for delayed CRT consisted of people had been implanted after one year or not implanted within the study period and is longer than is recommended in guidelines[4]. It is possible that lesser delays would have seen lesser difference between the groups. However, our description of a delayed strategy is likely to represent usual care in many regions.

## Conclusions

The implications of our findings are that a linear approach to HF therapy might lead to delays to optimal treatment in those patients with the most to gain from device therapy and the least to gain from GDMT. It may therefore represent a missed opportunity to intervene earlier in the disease process and prevent adverse events. GDMT failed to obviate the need for device therapy for most patients and an early approach is unlikely to lead to a large number of 'unnecessary' implants. These data should make us question our

approach to the timing of CRT implantation and the benefits of parallel implantation and attainment of GDMT should be tested in prospective, randomised trials.

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**Authorship**

SS and KKW researched the topic and devised the study.

RC and MTK collected and maintained a prospective patient registry of HFrEF patients.

SS and RC undertook primary statistical analysis.

SS and KKW produced the first draft manuscript.

All other co-authors contributed equally to manuscript preparation.

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**Figure titles and legends**

*Figure 1*

Title: Patient identification and exclusion criteria

Caption: A non-selected cohort of 408 patients underwent echocardiography at baseline and 1-year, the final dataset included 211 patients with LVEF [?]35% without CRT at baseline.

*Figure 2*

Title: Change in LV function and dimensions between groups.

Caption: Patients with NQRS or WQRS and early CRT implant had greater improvements in LVEF, LVEDd and LVEDs.

*Figure 3*

Title: Kaplan Meier plot to show survival in patients with WQRS who did or did not receive early CRT.

Caption: Patients with WQRS and early CRT had improved survival, but this was not statistically significant.

**Table 1**

Title: Baseline characteristics of patients

| | All patients (n=214) | NQRS (n=116) | WQRS with CRT (n=40) | WQRS without CRT (n=58) | *p*-value |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (years) | 67 (57,76) | 62.5 (52.3,72) | 72 (65,78.8) | 72 (59,79) | **<0.001** |

| | All patients (n=214) | NQRS (n=116) | WQRS with CRT (n=40) | WQRS without CRT (n=58) | *p*-value |
|---|---|---|---|---|---|
| Male sex [n(%)] | 163 (76) | 87 (75) | 33 (83) | 43 (74) | 0.58 |
| Past medical history | | | | | |
| Diabetes mellitus [n(%)] | 41 (19) | 22 (19) | 6 (15) | 13 (22) | 0.66 |
| Chronic kidney disease [n(%)] | 37 (17) | 21 (18) | 8 (20) | 8 (14) | 0.69 |
| Stroke [n(%)] | 19 (9) | 10 (9) | 2 (5) | 7 (12) | 0.48 |
| COPD [n(%)] | 20 (9) | 13 (11) | 3 (8) | 4 (7) | 0.59 |
| Malignancy [n(%)] | 11 (5) | 5 (4) | 4 (10) | 5 (4) | 0.30 |
| Hypertension [n(%)] | 57 (27) | 34 (29) | 12 (30) | 11 (19) | 0.30 |
| Aetiology of HF | | | | | |
| Ischaemic [n(%)] | 120 (56) | 59 (51) | 25 (63) | 36 (62) | 0.25 |
| Medications | | | | | |
| Aspirin [n(%)] | 86 (41) | 50 (43) | 16 (40) | 20 (36) | 0.65 |
| Beta-blocker [n(%)] | 174 (82) | 95 (82) | 32 (80) | 47 (84) | 0.88 |
| Bisoprolol equivalent dose (mg) | 2.5 (1.3,5.0) | 2.5 (1.3,5) | 2.5 (1.3,5.0) | 2.5 (1.3,5) | 0.30 |
| ACE-inhibitor [n(%)] | 148 (70) | 80 (69) | 28 (70) | 40 (71) | 0.95 |
| ARB [n(%)] | 36 (17) | 18 (16) | 8 (20) | 10 (18) | 0.79 |
| Ramipril equivalent dose (mg) | 5 (2.5,10) | 5 (2.5,10) | 5 (2.5,10) | 5 (1.6,8.8) | 0.54 |
| Loop diuretic [n(%)] | 174 (82) | 96 (83) | 34 (85) | 44 (79) | 0.69 |
| Furosemide equivalent dose (mg) | 40 (40,80) | 40 (40,80) | 40 (40,80) | 40 (25,80) | 0.54 |
| MRA [n(%)] | 99 (47) | 49 (42) | 21 (53) | 29 (52) | 0.34 |
| Thiazide diuretic [n(%)] | 5 (2) | 4 (3) | 1 (3) | 0 (0) | 0.38 |
| Statin [n(%)] | 114 (54) | 58 (50) | 23 (58) | 33 (59) | 0.48 |
| Anticoagulant [n(%)] | 79 (37) | 45 (39) | 13 (33) | 21 (28) | 0.78 |

Normally distributed continuous variables are expressed as mean ± SEM, non-normally distributed continuous variables are expressed as median (interquartile range), discrete variables are presented as number (percentage).

nQRS; narrow QRS, COPD; chronic obstructive pulmonary disease, HF; heart failure, IHD; ischaemic heart

disease, DCM; dilated cardiomyopathy, ACEi, angiotensin converting enzyme inhibitor, ARB; angiotensin II receptor antagonist, MRA; mineralocorticoid receptor antagonist.

**Table 2**

Title: Baseline investigation results

| | All patients (n=214) | NQRS (n=116) | WQRS with CRT (n=40) | WQRS without CRT (n=58) | *p*-value |
|---|---|---|---|---|---|
| Baseline echocardiogram | | | | | |
| LVESd (mm) | 53.6 ± 0.6 | 52.0 ± 0.7 | 57.1 ± 1.4 | 54.3 ± 1.2 | **0.005** |
| LVEDd (mm) | 61.8 ± 0.6 | 60.0 ± 0.7 | 65.4 ± 1.4 | 62.7 ± 1.1 | **0.001** |
| LVEF (%) | 27 (21,32) | 28 (22,32) | 25 (20.3,30.5) | 25.5 (22,30.3) | 0.25 |
| FS (%) | 13.2 (9.3,16.7) | 13.1 (9.1,16.2) | 11.5 (9.3,16.8) | 14.0 (10.0,16.7) | 0.54 |
| PASP (mmHg) | 34.6 ± 1.1 | 32.6 ± 1.5 | 37.3 ± 2.6 | 36.2 ± 2.3 | 0.18 |
| RWMA [n(%)] | 122 (58) | 58 (51) | 27 (68) | 37 (65) | 0.097 |
| Baseline EG | | | | | |
| Sinus rhythm [n(%)] | 142 (69) | 73 (65) | 27 (71) | 42 (76) | 0.33 |
| LBBB [n(%)] | 61 (29) | 0 (0) | 30 (75) | 31 (54) | **<0.001** |
| ECG rate (beats/min) | 71 (60,84.3) | 74.0 (62.0,89.0) | 72.0 (59.3,81.5) | 65.5 (59,75.8) | **0.028** |
| PR interval | 173.5 ± 3.1 | 162.5 ± 3.7 | 191.6 ± 9.6 | 182.2 ± 4.8 | **<0.001** |
| QRS interval (ms) | 124.5 ± 2.1 | 100.6 ± 0.9 | 159.0 | 148.6 ± 2.9 | **<0.001** |
| Blood tests | | | | | |
| Hb (g/L) | 14.1 ± 0.1 | 14.2 ± 0.2 | 14.1 ± 0.3 | 14.0 ± 0.2 | 0.69 |
| eGFR (ml/min/1.73m$^2$) | 54.4 ± 1.1 | 56.3 ± 1.6 | 48.7 ± 2.13 | 54.4 ± 1.9 | **0.043** |
| Albumin (g/L) | 43 (41,45) | 43 (41,45) | 43 (42,45) | 43 (41,45) | 0.72 |

Normally distributed continuous variables are expressed as mean ± SEM, non-normally distributed continuous variables are expressed as median (interquartile range), discrete variables are presented as number (percentage).

LA; left atrium, LVEDd; left ventricular end-diastolic dimension, LVESd; left ventricular end-diastolic dimension, LVEF; left ventricular ejection fraction, FS; fractional shortening, PASP; pulmonary artery systolic pressure, RWMA; regional wall motion abnormality, ECG; electrocardiogram, Hb; haemoglobin, WCC; white cell count, eGFR; estimated glomerular filtration rate.

**Table 3**

Title: Change in clinical status between baseline and follow-up at one year for patient groups.

| | All patients (n=214) | NQRS (n=116) | WQRS with CRT (n=40) | WQRS without CRT (n=58) |
|---|---|---|---|---|
| ΔBisoprolol equivalent dose (mg) | 1.3 (0,3.8) | 0.6 (0,2.5) | 2.5 (0.6,5)* | 0.6 (0,2.8) |

| | All patients (n=214) | NQRS (n=116) | WQRS with CRT (n=40) | WQRS without CRT (n=58) |
|---|---|---|---|---|
| ΔRamipril equivalent dose (mg) | 0 (0,5) | 0 (0,5) | 0 (0,2.5) | 0 (0,5) |
| ΔLVESd (mm) | -4 (-10,-2) | -4.5 (-10.8,0) | -3.5 (-9,2) | -2 (-7,2)* |
| ΔLVEDd (mm) | -1.5 (-7,1) | -2 (-8,1) | -2 (-7.5,1.5) | -1 (-5,3) |
| ΔLVEF (%) | 7 (1,15) | 9 (4,20) | 6 (1,12.5) | 2 (-1,9)*** |
| ΔNYHA class | 0 (-1,0) | 0 (-1,0) | 0 (-1,0) | 0 (-1,0)** |
| NYHA improving [n(%)] | 83 (39) | 49 (43) | 18 (45) | 16 (28)* |
| NYHA worsening [n(%)] | 29 (14) | 11 (10) | 5 (13) | 13 (22)* |

Normally distributed continuous variables are expressed as mean ± SEM, non-normally distributed continuous variables are expressed as median (interquartile range), discrete variables are presented as number and percentages in parentheses.

LVEDs; left ventricular end diastolic diameter, LVESd; left ventricular end systolic diameter, LVEF; left ventricular ejection fraction, NYHA; New York Heart Association.

$p$ <0.05*,<0.01**,<0.001*** compared to NQRS

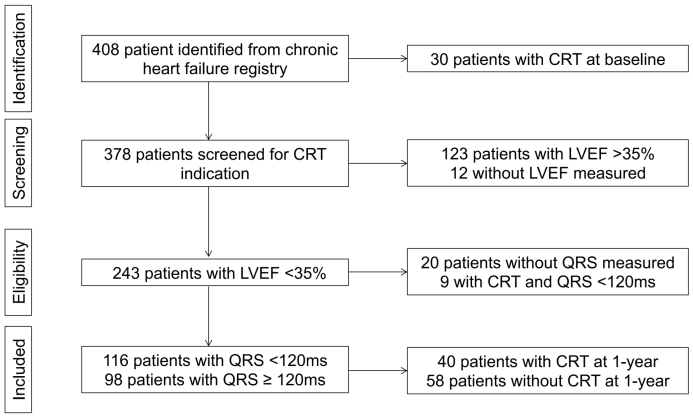
**Supplementary table 1**

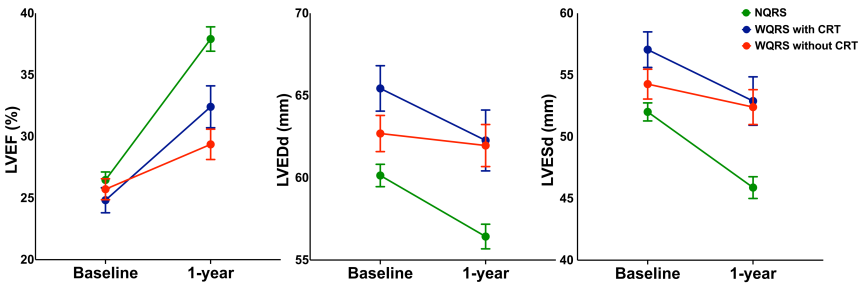
Title: Change in clinical status between baseline and follow-up at one year for patients with LBBB who did or did not receive early CRT

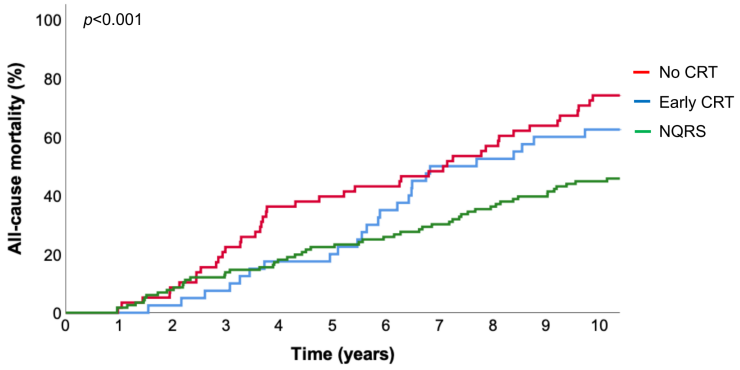
| | All LBBB patients (n=55) | LBBB with CRT (n=30) | LBBB without CRT (n=25) | $p$-value |
|---|---|---|---|---|
| ΔLVESd (mm) | -2.5 (-9,2) | -5 (-11,-1) | -1 (-5,3) | 0.32 |
| ΔLVEDd (mm) | -1 (-7,2) | -2.5 (-7.8,0.8) | 0 (-5,3) | 0.21 |
| ΔLVEF (%) | 5 (0,12) | 8 (5,13.8) | 2 (-1,8) | **0.035** |

Normally distributed continuous variables are expressed as mean ± standard deviation, non-normally distributed continuous variables are expressed as median and range in parentheses, discrete variables are presented as number and percentages in parentheses.

LVEDs; left ventricular end diastolic diameter, LVESd; left ventricular end systolic diameter, LVEF; left ventricular ejection fraction, NYHA; New York Heart Association.




| Time (years) | 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| WQRS no CRT | 58 | 57 | 37 | 33 | 25 | 15 |
| WQRS early CRT | 40 | 39 | 33 | 26 | 19 | 15 |
| NQRS | 116 | 107 | 95 | 86 | 74 | 61 |