Original article

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

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Aims In patients with chronic heart failure, QRS duration is a consistent predictor of poor outcomes. It has been suggested that for indicated patients, cardiac resynchronization therapy (CRT) could come sooner in the treatment algorithm, perhaps in parallel with the attainment of optimal guideline-directed medical therapy (GDMT). We aimed to investigate differences in left ventricular (LV) remodelling in those with narrow QRS (NQRS) compared with 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 Our cohort consisted of 214 consecutive patients with LV ejection fraction (LVEF) of 35% or less 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.

Results In the absence of CRT, patients with WQRS had less LV reverse remodelling compared with those with NQRS, with differences in ΔLVEF ($+2$ vs. $+9\%$, $P < 0.001$) ΔLV end-diastolic diameter (-1 vs. -2 mm, $P = 0.095$), ΔLV end-systolic diameter (-2 vs. -4.5 mm, $P = 0.038$), LV end-systolic volume (-12.6 vs. -25.0 ml, $P = 0.054$) and LV end-diastolic volume (-7.3 vs. -12.2 ml, $P = 0.071$). LVEF was more likely to improve by at least 10% if patients had NQRS or received CRT ($P = 0.08$). Thirteen (24%) patients with WQRS achieved an LVEF greater than 35% in the absence of CRT; however, none achieved greater than 50%.

Conclusion A strictly linear approach to heart failure 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.

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 of at least 120 ms cardiac resynchronization therapy (CRT) reduces hospitalizations, and 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) of 35% or less.[4,5]

GDMT is recommended as an initial step based largely on the inclusion criteria of randomized 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 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 LV remodelling in response to GDMT is lower in patients with WQRS compared with narrow QRS (NQRS) in the absence of CRT; early CRT implantation, during the attainment of optimal medical therapy would not be associated with unnecessary implantation; and 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 four 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 heart failure for 3 months, with LVEF of 35% or less on transthoracic echocardiogram. Inclusion was not dependent on the cause of heart failure and included patients with ischaemic heart disease and nonischaemic 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. Cause of LV impairment was classified as either ischaemic heart disease or nonischaemic 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 ECG interpreted by a cardiologist (R.M.C., K.K.W. or M.T.K.). LBBB was defined as QRS of at least 20 ms, 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 LVEF, LV end-diastolic diameter (LVEDd), LV end-systolic diameter (LVESd), LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) obtained by transthoracic echocardiogram interpreted by two British Society of Echocardiography accredited senior sonographers (J.G. and M.P.).

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

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 of at least 10%, which has previously 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 less than 120 ms and WQRS as at least 120 ms. The first clinic attendance during the study period was the point of enrolment for the purposes of analysis. Heart failure because of 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 noninvasive imaging or scar suggesting infarction on cardiac MRI. 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, New York, USA). 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 χ^2 tests for categorical data. Comparisons between groups adjusted for baseline LV dimensions and function were performed by one-way analysis of covariance. Unadjusted survival was illustrated by Kaplan–Meier plots, and differences between groups defined by log-rank tests. In all analyses, P less than 0.05 was regarded as statistically significant.

Ethical consideration

Consecutive patients were approached by a cardiologist (R.M.C., K.K.W. or M.T.K.) in an ambulatory heart failure clinic and provided informed, written consent. The study was approved by the Leeds West Research Ethics Committee (07/Q1205/17) and conducted according to the principles expressed in the Declaration of Helsinki.

Fig. 1
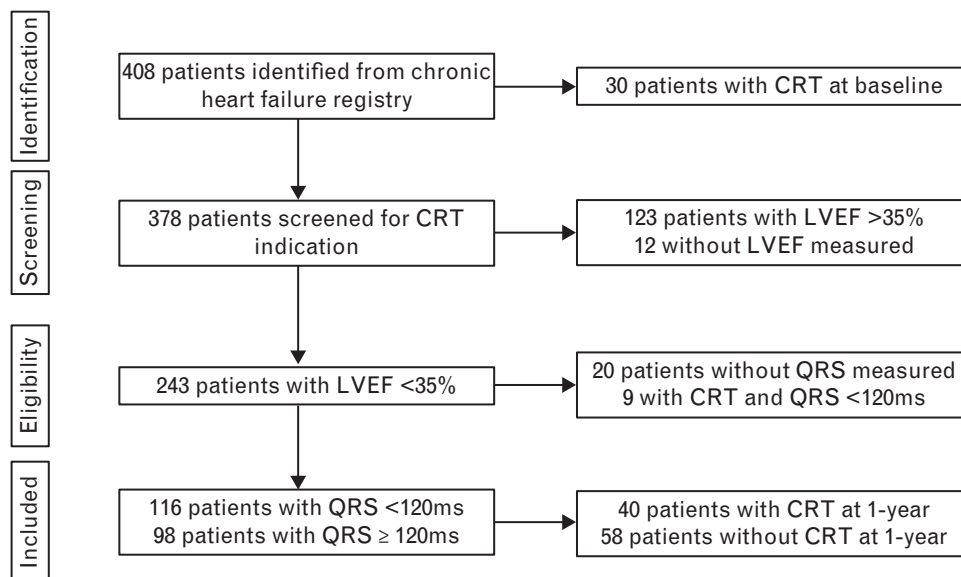
Patient identification and exclusion criteria. A nonselected cohort of 408 patients underwent echocardiography at baseline and 1 year; the final dataset included 211 patients with LVEF 35% or less without CRT at baseline. CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction.

Results

The final dataset included 214 patients with LVEF of 35% or less who did not have CRT at baseline, of whom 163 (76%) were men with an average age of 67 (57–76) years (Fig. 1). Of these, 116 patients had NQRS and 98 had WQRS, of whom 40 received CRT implant within 1 year and 58 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 similar at baseline, although those with WQRS were on average older than those with NQRS (although similar in those who did or did not receive CRT) (Table 1). Patients who received CRT had worse renal function, and a greater baseline LVEDd, LVESd, LVESV and LVEDV compared with those who did not (Table 2). The distributions of cause of heart failure and sinus rhythm were not different across groups. Patients who received early CRT were more likely to have LBBB (75%) compared with those who did not (54%) ($P = 0.031$).

Prescription and up-titration of guideline-directed medical therapy

There were no significant differences in the dosing of GDMT between groups at baseline; a total of 184 (86%) patients were prescribed an ACEi or ARB, 174 (82%) a beta blocker, and 99 (47%) an MRA. Following supervised up-titration of GDMT between baseline and 1 year,

the changes 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 (82–89%) and ACEi or ARB (87–90%) between baseline and 1 year.

Reverse remodelling in response to guideline-directed medical therapy and cardiac resynchronization therapy

The changes 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 with those with NQRS (Fig. 2) with significant differences in ΔLVEF (+2 vs. +9%, $P < 0.001$), ΔLVEDd (−1 vs. −2 mm, $P = 0.095$), ΔLVESd (−2 vs. −4.5 mm, $P = 0.038$), LVESV (−12.6 vs. −25.0 ml, $P = 0.054$) and LVEVD (−7.3 vs. −12.2 ml, $P = 0.071$). These observations persisted after correction for baseline LV dimension and function, with mean difference in ΔLVEF $+8.3 \pm 1.6\%$ ($P < 0.001$), ΔLVEDd -3.0 ± 1.1 mm ($P = 0.008$), ΔLVESd -4.5 ± 1.4 mm ($P = 0.002$), ΔLVESV -24.7 ± 7.7 ml ($P = 0.002$) and ΔLVEDV -9.6 ± 9.6 ml ($P = 0.32$).

In patients with NQRS, echocardiography follow-up at 1-year demonstrated that 64 (62%) patients attained a LVEF of more than 35% compared with 13 (24%) patients with WQRS who did not receive CRT ($P < 0.001$) and were, therefore, no longer indicated for CRT. Importantly, no patient with WQRS attained a

Table 1 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**
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, nonnormally distributed continuous variables are expressed as median (interquartile range), discrete variables are presented as number (percentage). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; CRT, cardiac resynchronization therapy; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; HF, heart failure; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NQRS, narrow QRS; WQRS, wide QRS.

LVEF of greater than 50% in the absence of CRT, whilst 9 (16%) achieved an LVEF of greater than 40%. A total of 79 (40%) patients achieved a ΔLVEF of at least 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 a sensitivity analysis restricted to patients with LBBB, findings were similar. Recipients of

CRT demonstrated improved cardiac function at 1 year compared with those without CRT, with greater improvement in ΔLVEF (+8 vs. +2%, P = 0.035) and trend to better reverse remodelling as measured by ΔLVEDd (−2.5 vs. 0 mm, P = 0.32), ΔLVESd (−5 vs. −1 mm, P = 0.21), ΔLVESV (−30.5 vs. −5.4 mm, P = 0.066) and ΔLVEDV −19.7 vs. 0 ml, P = 0.10) (Supplementary Table 1, http://links.lww.com/JCM/A389).

Table 2 Baseline investigation results

	All patients (n = 214)	NQRS (n = 116)	WQRS with CRT (n = 40)	WQRS without CRT (n = 58)	P value
Baseline echocardiogram					
LVEF (%)	27 (21–32)	28 (22–32)	25 (20.3–30.5)	25.5 (22–30.3)	0.25
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**
LVESV (ml)	141.3 (102.2–173.2)	129.5 (97.3–166.6)	160.0 (112.8–194.0)	138.3 (106.2–180.0)	**0.014**
LVEDV (ml)	190.5 (153.7–231.4)	176.6 (147.4–216.0)	216.0 (173.2–255.4)	194.0 (153.7–247.3)	**0.003**
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 ECG					
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/1.73 m^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, nonnormally distributed continuous variables are expressed as median (interquartile range), discrete variables are presented as number (percentage). CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FS, fractional shortening; Hb, haemoglobin; LVEDd, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; NQRS, narrow QRS; PASP, pulmonary artery systolic pressure; RWMA, regional wall motion abnormality; WCC, white cell count; WQRS, wide QRS. Bold denotes p<0.05.

Table 3 Change in clinical status between baseline and follow-up at 1 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)
ΔRamipril equivalent dose (mg)	0 (0,5)	0 (0,5)	0 (0–2.5)	0 (0,5)
ΔLVEF (%)	7 (1,15)	9 (4–20)	6 (1–12.5)	2 (−1 to 9)***
ΔLVESd (mm)	−4 (−10 to −2)	−4.5 (−10.8 to 0)	−3.5 (−9 to 2)	−2 (−7 to 2)*
ΔLVEDd (mm)	−1.5 (−7 to 1)	−2 (−8 to 1)	−2 (−7.5 to 1.5)	−1 (−5 to 3)
ΔLVESV (ml)	−22.6 (−50.9 to 10.2)	−25.0 (−58.7 to 0)	−23.3 (−50.7 to 14.4)	−12.6 (−39.4 to 13.2)
ΔLVEDV (ml)	−10.5 (−47.1 to 8.7)	−12.2 (−51.3 to 6.4)	−14.8 (−49.4 to 12.6)	−7.3 (−37.1 to 21.6)
ΔNYHA class	0 (−1 to 0)	0 (−1 to 0)	0 (−1 to 0)	0 (−1 to 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, nonnormally distributed continuous variables are expressed as median (interquartile range), discrete variables are presented as number and percentages in parentheses. CRT, cardiac resynchronization therapy; LVEDd, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; NQRS, narrow QRS; WQRS, wide QRS. P less than 0.05*, P less than 0.01**, P less than 0.001*** compared with NQRS.

Change in symptoms in response to guideline-directed medical therapy and cardiac resynchronization therapy

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 with 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 with those without CRT ($P = 0.008$). In patients with WQRS who did not receive CRT, only four (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 with 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 with those with WQRS who did not ($P = 0.001$; Fig. 3).
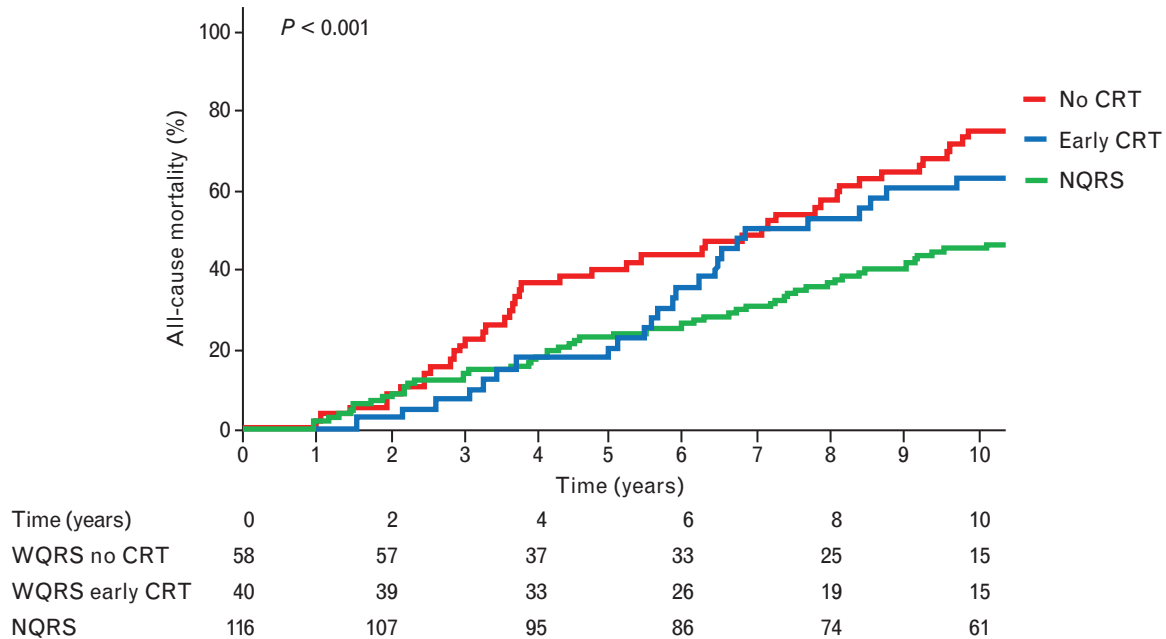
Discussion
Key findings

The findings of this study were: patients with NQRS had significantly greater reverse remodelling compared with those with WQRS not implanted with CRT; patients with WQRS implanted with CRT had significantly greater reverse remodelling compared with those who were not; these observations persisted in a sensitivity analysis restricted to those with LBBB and those with an improvement in LVEF because of 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 of at least 35% at follow-up would have received CRT outside of the current guidelines.[4]

Fig. 2
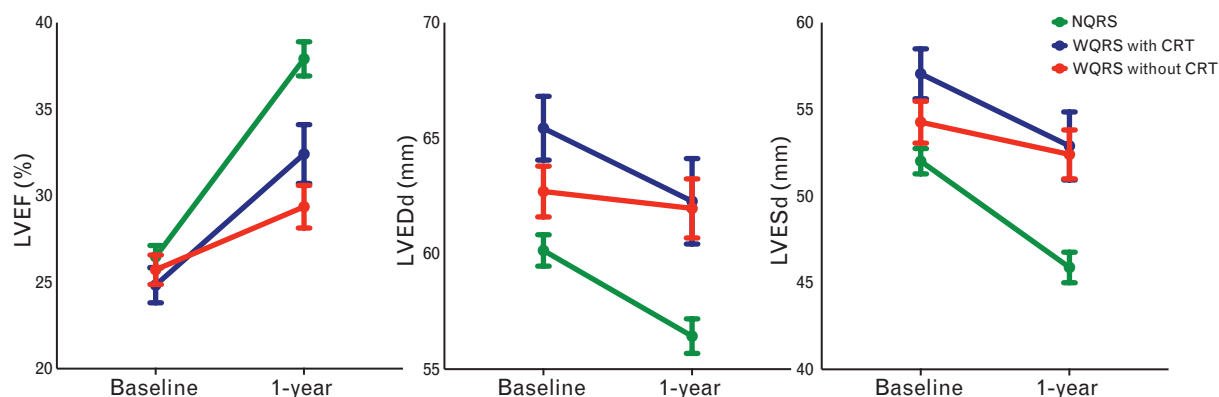
Change in left ventricular function and dimensions between groups. Patients with NQRS or WQRS and early CRT implant had greater improvements in LVEF, LVEDd and LVEDs. CRT, cardiac resynchronization therapy; LVEDd, left ventricular end-diastolic diameter LVEF, left ventricular ejection fraction; NQRS, narrow QRS; WQRS, wide QRS.

Fig. 3

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

Kaplan–Meier plot to show survival in patients with wide QRS who did or did not receive early cardiac resynchronization therapy. Patients with WQRS and early CRT had improved survival, but this was not statistically significant. CRT, cardiac resynchronisation therapy; WQRS, wide QRS.

Role and timing of guideline-directed medical therapy in patients with heart failure with reduced ejection fraction

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 sacubitril-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 hear failure hospitalization.[14–17] In PARADIGM-HF and TRANSITION, 29 and 34.4% of patients had de novo heart failure, and 52.1 and 24% were ACEi/ARB-naive, respectively. De novo heart failure 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 guideline-directed medical therapy in heart failure with reduced ejection fraction 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 SBP 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 at least 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 the local protocol to achieve maximally tolerated dosages. The change in beta blocker and ACEi 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 four attaining Class I symptoms.

Timing of cardiac resynchronization therapy implantation

The evidence base for CRT is strongest in patients with LBBB, which is independently associated with heart failure hospitalization and death[27] although data also support the use of CRT in patients with non-LBBB WQRS ($\geq$150 ms). 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 randomized 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 optimized 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 Nonischaemic 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 an LVEF of at least 35%. Approximately half of patients in the study cited waited for more than 9 months prior to CRT implantation, and so our description of what constitutes a 'delayed' strategy probably represents usual care in many regions,[30] although is longer than recommended by guidelines.[31] In an analysis of 15 619 eligible HFrEF patients from the Get With the Guidelines Heart Failure (GWTG-HF) database, CRT during heart failure hospitalization was associated with reduced re-hospitalization and improved survival compared with delayed CRT implantation after discharge.[32] 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 cardiac resynchronization therapy implantation

Patients with WQRS represent a group at high risk of hospitalization, 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 optimization 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. Thirteen (24%) patients with WQRS who did not receive CRT attained an LVEF greater than 35% and so were no longer indicated according to current guidelines[4,5] and nine (16%) would have been implanted beyond the evidence base supporting the use of CRT.[33] 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[33] and the Biventricular verses Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial[20] where inclusion criteria included an LVEF of 40% or less and 50% or less, 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 Multi-centre 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 an LVEF of greater than 30% (range 30.1–45.3%) 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.[34]

Strengths and limitations

Our study presents real-world outcomes from a highly characterized HFrEF population from four 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 generalizable to all indicated patients. Furthermore, in analysis restricted to patients with LBBB, findings were similar, although nonsignificant for comparisons of LVEDd, LVESd, LVESV and LVEDV.

This was a retrospective analysis with a small number of participants, and our findings must, therefore, be regarded as hypothesis-generating. 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 because of nonrandom allocation, which could only be accounted for by a randomized 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 because of 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 do not reflect further up-titration in subsequent consultations. This was a historic patient cohort predating the availability of ARNI, which may have resulted in less remodelling than would be seen in the modern era. However, there are as yet no published data clarifying the heterogeneity of remodelling between patients with and without a WQRS-receiving ARNI, and the addition of ARNI to pathways might result in even greater delays to implantation. Finally, our criteria for delayed CRT consisted of people who had been implanted after 1 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 broadly in line with previous studies,[30,32] and therefore likely to represent the usual care in many regions.

Conclusion

A strictly linear approach to heart failure 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. Our findings should be regarded as hypothesis-generating and the benefits of parallel implantation and optimization of GDMT should be tested in prospective, randomized trials.

Conflicts of interest

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