ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 668–674
Published online 25 June 2018 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12297

ORIGINAL RESEARCH ARTICLE

Eligibility for cardiac resynchronization therapy in patients hospitalized with heart failure

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Abstract

Aims Recent guidelines recommend cardiac resynchronization therapy (CRT) in mildly symptomatic heart failure (HF) but favour left bundle branch block (LBBB) morphology in patients with moderate QRS prolongation (120–150 ms). We defined how many patients hospitalized with HF fulfil these criteria.

Methods and results A single-centre retrospective cohort study of 363 consecutive patients hospitalized with HF (438 admissions) was performed. Electronic imaging, electrocardiograms, and records were reviewed. Overall, 153 patients (42%) had left ventricular ejection fraction (LVEF) $\leq$ 35%, and 34% of patients had QRS prolongation. Eighty patients (22%) were potentially eligible with LVEF $\leq$ 35% and QRS $\geq$ 120 ms or existing CRT. The majority (68 of 80) had a Class I or IIa recommendation according to international guidelines (LBBB or non-LBBB QRS $\geq$ 150 ms or right ventricular pacing). Only a minority (12 of 80) had moderate QRS prolongation of non-LBBB morphology. One-quarter (n = 22) of patients fulfilling criteria were ineligible for reasons including dementia, co-morbidities, or palliative care. A further eight patients required optimization of medical therapy. CRT was therefore immediately indicated in 50 patients. Of these, 29 were implanted or had existing CRT systems. Twenty-one of the 80 patients eligible for CRT were not identified or treated (6% of the total hospitalized cohort).

Conclusions Twenty-two per cent of elderly real-life patients hospitalized with HF fulfil LVEF and QRS criteria for CRT, most having a Class I or IIa indication. However, a large proportion is ineligible owing to co-morbidities or requires medical optimization. Although uptake of CRT was reasonable, there remain opportunities for improvement.

Keywords Cardiac resynchronization therapy; Heart failure; Bundle branch block; Eligibility

Received: 4 January 2018; Revised: 28 March 2018; Accepted: 3 April 2018
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Introduction

Cardiac resynchronization therapy (CRT) improves symptoms and survival in patients with heart failure (HF). The American College of Cardiology/American Heart Association (ACC/AHA) 2008 and European Society of Cardiology (ESC) 2007 guidelines recommended CRT in patients with sinus rhythm, left ventricular ejection fraction (LVEF) $\leq$ 35%, QRS $\geq$ 120 ms, and New York Heart Association (NYHA) Functional Class III or ambulatory IV symptoms.[1,2] Among unselected patients hospitalized with HF, the proportion meeting these historic criteria was relatively consistent, ranging from 6% to 10%.[3–7] Subsequent landmark clinical trials demonstrated similar benefits from CRT in patients with milder symptoms (NYHA Class I/II).[8,9] Evidence is also accruing of efficacy in patients with atrial fibrillation (AF) and milder left ventricular systolic dysfunction (LVSD) meeting criteria for pacing due to bradycardia.[10]

In parallel, analyses from trials and registries have consistently demonstrated limited efficacy of CRT in recipients with non-left bundle branch block (non-LBBB) conduction.[11,12] Updated international guidelines therefore expanded the indications for CRT to include mildly symptomatic patients, alongside clearer support for patients with AF and chronic right ventricular pacing.[13,14] A minor concomitant contraction in eligibility has occurred, with guidelines now favouring LBBB morphology in patients with moderate QRS prolongation. As

outlined in a recent systematic review, no study to date has examined the proportion of patients fulfilling these new criteria.[7]

Methods

Study cohort

A quality assurance programme utilizing retrospective chart review was expanded to assess device candidacy. The study was approved by the institutional ethics board. Inclusion criteria were adults ≥ 18 years discharged with a primary diagnosis of HF from two acute care facilities in the Vancouver Coastal Health region, between 1 November 2011 and 31 March 2013. Both new diagnoses and readmissions were included. Deaths during the index hospitalization were excluded.

Eligibility criteria for cardiac resynchronization therapy

CRT is recommended in patients with LVEF ≤ 35%, NYHA Class II to IV symptoms, LBBB, or QRS ≥ 150 ms of any morphology (*Table 1*).[13,14] For non-LBBB, QRS 120 to 150 ms, NYHA Class II to IV, receives an ESC Class IIb recommendation, while the ACC/AHA limits a similar recommendation to more advanced NYHA Class III/IV symptoms. CRT is supported in patients with AF who otherwise fulfil guideline criteria, and in those with NYHA Class III/IV symptoms likely to experience a significant proportion of right ventricular pacing for bradycardia.

CRT eligibility required quantitative LVEF ≤ 35% or qualitatively moderate to severe LVSD on the most recent echocardiogram, nuclear multiple-gated acquisition scan, contrast ventriculogram, or magnetic resonance imaging. The most recent LVEF was used in multiple assessments. In keeping with prior studies,[15] EF measurements dating back further than 1 year were accepted if results remained applicable and further update was inappropriate, e.g. documented dysfunction with no change in therapy planned.

All patients were hospitalized with a primary diagnosis of HF and, therefore, considered as NYHA Class II to IV. Electrocardiograms were recorded using the MUSE (GE Healthcare) system. Intraventricular conduction disturbance (IVCD) was defined according to ESC CRT guidelines.[13] Complete LBBB: QRS ≥ 120 ms; QS or rS lead V_1; broad notched or slurred R waves in lead I, aVL, V_5, or V_6; absent Q waves in leads V_5 and V_6. Complete right bundle branch block (RBBB): QRS ≥ 120 ms; rsr′, rsR′, and rSR′ in lead V_1 or V_2; wide S waves in leads I, V_5, and V_6. Non-specific IVCD was defined as QRS ≥ 120 ms without typical features of LBBB or RBBB. Ineligibility criteria included left ventricular assist device, heart transplant, home inotropes, palliative care treatment, and anticipated short life expectancy.

Previous studies have excluded patients with either missing LVEF or electrocardiogram (ECG). This approach discounts subjects unnecessarily, as those with narrow QRS or LVEF- 35% are ineligible for CRT irrespective of the alternate investigation. Although LVEF was unavailable for 12 patients, only two had concurrent QRS prolongation. Moreover, both these patients were receiving palliative or nursing home care. Therefore, overall eligibility could be satisfactorily determined for every patient.

Table 1 Recommendation and level of evidence for cardiac resynchronization therapy in international guidelines, according to eligibility criteria

Rhythm, QRS, morphology	NYHA class LVEF ≤ 35%	ESC 2013[13]	ACC/AHA 2012[14]
SR LBBB			
≥150 ms	II–IV	I A	I A or B
≥150 ms	I (LVEF ≤ 30%)	—	IIb C ischaemic
120 to 150 ms	II–IV	I B	IIa B
SR non-LBBB			
≥150 ms	II–IV	IIa B	IIa A NYHA III/IV IIb B NYHA II
120 to 150 ms	II–IV	IIb B	—
120 to 150 ms	III or IV	—	IIb B
AF or pacing			
≥120 ms	II–IV	—	IIa B
≥120 ms	III or IV	IIa B	—
RV pacing	III or IV	I B upgrade IIa B *de novo*	IIa C upgrade

AF, atrial fibrillation; BBB, bundle branch block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular; SR, sinus rhythm.

Data abstraction and statistical analysis

Two trained clinical care analysts reviewed medical charts to assess guideline-directed medical therapy rates and adherence to ACC Foundation/AHA clinical performance measures.[16] The primary author reviewed all data fields related to CRT eligibility. A second cardiologist reviewed all ECGs with QRS > 100 ms. Both the admission and most recent chest radiography of all patients were reviewed to determine device and lead configuration. Baseline characteristics of patients eligible and ineligible for CRT were summarized by means with standard deviations for continuous variables and by frequencies and percentages for categorical variables. Means were compared using the Student *t*-test and proportions compared using the χ^2 test.

Results

Cardiac resynchronization therapy eligibility overall and uptake

Of the 363 patients, 80 (22%) were broadly eligible with LVEF ≤ 35% and prolonged QRS ≥ 120 ms (*n* = 64), or existing

CRT (*n* = 16) (*Figure 1*). However, one-quarter (*n* = 22) of these patients were ineligible owing to dementia, co-morbidities, palliative intent, or severe symptoms requiring inotropes or mechanical support. A further eight patients required optimization of medical therapy. Overall, therefore, CRT was indicated in 50 patients (14%). Sixteen patients (4%) already had CRT, with another 13 patients (4%) implanted during admission or soon after discharge. However, 21 eligible patients (6%) were not identified, split across general medicine (*n* = 16) and cardiology (*n* = 5).

Baseline characteristics

Baseline characteristics are presented in *Table 2*. Three hundred sixty-three patients were identified in 438 consecutive hospitalizations including 75 readmissions. Mean age was 74 ± 14 years. The mean length of stay was 11.1 days, with more than half of patients (61%) admitted to internal medicine and one-third (33%) to cardiology. Co-morbidities were common. Approximately one-third of patients had diabetes (36%), chronic kidney disease (CKD) (32%), and angina (35%). Approximately two-thirds of patients (64%) were receiving either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, most of the remainder receiving hydralazine and nitrate in combination. Beta-blockers were prescribed in 81%, with a similar proportion receiving loop diuretic. More than one-third (35%) of patients received warfarin. Patients had a mean heart rate of 89 b.p.m. Sinus rhythm and AF were present in 56% and 41%, respectively.

Imaging and left ventricular ejection fraction

Mean EF was 42 ± 18%. Overall, 153 patients (42%) had LVEF ≤ 35%. One-third of patients (33%) had moderate or severe mitral regurgitation at baseline. Most patients had LVEF documented (97%), the majority using echocardiography (345 out of 363, 95%). Ejection fraction was measured during, before, and after admission in 63%, 24%, and 14% of patients, respectively. Of particular relevance, almost all patients with QRS prolongation (*n* = 125) had recent LVEF (*n* = 120, 96%), except those in which assessment was clearly inappropriate, e.g. advanced dementia.

Electrocardiogram

Overall, 34% of patients had QRS prolongation, increasing to 50% of those with LVEF ≤ 35% (*Table 3*). Intermediate QRS prolongation (120–150 ms) and severe QRS prolongation (≥150 ms) were both more common in patients with reduced LVEF ≤ 35% than in the overall population, respectively, 20% vs. 15% and 30% vs. 19%. LBBB was the dominant morphology, accounting for 40% and 51% of QRS prolongation, respectively, in the overall and LVEF ≤ 35% groups. RBBB was

Figure 1 Proportion eligible for CRT and reasons for exclusion. Eighty patients (22%) had LVEF ≤ 35% and prolonged QRS ≥ 120 ms. Twenty were ineligible owing to co-morbidities, and further eight patients required optimization of medical management. Out of remaining 50 eligible patients, 16 had existing CRT and further 13 were implanted during or soon after index admission. Twenty-one patients were not identified.

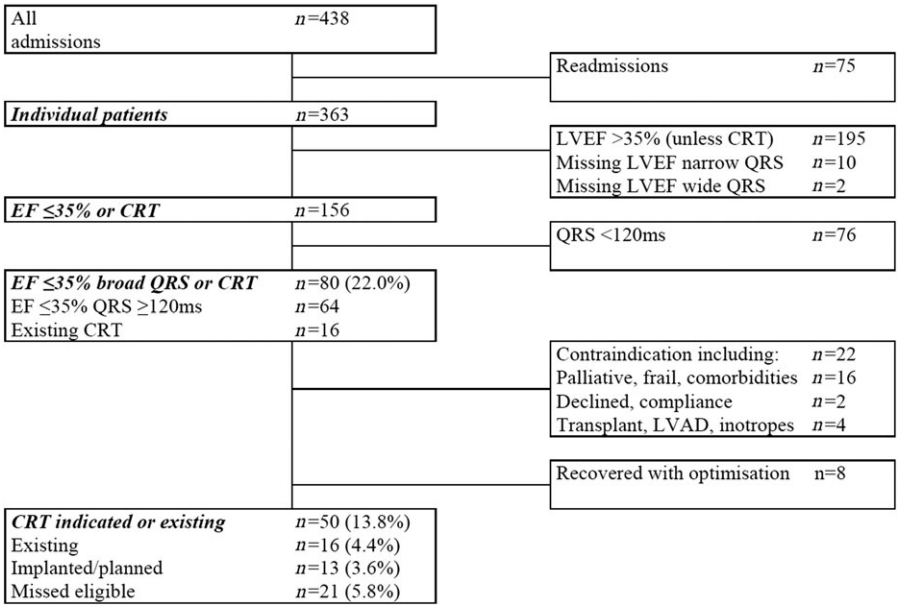

Table 2 Baseline characteristics

	Mean (±SD) or *n* (%) *n* = 363
Age (years)	73.5 ± 13.6
Men (%)	201 (55.4%)
Length of stay	11.1 ± 12.6
Medical history	
Myocardial infarction	75 (20.7%)
CABG	45 (12.4%)
Cerebrovascular disease	49 (13.5%)
Diabetes	129 (35.5%)
Angina	127 (35.0%)
COPD	66 (18.2%)
Chronic kidney disease	116 (32.0%)
Service	
Cardiology	120 (33.1%)
Internal medicine	197 (54.3%)
Clinical status	
Systolic blood pressure (mmHg)	141.7 ± 28.5%
Diastolic blood pressure (mmHg)	77.4 ± 16.0%
Medication at discharge	
ACEI or ARB	232 (63.9%)
Beta-blocker	296 (81.5%)
MRA	85 (23.4%)
Hydralazine	68 (18.7%)
Nitrate patch	88 (24.2%)
Loop diuretic	294 (81%)
Warfarin	127 (35.0%)
Ejection fraction	
During admission	227 (62.5%)
Prior to admission	86 (23.7%)
By transthoracic echocardiogram	345 (95%)
By other modalities	18 (5%)
Mean ejection fraction (%)	41.9 ± 17.7
Moderate–severe mitral regurgitation	120 (33.1%)
ECG	
Heart rate (b.p.m.)	88.6 ± 26.3
Sinus rhythm	202 (55.6%)
Atrial fibrillation	150 (41.3%)
Pacing rhythm	11 (3.0%)
Laboratory	
Haemoglobin (g/L)	120.7 ± 22.2
Creatinine (μmol/L)	126.8 ± 76.4
Brain natriuretic peptide	1127.1 ± 1059.2

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist.

less common in those with depressed ejection fraction than in the overall population. Finally, right ventricular pacing was often associated with severe QRS prolongation.

Strength of recommendation for cardiac resynchronization therapy-eligible patients

The majority of eligible patients (85%, *n* = 68 of 80) had a Class I or IIa recommendation according to ACC or ESC criteria (LBBB or non-LBBB QRS prolongation ≥ 150 ms or right ventricular pacing). Only 15% of eligible patients had non-LBBB with moderate QRS prolongation (*Table 4*).

Discussion

A number of studies have examined CRT candidacy in patients hospitalized with HF.[3–6,17–19] However, this is the first study to apply recent guideline criteria using both QRS duration and morphology, and to examine reasons for ineligibility in detail. A high proportion of patients fulfilled criteria, the majority being those most likely to benefit, i.e. LBBB or broad QRS prolongation ≥ 150 ms. Although CRT uptake was reasonable, 6% of the overall hospitalized population were eligible yet not identified.

Cardiac resynchronization therapy eligibility

Our findings are similar to a Belgian study of 322 consecutive hospitalized patients, in terms of overall eligibility (22% vs. 25%) and prevalence of LVEF ≤ 35% (42% vs. 40%).[17] Other studies reported a lower prevalence but relied on administrative or registry data with LVEF only available in one-thirds to two-thirds of cases.[3,5,6] This emphasizes the need for chart-level data to identify device eligibility. Ejection fraction was measured during admission in 65% and available in 97% of patients overall. To our knowledge, the one other study reporting timing of LVEF measurement yielded similar results (63% and 100% among 674 patients hospitalized with HF).[4]

Updated international guidelines recommend QRS prolongation ≥ 150 ms for non-LBBB morphology, with narrower non-LBBB receiving a lower-grade recommendation (IIb). The impact of this eligibility contraction, in terms of candidacy, appears relatively minor in our cohort. The dominant

Table 3 Prevalence of electrocardiogram abnormalities in the overall population and subgroup with reduced left ventricular ejection fraction

	All patients			LVEF ≤ 35%		
	n = 363	QRS 120–149 ms *n* = 55 (15%)	QRS ≥ 150 ms *n* = 70 (19%)	*n* = 153	QRS 120–149 ms *n* = 31 (20%)	QRS ≥ 150 ms *n* = 46 (30%)
LBBB	50 (14%)	23 (42%)	27 (39%)	39 (25%)	16 (52%)	23 (50%)
RBBB	19 (5%)	10 (18%)	9 (13%)	5 (3%)	2 (6%)	3 (7%)
IVCD	17 (5%)	16 (29%)	1 (1%)	11 (7%)	10 (32%)	1 (2%)
RV pacing	23 (6%)	5 (9%)	18 (26%)	9 (6%)	2 (6%)	7 (15%)
CRT pacing	16 (4%)	1 (2%)	15 (21%)	13 (8%)	1 (3%)	12 (4%)

CRT, cardiac resynchronization therapy; IVCD, intraventricular conduction disturbance; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; RV, right ventricular.

Table 4 Disposition and strength of recommendation for cardiac resynchronization therapy-eligible patients

$n = 363$	I or IIa recommendation LBBB *or* non-LBBB QRS ≥ 150 ms *or* RV pacing	IIb recommendation Non-LBBB QRS 120–150 ms
Total	68 (18.7%)	12 (3.3%)
Eligible fulfilling criteria	48 (13.2%)	2 (0.6%)
Existing CRT	16 (4.4%)	Not applicable
Implanted or planned	13 (3.6%)	0
Eligibility not recognized	19 (5.2%)	2 (0.6%)
Ineligible otherwise meeting criteria	20 (5.5%)	10 (2.8%)
Optimization with LVEF recovery—medical, revascularization, valve	6 (1.7%)	2 (0.6%)
Contraindication	14 (3.9%)	8 (2.2%)
DNAR, dementia, advanced age	5 (1.4%)	3 (0.8%)
Co-morbidities, frailty, palliative	4 (1.1%)	3 (0.8%)
Patient declined, non-compliance	2 (0.6%)	1 (0.2%)
Transplant/LVAD	3 (0.8%)	1 (0.2%)

CRT, cardiac resynchronization therapy; DNAR, do not attempt resuscitation; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; RV, right ventricular.

morphology of conduction disturbance was LBBB, particularly in those with significantly impaired ventricular function. Only 12 of the 80 eligible patients (15%) exhibited non-LBBB QRS of 120 to 150 ms.

Cardiac resynchronization therapy ineligibility

In the few studies reporting ineligibility for CRT, the prevalence ranges from 1% to 21%.[3,5,15,20,21] The highest estimates were obtained using detailed chart abstraction, emphasizing once more the granularity needed to identify contraindications. In our elderly unselected population, 30 of 80 (38%) patients fulfilling EF-QRS criteria were ineligible: 22 (28%) owing to medical contraindication or patient preference and eight (10%) requiring further medical optimization. This high prevalence of ineligibility reflects the frail, multi-morbid, hospitalized cohort. Of note, true guideline adherence rates will be significantly underestimated by failure to account for these patients and modify the eligible denominator.

Co-morbidities and generalizability

The prevalence of co-morbidities was similar to the Canadian Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study, the largest report of CRT eligibility in hospitalized patients.[5] Approximately one-third of patients had AF, angina, diabetes, and CKD, with somewhat fewer having cerebrovascular and chronic obstructive pulmonary disease. In our study, patients were elderly (mean age 73 years), again comparable with those in EFFECT (73 years) and contemporary HF registries.[22,23] Our patients are therefore comparable with real-world populations, but nearly a decade older than those enrolled in landmark clinical trials.[8] While age and co-morbidity should not be barriers to device therapy, the survival benefit and cost-effectiveness of CRT vs. defibrillators in such populations certainly merit consideration.

Cardiac resynchronization therapy uptake

The prevalence of existing CRT in our patients (4.4%) lies between estimates from the ESC-HF Pilot Survey (3.3%) and Italian IN-HF national registry (5.4%).[23,24] Moreover, the total rate of existing or newly implanted CRT in eligible patients (58%, 29/50) compares favourably with that of other series, including the Get With the Guidelines Heart Failure programme.[25] The IMPROVE-HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) quality improvement programme increased CRT utilization dramatically from 37% to 66% over 2 years in the outpatient setting.[26] No similar initiative has been undertaken for those hospitalized with HF. Our results suggest that 10–15% of all patients hospitalized with HF are candidates for CRT.

The opportunity of hospitalization

Our findings highlight the opportunity presented by hospitalization to identify device-eligible patients. First, patients are relatively unselected. Specialized clinics inherently have barriers to care, including primary care detection, referral practices, and socio-geographical factors.[27] By contrast, hospitalization defines a group of patients with severe HF, arguably selecting more deprived patients with less primary care contact.[28] Second, almost all patients had sufficient electronic information to assess device eligibility. Third, hospital-based heart function and electrophysiology services often share either physical location or at least common referral pathways. Finally, some patients may already be medically

optimized and appropriate for immediate device implantation or upgrade during the index hospitalization.

Limitations

A number of limitations merit consideration. The sample size prohibits detailed subgroup analysis and multivariable modelling to examine barriers to CRT. NYHA functional class was infrequently reported, although almost all hospitalized patients are symptomatic (98% in one cohort) and NYHA class is subjective and dynamic.[4] The results only represent the experience of two centres and associated systems of care.

Conclusions

Our results are encouraging, with rates of CRT uptake among eligible patients approaching that observed following intervention in IMPROVE-HF. Nevertheless, systems of care must improve. Failure to deliver guideline indicated life-prolonging therapy should be a 'never event'. Hospitalization may provide an opportunity to identify eligible patients but requires closer integration of data systems and services.

Conflict of interest

None declared.

Funding

This work was supported by Medtronic investigator initiated grant.

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