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Male sex and COPD predict a poor clinical response in patients undergoing cardiac resynchronization therapy

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Male sex and COPD predict a poor clinical response in patients undergoing cardiac resynchronization therapy

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Specialty area:	

Male sex and COPD predict a poor clinical response in patients
undergoing cardiac resynchronization therapy

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Short title : predictors response cardiac resynchronization therapy

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Abstract

30 Aims: Current guidelines advocate cardiac resynchronization therapy (CRT) in
 31 patients with class III/ IV NYHA heart failure, depressed left ventricular function
 32 and a broad QRS. However, a significant proportion of patients do not derive any
 33 benefit from CRT. The aim of this study was to identify clinical,
 34 electrocardiographic and echocardiographic predictors of response to CRT.

35 Methods: A retrospective analysis of patients undergoing CRT in our institution
 36 was performed. A favourable clinical response to CRT was defined as an
 37 improvement in NYHA Heart failure class of ≥ 1 and lack of hospitalization with
 38 heart failure. Comparisons were made between responders and non-responders
 39 in terms of baseline characteristics and potential predictors of CRT response
 40 (QRS width, presence of LBBB, atrial fibrillation, evidence of mechanical
 41 dyssynchrony on echocardiography and LV lead position).

Results: 164 patients had full follow up data. The mean follow up was 293 days.

Of patient undergoing CRT, 90 (58.9%) had a favourable clinical response to

CRT. Predictors of a lack of clinical response to CRT were male sex ($p=0.012$),and

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fibrillation (0.017).

45 COPD (0.008). Pre-implant echocardiographic dyssynchrony assessment

appeared not to predict response to CRT ($p=0.87$), however there was a trend in
 a positive response in those patients with significant dyssynchrony ($p=0.09$)
 defined as interventricular delay >40 ms or maximal LV delay of >80 ms.

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fibrillation

Conclusion: Male sex and coexisting COPD, were shown to be independent

50 predictors of non-response to CRT in this cohort of patients fulfilling current
 51 criteria for CRT.

What is already known about this topic

Approximately a third of patients fulfilling the criteria for cardiac resynchronization therapy derive little or no benefit following implantation.

What this article adds

We have identified that males and patients with underlying chronic obstructive pulmonary disease respond poorly to cardiac resynchronization therapy and therefore should be taken into consideration when selecting these patients for these complex devices.

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients with left ventricular systolic function and prognosis in patients with moderate or severe heart failure, reduced left ventricular function and a wide QRS complex [1-9]. CRT improves heart failure symptoms, quality of life,

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exercise capacity. Based on the current evidence, the American Heart Association/American College of Cardiology/ Heart Rhythm Society and European Society of Cardiology consider CRT a class I indication in patients with drug refractory class III or IV heart failure, with a left ventricular ejection fraction of $\leq 35\%$ and a wide QRS complex [10, 11]. However, approximately 30% of patients selected for CRT based on these criteria do not have a beneficial

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2 response. This may be due to several potential causes including appropriate
3 patient selection (evidence of dyssynchrony), the site of the left ventricular
4 placement and whether post implant optimization is performed.
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8 Echocardiographic measures have been used to try to improve patient selection,
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11 70 implantation and optimization, but have been disappointing. In order to enhance
12 patient selection, the PROSPECT study evaluated several echocardiographic
13 measures of mechanical dyssynchrony to predict response to CRT using the
14 assumption that correction of dyssynchrony underlies the major mechanism of
15 CRT [12]. From this study, it appeared that these echocardiographic markers had
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21 75 only modest accuracy to predict response to CRT.
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23 Patients with heart failure represent a heterogeneous group with
24 variability in aetiology and the presence of comorbidities such as atrial
25 fibrillation and COPD. Response to CRT is therefore likely due to a combination
26 of these factors rather than dyssynchrony alone. We therefore aimed to
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31 80 investigate and identify predictive factors of non-response to CRT in a group of
32 patients referred for CRT at our institution, which represents a real world
33 experience of patients undergoing CRT worldwide.
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39 **Methods**

40 41 85 **Inclusion criteria**

42 All consecutive patients who underwent CRT implantation between
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44 January 2004 and November 2007 at St Thomas' Hospital were retrospectively
45 analysed. Standard criteria for implantation of a CRT system were used: Class III
46 or IV NYHA (New York Heart Association) class heart failure refractory to drug
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3 90 treatment, left ventricular ejection fraction $\leq 35\%$ and evidence of ventricular
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5 dyssynchrony using the surface ECG or echocardiography.
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8 9 Collection of outcome measures

10 Using a dedicated CRT database and analysis of medical records the

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12 95 multiple variables were collected for each patient at baseline: age, sex, aetiology
13
14 of heart failure, drug treatment, presence of comorbidities (COPD, diabetes and
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16 hypertension), atrial fibrillation (AF), NHYA class and the presence of ventricular
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18 dyssynchrony using the surface ECG and echocardiography [13]. This was

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19 defined as a QRS duration of ≥ 150 ms in at least two derivations of an ECG. In

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22 100 patients with a QRS duration of 120ms to 149ms either direct referral for a
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24 biventricular pacemaker was made, or echocardiographic assessment of
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26 mechanical dyssynchrony was performed; this was left to the discretion of the
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28 referring physician. In those undergoing echocardiographic assessment of
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30 mechanical dyssynchrony 2 out of the following 3 criteria were required: i)

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>120ms at least

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32 105 aortic pre-ejection delay >140 ms, defined as the interval between the onset of
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34 the QRS complex and the onset of aortic flow using pulsed wave Doppler ii)
35
36 interventricular mechanical delay >40 ms, defined as the time difference between
37
38 the onset of pulmonary ejection and aortic ejection using pulsed wave Doppler
39
40 iii) delayed activation of the posterolateral left ventricular wall, defined as the
41
42 maximal posterolateral wall inward movement, using M-mode or tissue Doppler
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44 110 echo, occurring later than the start of left ventricular filling, using the transmitral
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46 Doppler signal [14]. Following implant, selected patients underwent
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48 echocardiographic optimization, which included optimization of AV delays, and
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RV and LV delay. These patients were selected according to the referring

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3 115 | physicians" preference. Optimization of AV delays was performed using the
4 iterative method and VV delay using aortic vti [15].

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7 Follow up measures were recorded for each patient including: NYHA
8 symptom class, percentage of biventricular pacing, site of LV lead placement and
9 whether echocardiographic optimization was performed.

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13 Study groups

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15 The study groups were divided into non-responders and responders. A
16 favourable clinical response to CRT was defined as an improvement in a patient's
17 NYHA class by ≥ 1 and lack of hospitalization for heart failure for 1 year following
18 pacemaker implantation. Comparisons were made between the two groups with
19 regards to baseline characteristics (age, sex, presence of co morbidities and drug
20 treatment) and potential predictors of response to CRT (atrial fibrillation, QRS
21 width, pre-implant echocardiographic dyssynchrony, post-implant optimization
22 and the site of the left ventricular lead).

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34 Statistical analysis

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36 Continuous variables are expressed as a median (interquartile range).
37 Comparisons between continuous variables were made using the Mann Whitney
38 U Test and for categorical variables the χ^2 test and univariate logistics
39 regression. Multivariable logistic regression for predictors of clinical response
40 deemed significant at univariate analysis was performed. A p value of <0.05 was
41 considered statistically significant.

1
2 140 **Results**

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4 Study population

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6 During the study period 288 consecutive patients underwent CRT and
7
8 were retrospectively analysed. Of these 167 patients had full follow up data
9
10 available to establish the presence of a symptomatic response of which 164 had
11
12 successful CRT implants. Baseline characteristics of the study population are
13 145 summarized in Table 1.
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16 The mean age was 67±13 years and most patients (78%) were males. The
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18 underlying aetiology of heart failure was ischaemic in 64% of patients. At the
19
20 time of CRT implantation 73% were in NYHA class III heart failure and 15% in
21
22 NYHA class IV. The mean baseline QRS width was 156ms with left bundle branch
23 150 block present in 87% of patients. The baseline left ventricular ejection fraction
24
25 was between 20-40% in 84% of patients and less than 20% in 16%. 46% of
26
27 patients had atrial fibrillation pre-implant. Medication included β blockers in
28
29 69%, angiotensin converting enzyme inhibitor or angiotensin receptor blockers
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31 in 92% and diuretics in 82% of patients. The LV lead was implanted in a lateral
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33 155 of posterolateral vein in 87% of cases. 58% had a CRT-D and the remaining 42%
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35 of patients had a CRT-P.
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41 Clinical indicators of responders vs. non responders

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43 160 The median follow up was 293 days with a maximum of 1474 days. 90
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45 (58.9%) patients had a favourable clinical response to CRT. This was
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47 predominantly by converting the patients from NYHA class III heart failure to
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49 class II (Figure 1).
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3 Baseline characteristics of responders and non-responders to CRT were
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5 165 similar in terms of concurrent drug treatment, age and the presence of
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7 defibrillator functionality. There was a trend towards better response rates in
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9 patients with non-ischaemic heart failure compared to ischaemic heart failure
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11 (ischaemia 50% vs. non-ischaemic 62%) although this did not reach statistical
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13 significance. (p=0.131) (Table 2). Females were more likely to respond to CRT
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15 170 (P=0.012), whereas patients with COPD were not (p=0.008).

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17 Comparison between potential predictors of response to CRT between the
18
19 two groups demonstrated that the presence of permanent atrial fibrillation
20
21 predicted a lack of response to CRT (p=0.017) (Table 3). The percentage of
22
23 biventricular pacing and the site of LV lead placement were not significantly
24
25 175 different between the two groups. The pre-implant QRS width was similar in
26
27 non-responders and responders to CRT 152ms (CI 131-181ms) and 150ms (CI
28
29 122-176ms) respectively.

33 Predictors of Non response to CRT

35 180 *Atrial fibrillation*

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37 To evaluate patients with atrial fibrillation pre-implant, further analysis
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39 was performed in those with paroxysmal AF compared to permanent AF.
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41 Analysis of patients in sinus rhythm compared to those with paroxysmal AF
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43 (PAF) and persistent AF revealed no significant difference in terms of age, pre-
44
45 185 implant NYHA class, ejection fraction and median QRS width (Table 4).

46
47 Univariate logistic regression suggests that the presence of persistent AF
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49 to be negatively predictive of a symptomatic response to CRT (odds ratio: 0.408,
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51 95% CI: 0.196-0.849, p=0.016), however, multivariable logistic regression did not
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reach statistical significance (odds ratio: 0.482, 95% CI 0.215-1.081, p=0.077).

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190 Median best proportion of time pacing both ventricles measured at pacing check
was 88.3% for symptomatic responders and 98% for symptomatic non-
responders in patients with persistent AF. AV node ablation was performed in 3
patients with persistent AF, of whom none responded symptomatically.

195 *Pre-implant echocardiographic assessment of mechanical dyssynchrony*

196 Of the 164 patients selected for CRT in the study, 95 patients had a pre-
197 implant echocardiographic dyssynchrony study. Table 5 shows the
198 characteristics and response rates for patients with and without pre-implant
199 assessment of mechanical dyssynchrony. Both groups had similar baseline QRS
200 widths and pre-implant LV ejection fractions. There was no significant difference
201 in symptomatic response rates between the two groups using the χ^2 test
202 (p=0.877) or using univariate logistic regression (OR: 0.903, 95% CI: 0.478-
203 1.704, p=0.752), implying that there is no difference in response rates following
204 CRT whether a pre-implant echocardiographic dyssynchrony assessment is
205 performed or not.

206 Of the 95 patients who had a pre-implant dyssynchrony study, 54 (56.8%)
207 had a positive response rate and 41 (43.2%) a negative response rate to CRT.
208 However of the patients who had a pre-implant dyssynchrony study, 62% had a
209 positive study as defined above. Of those who had a positive dyssynchrony study,
210 67% had a positive response rate to CRT, compared to 54% positive response in
those who had a negative study (p=0.09). There was no difference in baseline
ejection fraction.

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Chronic obstructive pulmonary disease (COPD)

215 Patients with significant COPD were defined as those with a diagnosis of underlying airways disease on the basis of respiratory assessment including lung function testing for which they were receiving concomitant treatment (typically a steroid inhaler and/or bronchodilator). On this basis 22 patients had coexisting COPD of which only 6 patients (28%) responded to CRT (p=0.008).

220 Multivariate logistic regression showed that males and patients with COPD were the only negative independent predictors of response to CRT with an overall p=0.0002 and overall accuracy of 64% (percentage of cases correctly identified) (Table 6). There was a trend towards the presence of permanent atrial fibrillation to be associated with a poor clinical response.

225

Discussion

Our results demonstrate that male sex, COPD and chronic atrial fibrillation are predictors of poor response to CRT in our patient cohort. There was a trend towards better response in patients with echocardiographic evidence of interventricular or intraventricular dyssynchrony but this did not reach statistical significance.

230 Importantly we have shown that patients with COPD responded poorly to CRT. Although this has not been previously reported, it is likely that differentiating breathlessness due to lung disease and left ventricular impairment can be difficult and when faced with a very symptomatic patient refractory to heart failure treatment, it was reasonable to implant a CRT device. In addition the poor response in this group might be related to limited up titration of medication and in fact of the 22 patients with COPD, 15 (68%) were

not commenced on a β blocker due to poor tolerance. Therefore, more objective
 240 measures of the severity of lung disease such as a formal lung function testing
 and measurements of maximal oxygen consumption using cardiopulmonary
 exercise testing might be more appropriate in order to ascertain the aetiology of
 the patient's symptoms before embarking on CRT implantation.

Previous studies have shown improved response rates to CRT in females.

245 Lilli *et al* [16] showed greater reductions in LV volumes in women compared to
 men (76% in women vs. 59% in men, $p < 0.05$) and significant reductions in LV
 end systolic volumes (LVESV) of $\geq 10\%$ compatible with LV reverse remodeling
 at 12 months follow up after controlling for confounding factors such as
 aetiology. Similar findings were shown in a subgroup analysis of the PROSPECT
 250 trial, with $\geq 30\%$ reduction in LVESV in 53.6% of women compared to 31.2% of
 men ($p = 0.0005$), suggesting a true gender specific effect [17]. Previous studies
 have shown different degrees of physiological and pathological remodeling
 associated with end stage ischaemic heart failure [18], hypertension [19] and
 aortic stenosis [20] in males and females. In addition, in failing human hearts a
 255 higher myocyte death (necrosis or apoptosis) has been clearly demonstrated in
 men than in women [21]. Based on these observations it is possible that females
 have a more favourable substrate for reverse remodeling during CRT.

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Measures of mechanical dyssynchrony using echocardiography have
 revealed conflicting results. Initial single centre studies reported a strong
 260 association between measures of dyssynchrony and outcomes following CRT
 [22-25]. The recently published multicentre PROSPECT trial only demonstrated
 modest sensitivity and specificity of measures of dyssynchrony to predict CRT
 response. This in part was thought to be related to a variety of measures of

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265 correlation between these parameters and extent of LV reverse remodeling at
6month follow up [17]. In addition, “super-responders” (defined as an LVESV
reduction of $\geq 30\%$ at follow up) had more extensive dyssynchrony suggesting
that echocardiographic measures of dyssynchrony might predict LV reverse
remodeling. In our current study there was a trend in better response to CRT in
270 patients with significant dyssynchrony defined by the previously described
criteria, however our study was under-powered to detect significant differences
between these two groups. More promising data is emerging with regards to 3D
echocardiographic assessment of dyssynchrony [26], and speckle tracking
echocardiography [27], which might prove better predictors of response to CRT.
275 There was a trend in poor response to biventricular pacing in patients
with persistent atrial fibrillation. Although this might have been related to more
rapid ventricular rates and therefore a lower percentage of biventricular pacing
(sinus rhythm $97 \pm 24\%$, PAF $98 \pm 31\%$, chronic AF $90 \pm 39\%$, $p=0.01$), it appeared
that the permanent AF responders were paced 88% of the time and the non-
280 responders 98%. Previous studies have postulated that patients with AF can
have fusion and pseudofusion beats resulting from interaction between
intrinsically conducted and paced beats, which could result in ineffective pacing
despite the apparent delivery of CRT. Therefore it is possible that the recorded
proportion of the time spent pacing both ventricles might be an
285 overestimate. [28]. This can be overcome by performing an AV node ablation. A
study by Gasparini *et al* [29], showed that patients with AF only showed an
increase in ejection fraction, reverse remodeling, improved exercise tolerance
and reduced mortality if they underwent AV node ablation. Similar findings were

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1 reported by Ferreira *et al* [30], who demonstrated comparable outcomes with
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 4 290 CRT in patients in sinus rhythm and AF with AV node ablation. This suggests the
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 6 importance of ensuring close to 100% biventricular pacing although loss of
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 8 atrioventricular synchrony might also play a role in poor response to CRT in this
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 10 patient group.
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 13 Currently it is recommended that the LV lead should be positioned at the
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 15 295 LV free wall, which corresponds to the myocardium drained by the lateral or
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 17 posterolateral cardiac veins. 87% of our patients had LV lead implanted within
 18
 19 these veins. There appeared to be no significant difference between responders
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 21 and non responders with regards to lead positioning. This is in agreement with a
 22
 23 subanalysis of the COMPANION study which showed that LV lead placement was
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 25 300 not predictive of response to CRT therapy [31]. However, implantation of the LV
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 27 lead adjacent to an area of transmural scar is predictive of poor response to CRT
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 29 [32].
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 32 Approximately two-thirds of our patients had ischaemic heart failure.
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 34 305 Response rates appeared to be no different between the ischaemic and non
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 36 ischaemic group. The aetiology of heart failure has been shown previously to be
 37
 38 predictive of clinical response to CRT. Initial work by Marsal *et al* [33] and more
 39
 40 recent evidence from CARE-HF [34] and PROSECT [17] have shown improved
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 42 clinical outcome and larger decreases in LVESV in patients with non-ischaemic
 43
 44 310 heart failure compared to ischaemic patients. However the CARE-HF
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 46 demonstrated similar reductions in mortality in both groups [7]. In our study
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 48 there was a trend in better response to CRT in patients with non-ischaemic heart
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failure, however, this study was under-powered to detect significant differences between these two groups,

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315 We have demonstrated that in a large cohort of patients undergoing CRT, that a number of factors can influence response. Current guidelines only use LV ejection fraction, NYHA class and QRS width to select patients for these devices.

We have shown that in addition to these measures it is important to consider comorbidities in particular COPD when considering patients for CRT.

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320 **Limitations of the study**

This study is limited by the retrospective design. In addition our definition of response to CRT was confined as an improvement in NYHA class and lack of hospitalization with heart failure. It is unclear whether an

325 improvement in clinical status translates into improved mortality. Other studies have adopted more objective measures including echocardiographic evidence of LV reverse remodeling which correlates well with survival in heart failure trials of medical interventions [35], which was not analysed in this study. In addition

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we have defined non responders as no change in symptom class, however this 330 may represent a positive outcome as disease progression might be reduced compared with the natural history without CRT. As a result, CRT response rates are dependent on the definition of 'response' [36],

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46 **Conclusion**

335 This study showed that gender (males) and the coexisting COPD were predictors of poor response to CRT. This highlights the importance of

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considering baseline patient characteristics, in particular the presence of comorbidities that might affect the response to CRT.

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Table 1 : Baseline characteristics (n=164), IHD- ischaemic heart disease, CABG – coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease, NYHA – New York Heart Association, ICD – internal cardiac defibrillator, LBBB – left bundle branch block, RBBB – right bundle branch block, IVCD – intraventricular conduction delay.

Age(mean yrs±SD)	67±13
Men/Women (%)	78/22
Ischaemic Heart Failure (%)	64
Non ischaemic Heart Failure (%)	36
Comorbidities (n)	
IHD	105
CABG	46
COPD	22
Hypertension	70
Valvular heart disease	37
Diabetes	36
Symptoms at baseline (%)	
NYHA Class I	0.6
NYHA Class II	11
NYHA Class III	73
NYHA Class IV	15
Sinus Rhythm / AF (%)	54/46
Preexisting pacemaker	17
Preexisting ICD	5
QRS duration	
Mean (ms)	156
120-149 (%)	49
>150 (%)	51
Resting ECG (%)	
LBBB	88
RBBB	4
IVCD	8
Ejection Fraction (%)	
<20%	16
20-30%	40
30-40%	44
LV lead implantation site (%)	
Posterolateral or lateral vein	87
Middle cardiac vein	4
Anterior	9

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370 Table 2 : Comparison of baseline characteristics for responders and non
 responders to cardiac resynchronization therapy.

Variable	Non- Responders	Responders	P value
Median age	73 (61-78)	68 (58-76)	0.085
Sex (M:F)	64:10	63:27	0.012
Ischaemic (Y:N)	52:22	53:37	0.131
CAD (Y:N)	54:23	53:38	0.151
HTN (Y:N)	32:43	38:48	0.972
CABG (Y:N)	25:50	22:65	0.341
Valvular heart disease (Y:N)	16:59	21:66	0.813
Beta blocker (Y:N)	48:26	60:38	0.742
Digoxin (Y:N)	24:50	33:57	0.688
ACEorARB(Y:N)	65:12	81:10	0.515
Ksparing diuretic	50:24	56:34	0.583
Amiodarone	20:54	17:73	0.292
Diuretic	12:62	16:74	0.955
COPD (Y:N)	16:56	6:80	0.008
Diabetes (Y:N)	16:58	20:66	0.954
CRT-D (Y:N)	48:29	50:41	0.417

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Table 3: Comparison of potential predictors of response to CRT the non responders and responders.

Variable	Non- Responders	Responders	P value
Ischaemic (Y:N)	52:22	53:37	0.131
AF (Y:N)	36:38	35:54	0.124
Pers/permaAF (Y:N)	24:36	14:54	0.017
PAF(Y:N)	15:61	22:67	0.564
Median QRS width (ms)	152(131-181)	150(122-176)	0.527
QRS 120ms-149ms (Y:N)	3:25	6:31	0.525
QRS > 150ms (Y:N)	15:13	19:18	0.859
Dyssynchrony echo (Y:N)	45:26	54:35	0.726
LBBB (Y:N)	41:12	54:12	0.542
Optimised (Y:N)	34:42	29:62	0.121
Median Bivent paced (%)	99(96-100)	99(98-100)	0.197
LV lead Posterior/lateral (Y:N)	57:8	73:10	0.961
Median Interventricular delay (ms)	48(27-84)	48(23-61)	0.450
Median maximum Intraventricular delay (ms)	57(29-83)	48(32-70)	0.494

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Table 4: Characteristics for patients with atrial fibrillation (paroxysmal and chronic) and sinus rhythm.

	Sinus rhythm	Paroxysmal AF	Persistent AF
Median age (years)	68 (24-85)	68 (41-83)	74 (45-87)
Mean pre-implant NYHA class	2.99	3.0	3.15
Median pre-implant ejection fraction	25% (11-45)	25.5%(13-58)	30% (10-58)
Median QRS duration (ms)	149.5(104-214)	142(107-189)	152(116-224)

Table 5: Characteristics and response rates for patients with and without pre-implant assessment of mechanical dyssynchrony

	Pre-implant dyssynchrony echo	No pre-implant dyssynchrony echo
Median age (years)	67 (24-85)	72.5 (31-87)
Mean pre-implant NYHA class	3.07	2.88
Median pre-implant ejection fraction	25% (10-48)	30% (15-58)
Median QRS duration (ms)	148 (100-250)	150 (100-234)
Response rate	55/102 (54%)	35/62 (56%)

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Table 6: Multivariable logistic regression for predictors of clinical response deemed significant at univariate analysis. Only sex (male) and COPD are negatively associated with clinical response, overall $p = 0.0002$, and overall accuracy (percentage of cases correctly classified) is 64%. Having a large AF burden is almost statistically significant for having a poorer clinical response.

Variable	Odds ratio	95% CI OR	p-value
Age	0.979	0.952-1.005	0.117
Sex (male)	0.273	0.111-0.671	0.005
COPD	0.225	0.075-0.671	0.007
Pers/permaf	0.482	0.215-1.081	0.077
Echo dyssynchrony pre-implant assessment	0.903	0.478-1.704	0.752

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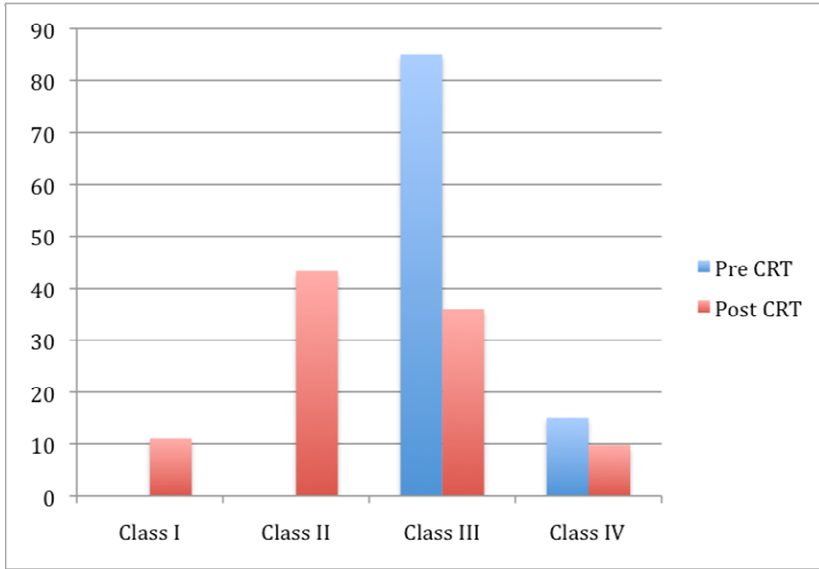
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415 **Figure Legend**

Figure 1 : Distribution of NHYA Heart failure class at baseline and following CRT (%).

Figure

Figure 1



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Review Only

440 **Authors' contribution**

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5 S. Kirubakaran : Data analysis/interpretation, drafting article
6
7 Andrew Ladwiniec Data analysis/interpretation, Statistics
8
9 Aruna Arujuna Data analysis and collection
10
11 Mathew Ginks Critical revision of article
12
13 445 Mark McPhail Statistics
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15 Julian Bostock Data collection, data analysis, concept/design
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17 Gerry Carr-White Concept/design, critical revision of article
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19 CA Rinaldi Concept/design, critical revision of article, approval of
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