Long-term effects of upgrading from right ventricular pacing to cardiac resynchronization therapy in patients with heart failure

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Aims
To determine the effects of upgrading from right ventricular (RV) pacing to cardiac resynchronization therapy (CRT) in patients with heart failure.

Methods and results
Patients with heart failure [age 67.3 ± 9.6 years (mean ± SD), NYHA class III or IV, left ventricular ejection fraction (LVEF) ≤ 35%, QRS ≥ 120 ms] underwent de novo CRT (n = 336) or upgrading from RV pacing [n = 58; VVIR in 24, DDDR in 34] to CRT. The endpoint of death from any cause or major cardiovascular events, cardiovascular death or hospitalization for heart failure, and cardiovascular death or death from any cause was determined after a maximum follow-up of 7.7 years. No differences emerged between the de novo CRT and the upgrade-to-CRT groups with respect to any of the clinical endpoints. The de novo CRT and upgrade-to-CRT groups derived similar improvements in NYHA class [−1.2 vs. −1.3 (mean), both P < 0.0001], 6 min walking distance [75.9 (P = 0.0001) vs. 46.4 (P = 0.0205) m], and quality of life scores [−25.2 vs. −18.7 (both P < 0.0001)] 1 year after implantation. Response rates using a combined clinical score (≥1 NYHA classes or ≥25% increase in 6 min walking distance plus survival with freedom from heart failure hospitalizations for 1 year) were 73.2% and 75.4%, respectively (P = NS). There were reductions in left ventricular end-systolic volume [median of 20.3 mL (P = 0.0012) and 22.7 mL (P = 0.0066), respectively] and improvements in LVEF [median of 2.9% and 9.3%, respectively (both P < 0.0001)].

Conclusion
In patients with heart failure who are RV-paced, upgrading to CRT is associated with a similar long-term risk of mortality and morbidity to patients undergoing de novo CRT. Symptomatic improvements and degree of reverse remodelling are also comparable.

Keywords
Cardiac resynchronization therapy • Pacing • Heart failure

Introduction
The benefits of de novo cardiac resynchronization therapy (CRT) by means of biventricular pacing are well established. In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION)1 and the Cardiac Resynchronization Heart Failure (CARE-HF)2 studies, de novo CRT was associated with a reduction in all-cause mortality. These and other studies have shown that CRT also leads to an improvement in symptoms, exercise capacity, and quality of life.3–5

Heart failure is frequently found in the conventional pacemaker population. A cross-sectional study has shown that up to 27% of patients attending a typical pacemaker clinic have heart failure.6 Randomized studies comparing the effects of atrial vs. right ventricular (RV) pacing in patients with sick sinus syndrome indicate that up to 40% of patients develop heart failure during VVIR pacing.7,8 In the Dual Chamber and VVI Implantable Defibrillator (DAVID)9,10 and the MOde Selection Trial (MOST)11 studies, RV pacing led to an increase in hospitalizations from heart failure. Pathophysiologically, this association might be expected from the
fact that RV pacing leads to left ventricular (LV) dyssynchrony, abnormal LV relaxation,12,13 asymmetric septal hypertrophy,14 myofibrillar disarray,15 and perfusion defects.16

Several studies have shown that upgrading from RV pacing to CRT corrects interventricular and intraventricular dyssynchrony.17–19 It is on this basis that upgrading to CRT has been proposed as an option for conventionally paced patients with heart failure.20 In this prospective observational study, we have explored the effects of mortality and morbidity of upgrading from conventional RV pacing to CRT in patients with heart failure. The effects on symptoms, clinical events, and survival were also assessed.

Methods

Patients
From September 2000 to April 2008, 417 patients underwent attempt at CRT implantation without cardioverter defibrillator back-up. Of these, 23 patients who had failed implants (5.5%) were excluded from this study. Criteria for inclusion for paced or unpaced patients were as follows: heart failure in NYHA class III or IV, impaired LV function (left ventricular ejection fraction (LVEF) ≤ 35%), QRS ≥ 120 ms, optimal tolerated treatment with diuretics, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), β-blockers, spironolactone, and digoxin. Exclusion criteria included: myocardial infarction or acute coronary syndrome within the previous 3 months, severe structural valvular heart disease, and presence of co-morbidities likely to threaten survival for 12 months. In this study, we were particularly interested in comparing upgrading to CRT with RV pacing per se. We were also interested in comparing our findings with the CARE-HF study, which included only patients undergoing CRT-P. For this reason, only patients undergoing CRT without defibrillator back-up were included in this study.

All participants had undergone coronary angiography. The clinical diagnosis of heart failure was made on the basis of symptoms of heart failure plus systolic dysfunction on echocardiography. The diagnosis of ischaemic cardiomyopathy was made if systolic dysfunction was associated with a history of myocardial infarction11 and/or if the pattern of late-gadolinium hyperenhancement on magnetic resonance imaging was the characteristic of a myocardial infarction.22 All patients gave written informed consent and the study was approved by the North Birmingham Ethics Committee.

Study design
Patients referred for CRT underwent pacemaker implantation during an elective admission or after stabilization during the course of an unplanned admission for acute decompensated heart failure. Patients underwent a clinical assessment and echocardiography on the day prior to implantation and at 1, 3, and every 6 months thereafter.

Clinical assessment and echocardiography
Assessments included documentation of NYHA class, a quality of life assessment using Minnesota Living with Heart Failure questionnaire,23 and a 6 min hall walk test.24 Transthoracic echocardiography was performed using Systems 5 and 7 scanners with EchoPAC (GE Healthcare, Slough, UK). Left ventricular volumes were estimated using Simpson’s equation by planimetry of apical four-chamber views.

Device therapy
Transvenous biventricular pacemaker implantation was undertaken using standard techniques under local anaesthesia. Following implantation, patients underwent transmural Doppler-directed optimization of atrioventricular delay25 prior to discharge and at every scheduled visit thereafter. For patients in chronic atrial fibrillation (AF), RV and LV leads were implanted and a biventricular generator was used, plugging the atrial port and programming the generator to a ventricular triggered mode. Patients were followed-up in a dedicated device therapy clinic.

Endpoints
The clinical endpoints considered were the composite of cardiovascular death or an unplanned hospitalization for major cardiovascular events (MCEs), which included cardiac transplantation, Hospitalizations for worsening heart failure, myocardial infarction, unstable angina, arrhythmia, stroke, or pulmonary embolism were included in this endpoint. The first event was included in the analysis. The second endpoint considered was the composite of cardiovascular death or unplanned hospitalization with worsening heart failure. The other endpoints considered were cardiovascular death and death from any cause. Mortality data were collected through medical records, and where appropriate, from interviews with patients’ carers. Information regarding clinical outcome was collected by an investigator who was blinded to all other study data. Sudden cardiac death was defined as ‘a natural, unexpected death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 h of the onset of acute symptoms’.26

Statistical analysis
Continuous variables are expressed as mean ± SD. Normality was assessed using the Shapiro–Wilks test (the W-statistic). Comparisons between normally distributed continuous variables were made using ANOVA with Fisher’s protected least significance difference test for multiple comparisons. Categorical variables were analysed using chi² tests. Differences in survival curves between the groups were assessed using the log-rank (Mantel–Cox) test. Cox statistical analyses were performed using Statview (Cary, NC, USA) and NCSS (Kaysville, UT, USA). A two-tailed P-value of <0.05 was considered statistically significant.

Results
The characteristics of the study group are shown in Table 1. Compared with patients undergoing de novo CRT, patients who were upgraded to CRT were older and more likely to have chronic AF (P = 0.0378). As expected, patients in the upgrade-to-CRT group had a wider QRS duration (P = 0.0042). The groups were well matched for gender, ischaemic aetiology, co-morbidities, and medication.

The indications for conventional pacemaker implantation and pacing modes are shown in Table 2. Across the group, the percentage of RV pacing at the time of pacemaker interrogation prior to upgrade to CRT was 81%.

Symptom-related variables
In patients who died, the clinical data at follow-up pertain to the latest available follow-up. After a median follow-up of 372 days, similar improvements were observed with respect to NYHA class, 6 min walking distance, and quality of life scores in the de novo CRT and the upgrade-to-CRT groups (Figure 1).
Combined clinical score

The combined clinical score was assessed using a combined clinical score, defined as improvements by increase in NYHA class or 25% in 6 min walking distance plus survival with freedom from heart failure hospitalizations for a year following implantation. According to this definition, response rates were 73.2% in the de novo CRT group and 75.4% in the upgrade-to-CRT group (P = NS).

Echocardiographic variables

Complete echocardiographic follow-up data were available in 270/336 (80%) patients in the de novo group and in 54/58 (93%) of the upgrade-to-CRT group. As shown in Table 3, the upgrade-to-CRT group had lower left ventricular end-diastolic volumes (LVEDV, P = 0.0002) and left ventricular end-systolic volumes (LVESV, P = 0.0078). At follow-up, there were no group differences in LVEDV, but the upgrade-to-CRT group had a lower LVESV (P = 0.0035) and a higher LVEF (P = 0.0021). There was reverse remodelling in both groups, evidenced by a reduction in LVESV by a median of 20.3 mL in the de novo group (P = 0.0012) and 22.7 mL in the upgrade-to-CRT group (P = 0.0066). The LVEF increased by a median of 2.9% and 9.3%, respectively (both P < 0.0001). Taking a 15% reduction in LVESV as the definition of echocardiographic response, there were 47% responders in the de novo group and 46% in the upgrade-to-CRT group (P = NS).

Endpoints

After a median follow-up of 757 days for clinical endpoints, there were 108/336 (32%) and 20/58 (32%) deaths from any cause and 91/336 (27%) and 15/58 (26%) cardiovascular deaths in the de novo CRT group and the upgrade-to-CRT group, respectively. There were 28/336 (8%) and 7/58 (12%) sudden cardiac deaths in the de novo group and the upgrade-to-CRT group, respectively (P = NS). In Kaplan–Meier analyses, there were no group differences with respect to any of the clinical endpoints (Figure 2).

Power calculations

There are no published data on which to base power calculations for the present study. Our findings, however, can be used to estimate the sample number required to prove superiority of de novo CRT over upgrade-to-CRT with respect to cardiovascular mortality. Based on the findings of the present study, a Cox regression of the log hazard ratio on a covariate with an SD of 0.4999 based on a sample of 4442 observations and an event rate of 0.32 (by the
end the study) achieved 90% power at a two-sided significance level of 0.05 to detect a regression coefficient equal to the observed \( \beta \) coefficient of 0.1720 in this study. Therefore, a sample size of 4442 would be required to prove a statistical difference in outcome between patients undergoing de novo CRT or upgrade-to-CRT.

### Discussion

We have shown that in patients with heart failure who are chronically RV-paced, upgrading to CRT is associated with similar long-term mortality and morbidity to patients undergoing de novo CRT. Over a median follow-up period of 2.1 years, we have observed no difference between these groups in terms of the composite endpoints of death or unplanned hospitalization for MCEs, death from any cause or unplanned hospitalization for HF, death from any cause or cardiovascular death. Improvements in NYHA class, 6 min walking distance, and quality of life scores were similar. In addition, upgrading to CRT was associated with reverse LV remodelling.

The only randomized trials of CRT with mortality endpoints excluded patients with pre-existing conventional pacemakers. Several studies have reported on the effects of upgrading from RV pacing to CRT in either the acute setting or in the short-term. A symptomatic benefit from upgrading to CRT was shown in the cross-over study of Leclercq et al., who compared RV pacing with CRT in 44 patients with heart failure. In this study, NYHA class, 6 min walking distance, and quality of life scores improved with CRT, compared with RV pacing. Similar findings emerged from another small cross-over study and an observational study. Comparing with patients undergoing de novo CRT, Marai et al. found similar improvements in NYHA class and 6 min walking distance at 3 months following upgrading to CRT. A retrospective study of 32 patients upgraded to CRT and 39 patients receiving de novo CRT also found similar improvements in NYHA class.

To further assess the effects of upgrading to CRT in relation to chronic RV pacing, we have compared our findings with a treatment arm of the DAVID study, in which recipients of implantable cardioverter defibrillators were programmed to RV pacing (DDDR with a lower rate of 70 bpm). Figure 3 shows Kaplan–Meier curves

### Table 3  Echocardiographic variables in patients undergoing de novo or upgrade to CRT

<table>
<thead>
<tr>
<th>Variable</th>
<th>De novo CRT</th>
<th>Upgrade to CRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>270</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>253.5 ± 99.4</td>
<td>212.5 ± 98.0</td>
<td>0.0059</td>
</tr>
<tr>
<td>Follow-up</td>
<td>234.9 ± 96.3*</td>
<td>208.4 ± 91.8</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>197.2 ± 87.8</td>
<td>168.2 ± 89.8</td>
<td>0.0278</td>
</tr>
<tr>
<td>Follow-up</td>
<td>175.0 ± 87.0**</td>
<td>145.5 ± 85.7*</td>
<td>0.0235</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23.2 ± 10.2</td>
<td>23.1 ± 10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>27.4 ± 11.9***</td>
<td>33.1 ± 13.9***</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± SD. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction. Asterisks refer to P-values of differences from baseline values within the group. *P < 0.05; **P < 0.001; ***P < 0.0001. P-values in the table refer to group differences at baseline and at follow-up.
for the primary endpoint of death from any cause or first hospitalization for new or worsening heart failure in patients included in the DAVID study and in the current study. Because we had no access to the original dataset from the DAVID study, this comparison is only qualitative. It would appear, however, that the survival curves are more favourable in the upgrade-to-CRT arm of our cohort, despite the fact that only 69% of patients in the DAVID study had heart failure prior to implantation. Although
selection criteria for these studies were very different, it does suggest that patients with heart failure who are upgraded to CRT fair better than patients who receive chronic RV pacing.

To compare with a population of patients with heart failure receiving de novo CRT or optimum pharmacological treatment (OPT) alone, Kaplan–Meier curves were superimposed on the survival curves from the CARE-HF study. As we had no access to the original dataset from the CARE-HF study, this comparison is also qualitative. As shown in Figure 4, this qualitative comparison suggests that patients with heart failure who are upgraded from RV pacing to CRT fair as well as patients receiving CRT, and better than patients receiving OPT alone.

Nearly one-third of patients in the upgrade-to-CRT group had chronic AF. Evidence for a benefit from upgrading to CRT in patients with AF has emerged from several studies. In a study of 20 patients with prior atrioventricular junction ablation and RV pacing for permanent AF, Leon et al. found that upgrading to CRT led to a 29% improvement in NYHA class, a 33% improvement in quality of life scores, a 44% improvement in LVEF, and an 81% reduction in hospitalizations. In a study of 16 patients with AF treated with the ‘ablate-and-pace’ approach, upgrading to CRT after a mean follow-up of 20 months was associated with a reverse LV remodelling. Together, these studies suggest that even in the context of AF, the interventricular and intraventricular resynchronization afforded by upgrading to CRT confers significant benefits.

Limitations
Unfortunately, hospital records revealed that LV function was not systematically assessed prior to implantation of conventional pacemakers. We do not, therefore, have reliable documentation on LV function or heart failure symptoms and signs prior to implantation of the initial pacemaker. These data would have been helpful in determining the degree to which RV pacing alone had contributed to the development of heart failure by the time of upgrading to CRT. This is a non-randomized observational study comprising a relatively small number of patients, and therefore, the findings should be interpreted with caution. Because we had no access to the DAVID or the CARE-HF study data, we were unable to perform statistical analyses. Comparisons with these studies are, therefore, only qualitative. Our findings may not be generalizable to patients who are upgraded to CRT with defibrillator back-up, but do demonstrate the benefits of upgrading from RV pacing to CRT per se.

Conclusions
We have shown that in patients with heart failure who have been chronically RV-paced, upgrading to CRT is associated with a similar long-term risk of mortality and morbidity to patients undergoing de novo CRT. Proof of a benefit from upgrading to CRT requires a randomized comparison with RV-paced patients with heart failure who are not upgraded to CRT. On the basis of emerging evidence of the deleterious effects of RV pacing, however, it seems unlikely that such a study will ever be undertaken.

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Upgrading to CRT

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