Inpatient vs. elective outpatient cardiac resynchronization therapy device implantation and long-term clinical outcome

Olujimi A. Ajijola1, Eric A. Macklin2, Stephanie A. Moore3, David McCarty4, Kara E. Bischoff1, Edwin Kevin Heist1, Michael Picard4, Jeremy N. Ruskin1, George William Dec1, and Jagmeet P. Singh1

1Cardiac Arrhythmia Service, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, GRB 109, Boston, MA 02114, USA; 2Biostatistics Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA; 3Heart Failure Service, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA; and 4Echocardiography Service, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

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Aims

It remains unclear whether cardiac resynchronization therapy (CRT) device implantation during inpatient (IP) hospitalization affords the same benefit as elective outpatient (OP) implantation. We hypothesized that IPs undergoing CRT device implantation during acute hospitalization may have worse outcomes compared with elective OP implantation.

Methods and results

We retrospectively separated patients undergoing CRT implants at Massachusetts General Hospital into OP (n = 196) and IP (n = 105) cohorts. Long-term outcomes, measured as heart failure (HF) hospitalization, all-cause mortality, ventricular assist device placement, or heart transplant over a 2-year follow-up period, were estimated by the Kaplan–Meier method. Propensity scores were generated to balance the baseline co-morbidities between IP and OP. Baseline age, gender, left ventricular ejection fraction, and aetiology of cardiomyopathy were comparable between OP and IP (66.8 ± 11.8 vs. 67.5 ± 13.4 years, 78 vs. 84% males, 24 vs. 23%, and 39 vs. 50% ischaemic, P = NS). Inpatients had greater burden of diabetes mellitus (40 vs. 27%, P = 0.028), renal insufficiency (47 vs. 25%, P = 0.001), and right ventricular dysfunction (54 vs. 39%, P = 0.026) compared with OPs. At 2-year follow-up, IP implant was associated with greater risk of HF hospitalization (HR 1.6, 95% CI 1.03–2.48, P = 0.038) compared with elective OP implants. After propensity score adjustment, there was no statistically significant difference in HF hospitalization between the IP and OP groups (HR 1.031, 95% CI 0.61–1.78, P = 0.91).

Conclusion

Compared with OP CRT implants, IPs are at increased risk for recurrent HF hospitalization; however, the increased risk is attributable to greater co-morbidities in the IP population.

Keywords

Cardiac resynchronization therapy • Heart failure • Pacing • Clinical outcomes

Introduction

A number of clinical trials have supported the efficacy of cardiac resynchronization therapy (CRT) in patients with New York Heart Association (NYHA) Class III or IV heart failure (HF) refractory to optimal medical therapy, left ventricular ejection fraction (LVEF) under 35%, and evidence of electromechanical delay, best evidenced by a QRS duration of >120 ms.1–4 These trials, however, demonstrate a lack of response in approximately a third of patients undergoing CRT. Although several strategies to enhance patient selection continue to be examined, there is little information regarding the impact of the ‘in-hospital status’ on the outcome of CRT implants.5–7 Although a large proportion of the patients meeting criteria for CRT are identified as inpatients (IPs), device implantation during hospitalization for an acute cardiac decompensation has not been addressed in the literature.

* Corresponding author. Tel: +1 617 726 4662; fax: +1 617 726 7519; Email: jsingh@partners.org

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and remains a potential avenue to improve response rates to CRT. The objective of this study was to determine whether patients receiving their CRT implantation during the course of a hospitalization for an acute cardiovascular event had a worse long-term clinical outcome compared with those who receive their device electively via an outpatient (OP) admission.

**Methods**

**Patient population**

The current study retrospectively analysed a cohort of consecutive patients who were implanted and received their entire follow-up at Massachusetts General Hospital (MGH) over a 4-year period (May 2003–March 2007). Based on their admission status, patients were subdivided into two groups: IP (n = 105) and elective OP (n = 196) implants. The IP group comprised of patients who received their implants during the course of a hospital admission for an acute cardiovascular event, including decompensated HF, arrhythmia, syncope, and non-ST-segment elevation myocardial infarction (NSTEMI). Of note, the primary intent for the hospitalization in the IP group was not the CRT implant. The OP group included patients who were admitted electively and primarily for the CRT implant. Only patients undergoing a primary CRT implant/upgrade were included, whereas those undergoing generator change and lead revisions were excluded. The position of the LV lead was left to the discretion of the implanting physician. In all cases, the LV lead was positioned in the most appropriate vein, taking into account anatomical location, the sensed electrical delay from the LV lead, stability, and absence of phrenic nerve stimulation. Patients with unsuccessful device implantations, who essentially did not receive CRT, were excluded. Post-implant lead dislodgements and revisions (IP, n = 3, OP, n = 5, P = NS) were comparable between both groups.

Baseline evaluation was performed in all patients. Details of NYHA functional status, HF aetiology, concomitant cardiovascular conditions, creatinine, haemoglobin, EKG's, and transthoracic echocardiograms were obtained.

**Follow-up**

Standard settings (i.e. pacing mode, base rate, etc.) were left to the discretion of the treating physician. During the early part of this study, atroio-ventricular and interventricular settings on the CRT device were standard out-of-the box settings. Since December 2005, all patients were uniformly optimized at their first month follow-up visit at the CRT multidisciplinary clinic. Echocardiograms were repeated at 1 month and once again at 3–6 months. The outcome measures recorded included HF hospitalization, overall mortality, left ventricular assist device (LVAD) placement, and heart transplant at 2-years post-implant.

**Statistical analysis**

Baseline characteristics were compared between the IP and OP implant cohorts using two-group t-test and Fisher’s exact test. Unadjusted 1- and 2-year probabilities of (i) HF hospitalization, (ii) mortality, LVAD, or heart transplant, and (iii) combined HF hospitalization/mortality/LVAD/transplant were estimated by Kaplan–Meier product–limit estimates. Unadjusted IP and OP survival curves were compared by using log-rank tests. Cox proportional hazards regression was used to estimate the hazard ratios for survival outcomes between IP and OP cohorts after adjustment for age, gender, and NYHA classification. A propensity score analysis was used to more completely adjust for the baseline differences that confounded IP vs. OP implantation. The probability of IP implantation was estimated by logistic regression based on the following baseline predictors: age, gender, NYHA classification, conduction abnormality (bundle branch block, intraventricular conduction delay, or paced rhythm), number of prior HF admissions (categorized as 0, 1, or ≥2), LVEF, diastolic LV diameter in end-diastole, QRS duration, presence of atrial fibrillation, ventricular tachycardia (VT), pulmonary hypertension, renal failure, diabetes, anaemia, and right ventricular dysfunction. Deciles of the propensity scores obtained from this model were used to stratify Cox regression models. Each of these baseline predictors was also evaluated in univariate Cox models and in Cox models adjusting for age and gender. Stepwise Cox regression was used to select parsimonious models of adjusted hazard for survival outcomes. Terms for age, gender, and implant location were included in all models. The other predictors listed above were considered for inclusion in the final model. All analyses were performed using SAS (version 9.1.3, SAS Institute, Cary, NC, USA). All comparisons were two-tailed at α = 0.05.

**Results**

A total of 301 patients who underwent CRT implantation, with complete follow-up at MGH between May 2003 and March 2007 were divided into IP (n = 105) and OP (n = 196) cohorts. Baseline characteristics between the two groups are shown in Table 1. Patients were observed to have a higher NYHA class and a greater burden of co-morbid conditions, including a significantly greater predominance of diabetes mellitus (P = 0.028), atrial fibrillation (P = 0.035), right ventricular dysfunction (P = 0.026), and renal insufficiency (P < 0.001) at baseline. Admitting diagnoses for the IPs were HF exacerbation (64%), VT (10.7%), syncope (4.7%), NSTEMI (3.8%), and digoxin toxicity (1.9%).

**Heart failure hospitalization**

Over the first 2-years post-implantation, unadjusted Kaplan–Meier estimates showed that IP implantation was associated with a higher probability of HF hospitalization compared with OP implants (P = 0.020; Figure 1A). At 1 year, the event-free proportion of OP and IP was 77.5 and 67.3%, respectively, whereas at 2 years, 68.2% of the OP and 54.9% of the IP were free of HF hospitalization, respectively. After adjusting for age, gender, and baseline NYHA class, IP implantation was still associated with a higher probability of HF hospitalization compared with elective OP implants (HR 1.62, 95% CI: 1.01–2.60, P = 0.038; Figure 1A).

**Mortality, left ventricular assist devices, and heart transplant**

When the combined endpoint of death from any cause, decompen-sation requiring LVAD placement, or progression to cardiac transplantation was examined using unadjusted Kaplan–Meier estimates, and IP was associated with a higher likelihood of this adverse outcome compared with OP over the first 2 years (P = 0.051; Figure 1B). One- and 2-year event-free survival for OP vs. IP were 94.7 vs. 86.8% (1 year) and 89.4 vs. 79.6% (2 year), respectively. No statistically significant difference was found between the two groups after adjusting for age, gender, and baseline NYHA (HR 1.62, 95% CI: 0.70–3.75, P = 0.26). When the composite endpoint inclusive of all events (HF hospitalization, mortality, LVAD, and cardiac transplant) was considered, IP
implants had a greater probability of a worse outcome compared with OP ($P = 0.041$; Figure 1C). At 1 year, 75.2% of OP compared with 65.0% of IP were free of events, with a similar difference maintained at 2 years (63.8 vs. 53.0%, respectively) for OP and IP. However, after adjusting for age, gender, and baseline NYHA class, no statistically significant difference was seen over 2 years in IP vs. OP (HR 1.43, 95% CI 0.91–2.25, $P = 0.13$).

### Adjustment for propensity scores

To account for the difference in baseline characteristics between IP and OP, propensity scores generated using 16 baseline characteristics were used to stratify the cohort into groups with roughly equal probability of baseline conditions. After propensity score adjustment, no statistically significant difference was seen in HF hospitalization between IP and OP implants (HR 1.03, 95% CI 0.61–1.76, $P = 0.91$; Table 2). Similarly, there was no difference seen between these two groups in all-cause mortality, LVAD placement, heart transplantation (HR 1.41, 95% CI 0.55–3.62, $P = 0.48$), or in the overall composite endpoint (HF hospitalization, all-cause mortality, LVAD placement, and cardiac transplant; HR 0.94, 95% CI 0.56–1.57, $P = 0.80$).

### Pre-implant hospitalization time, heart failure duration, and admissions

We examined whether the length of pre-implant hospitalization time (number of days between admission for a cardiovascular event and implantation of CRT device for IP), duration of congestive HF (length of time patients had carried the diagnosis of HF prior to CRT for all patients), and number of prior HF admissions (for all patients) were associated with adverse clinical outcomes over the 2 years after CRT implant across the entire cohort. In the IP group, after adjustment for age, gender, and NYHA class, there was no significant association between HF hospitalization over 2 years and optimization time (HR 1.04 per day, 95% CI 0.97–1.11, $P = 0.31$) or the duration of HF (HR 1.00 per year, 95% CI 0.96–1.04, $P = 0.80$). However, patients with two or more prior HF admissions compared with those with no admissions were almost twice as likely to be hospitalized for HF within 2 years after CRT (HR 1.94, 95% CI 1.14–3.31, $P = 0.015$).

A longer duration of medical treatment required to stabilize the patients prior to device implantation was associated with a higher likelihood of all-cause mortality, LVAD placement, or heart transplant (HR 1.19 per day, 95% CI 1.08–1.31, $P < 0.001$). The risk increased linearly from 1 to 25 days of optimization. There was no significant association between the composite outcome and HF duration (HR 0.99 per year, 95% CI 0.93–1.06, $P = 0.80$) or prior HF admissions (HR 1.02, 95% CI 0.87–1.20, $P = 0.78$).

### Determinants of adverse cardiac resynchronization therapy outcomes

We examined the entire cohort to identify clinical factors that may predict adverse outcomes after CRT. Diabetes mellitus was the strongest observed determinant of adverse outcomes (HR 2.99, 95% CI 1.83–4.89, $P < 0.001$; Table 3). Other strong determinants included concomitant renal insufficiency, right ventricular dysfunction, and a history of recurrent VT. Interestingly, we observed a protective effect of increased baseline QRS duration on electrocardiography (HR 0.92 per 10 ms, 95% CI 0.86–0.99, $P = 0.023$). Inpatient implantation was not predictive of adverse outcomes after CRT after adjusting for these factors (Table 3).

### Discussion

This study addresses, for the first time, the important question as to whether in-hospital status prior to a CRT implantation has an impact on clinical outcome. The main findings of the present
investigation are: (i) inpatients undergoing CRT implantation are at a high risk for HF hospitalization after CRT compared with OP elective implants, (ii) two or more HF admissions prior to CRT implant was associated with greater risk for HF hospitalization after CRT; (iii) IP with prolonged in-hospital course prior to CRT implantation have a worse outcome.

**Inpatient vs. outpatient status**

For IPs meeting criteria for CRT, there are no standards or guidelines regarding when to implant the device. It is unclear whether the most optimal time is during the course of a hospital admission, or as an elective OP. Our non-randomized retrospective evaluation of a cohort of patients demonstrates that device placement during the course of a hospitalization is associated with a greater probability of HF hospitalization compared with an elective OP implantation. This discrepancy in response to CRT appears to largely be attributable to a greater burden of co-morbid disease in the IP group, as shown by propensity score adjustment. It is important to emphasize that the higher prevalence of atrial fibrillation, end-stage renal disease, and NYHA Class IV in the IP group, although reflective of greater co-morbid conditions, could in turn be markers of underlying severity of HF or LV dysfunction.

**Predictors of poor prognosis**

Although it may appear intuitive that patients hospitalized for a prolonged period of time may reflect a sicker population and thereby serve as a predictor of poor prognosis, this hypothesis has never been examined. The prolonged IP stay group among the overall IP cohort was most likely representative of patients with more severe HF, requiring a longer period of parenteral diuretics and medication optimization. It is plausible that these patients, at the outset, had an intrinsically greater likelihood of mortality or evaluation for heart transplantation because of the severity of their disease. Along the same lines, patients with two or more prior admissions for HF exacerbations had a greater probability for HF hospitalization compared with patients with no prior exacerbations. This also likely reflects the severity of HF in these patients. It was, however, difficult to exactly quantify where these patients lie in the continuum of the disease. Although, most patients were stabilized during their IP period and implanted when they had attained ambulatory NYHA class IV status. In our study, the observed determinants of adverse outcomes after CRT, such as diabetes mellitus and renal insufficiency, are similar to prior studies. The metabolic interaction of these conditions with the heart or the association with ischaemic cardiomyopathy may attenuate the ability of the heart to undergo reverse remodeling, limiting the long-term benefits of CRT.

The present study highlights the impact of the clinical differences between the IP and OP groups that may explain the worse clinical outcome in the IP group. This would help us better risk stratify and prognosticate within this patient group. The presence of multiple co-morbidities and a worse trajectory in the IP when compared with the OP group show that we may need to be more aggressive in the post-implant follow-up and monitoring of these patients.

**Limitations**

Our single-centre experience is limited by the inherent biases of a retrospective analysis. Since our institution is a tertiary referral centre, and the patients are often followed up back in the community with their primary cardiologists/physicians, we included only patients who had their complete care at MGH. Temporal trends of change in practice with the commencement of a multidisciplinary clinic (December 2005), uniform device optimization protocol,
and standardized OP follow-up could have also impacted our findings. These changes were, however, uniformly implemented for both the IP and OP groups, and unlikely to have had a differential impact on one group vs. the other. From the statistical analysis perspective, the step-wise regression model used to identify predictors of adverse outcomes can yield biased estimates of the strength of association of the selected predictors, and the results from these analyses should be viewed as exploratory. However, the relatively small number of clinically derived predictors considered for inclusion, the addition of implant location (IP vs. OP) in all models, and lack of significance of implant location after adjustment leads us to feel confident in our inference from these models, as such, our results should be considered hypothesis generating and need further prospective validation.

### Conclusion

In summary, implantation of CRT in an IP setting is associated with a shorter time to HF hospitalization, and a worse combined outcome of HF, all-cause mortality, LVAD placement, or cardiac transplant. This association is largely driven by a greater prevalence of baseline co-morbid conditions in the IP group. Further prospective studies are needed to clarify the relationship between IP CRT implantation and adverse outcomes, including optimal timing of CRT implantation after acute cardiac decompensation.

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**Table 2** Two-year outcomes after adjustment for propensity scores

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age, gender, NYHA adjusted HR (95% CI)</th>
<th>P-value</th>
<th>Propensity score adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF hospitalization</td>
<td>1.6 (1.027–2.479)</td>
<td>0.038</td>
<td>1.0 (0.605–1.76)</td>
<td>0.910</td>
</tr>
<tr>
<td>Mortality/LVAD/transplant</td>
<td>1.6 (0.70–3.75)</td>
<td>0.256</td>
<td>1.4 (0.546–3.62)</td>
<td>0.481</td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>1.4 (0.905–2.246)</td>
<td>0.126</td>
<td>0.94 (0.557–1.57)</td>
<td>0.798</td>
</tr>
</tbody>
</table>

Composite endpoint includes HF hospitalization, mortality, LVAD placement, or cardiac transplant. NYHA, New York Heart Failure; HF, heart failure; LVDD, left ventricular assist device.

**Table 3** Determinants of adverse outcomes after cardiac resynchronization therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2.99 (1.826–4.893)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2.20 (1.407–3.433)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Right ventricular dysfunction</td>
<td>2.02 (1.303–3.129)</td>
<td>0.0070</td>
</tr>
<tr>
<td>History of VT</td>
<td>1.99 (1.230–3.217)</td>
<td>0.0050</td>
</tr>
<tr>
<td>Inpatient implantation</td>
<td>1.18 (0.775–1.806)</td>
<td>0.4364</td>
</tr>
<tr>
<td>QRS increments &gt;10 ms</td>
<td>0.921 (0.858–0.989)</td>
<td>0.0229</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia.

**Conflict of Interest:** J.P.S receives research grants and is a consultant to Medtronic, Inc., St Jude Medical, Boston Scientific, and Biotronik. J.N.R is a consultant to Medtronic, Inc. He delivers speech annually for Boston Scientific and St Jude Medical. E.K.H. is a consultant to Biotronik, Boston Scientific, Medtronic, Sorin, and St Jude Medical.

**References**