Optimization of heart failure medication after cardiac resynchronization therapy and the impact on long-term survival

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Aims
Treatment with evidence-based heart failure (HF) medication reduces morbidity and mortality, yet they remain under-used and underdosed. Cardiac resynchronization therapy (CRT) improves haemodynamics, and might allow for optimization of HF medication. We analysed treatment with HF medication after CRT implantation, long-term adherence to this treatment, and its association with patient survival.

Methods and results
This observational study included 826 consecutive patients who received a CRT device at a tertiary centre. Data were obtained from patient files and prescription data from the Danish National Prescription Registry. Doses are expressed as percentages of target doses. We used Cox proportional hazard model to compute adjusted hazard ratios (aHRs) for survival with 95% confidence intervals (CIs), adjusted for potential confounders. During the median (quartiles) follow-up of 4.4 (3.0–6.7) years, 324 patients died. Daily doses of beta-blocker (BB) (53 (27–90) vs. 43 (22–75); P = 0.001) and angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) (78 (45–100) vs. 74 (44–97); P = 0.02) had increased after 6-month follow-up compared with pre-implantation doses. After 4 years, adherence was 95% to BB and 94% to ACEi/ARB. Treatments with low (< 50%) and high (> 50%) doses were associated with prolonged survival for BB (low: aHR 0.65 (0.47–0.90); P = 0.009, and high: aHR 0.50 (0.35–0.70); P < 0.001) and for ACEi/ARB (low: aHR 0.68 (0.46–1.00); P = 0.09, and high: aHR 0.55 (0.38–0.80); P = 0.002).

Conclusion
After CRT implantation, optimization of HF treatment is possible, and long-term adherence to HF medication remains high. Higher doses of BB and ACEi/ARB were associated with prolonged survival.

Keywords
Chronic heart failure • Optimal medical therapy • Compliance/adherence • Cardiac resynchronization therapy

Introduction
Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF) due to left ventricular systolic dysfunction and intraventricular conduction delay.1–3 Prior to CRT implantation, patients are required to receive recommended, or highest tolerated dose of HF medication,4 which includes neurohormonal therapy with beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and aldosterone antagonist. In daily clinical practice, achieving target doses are often challenging due to side-effects or co-morbidity.5–9 Likewise, the long-term adherence is important to ensure optimal benefit of these therapies.10

Studies have reported that patients with CRT are treated with sub-optimal doses of HF medication.5,11 Thus after CRT implantation, re-evaluation of HF medication is important, as increase in blood pressure, improved renal function, and avoidance of bradycardia might facilitate initiation or further optimization of medical therapy in patients who previously did not tolerate this treatment.4 Accordingly, recent studies indicated that higher doses of HF medication are achieved after CRT implantation,11,12 as well as in patients with CRT when compared with patients without such device.5

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The purpose of this study was to describe the changes in HF medication during the first 6 months after CRT implantation and the adherence to medical therapy during long-term follow-up. Furthermore, we aimed to examine patient survival according to doses of HF medication after CRT implantation.

Methods
Study population
We screened a cohort of 1101 consecutive patients who received their first CRT device at Aarhus University Hospital, Denmark between 2000 and 2010. Of those, 936 patients had reduced left ventricular ejection fraction (LVEF) (≤35%) and a wide QRS complex (≥120 ms). We excluded patients who died, underwent heart transplantation or system downgrade to implantable cardioverter-defibrillator (ICD) or cardiac pacemaker within 225 days of implantation to ensure a 90-day period for calculation of daily drug doses around the point in time of 6 months after implantation, resulting in a study cohort of 826 patients. Patients were followed until September 2013. The study was approved by the Danish Health and Medicines Authority and the Danish Data Protection Agency.

Clinical data
We collected clinical, electrocardiographic, and echocardiographic data retrospectively by review of all patient medical charts at baseline and during follow-up. One investigator (C.T.W.) performed this review. All patients underwent follow-up at 1 and 6 months after implantation, and afterwards every 6 months at their local hospital. Patients who had an improvement in New York Heart Association (NYHA) functional class from baseline to the 6-month follow-up visit were defined as responders.

The primary outcome was all-cause mortality, and patients were censored at the time of heart transplantation, or system downgrade to ICD or cardiac pacemaker. Information on vital status and date of death was obtained from the Danish Civil Registration System. All data sources were linked by the use of the personal identification number, a unique identifier assigned to all Danish residents.

Medical treatment
In Denmark, information of all prescriptions dispensed from Danish pharmacies since 1995 are recorded in the Danish National Prescription Registry. The prescriptions are coded according to the Anatomic Therapeutical Chemical system. The registry includes information about the dispensing date of the prescription, the strength of the drug, and the total number of tablets dispensed, but no information about the prescribed dose of the individual drug.

Initiation of medical therapy was defined as the date of claiming a prescription. The daily dose of BB, ACEi/ARB, aldosterone antagonist, and loop diuretics was calculated from the average daily dose given during a 90-day period, which could include more than one prescription. If a dose was administered for <40 consecutive days during the 90-day period, it was counted as no treatment. Doses were assessed in a 90-day period prior to implantation, and subsequently at 6 months, 1, 2, 3, and 4 years after implantation in a period from 45 days before until 45 days after each time point. Doses are presented as the percentage of target dose according to guidelines, except for loop diuretics, which was presented as milligram equal to treatment with furosemid. The presented mean daily doses represent doses prescribed among patients who received medication. The following daily target doses were used for the most frequently prescribed drugs: carvedilol 50 mg; metoprolol 200 mg; bisoprolol 10 mg; ramipril 10 mg; trandolapril 4 mg; losartan 50 mg; enalapril 20 mg; spironolactone 50 mg. During the study period, the daily target dose of losartan increased from 50 to 150 mg. We set the target dose at 50 mg per day until end 2009 and 150 mg per day afterwards. Doses of BB and ACEi/ARB prescribed were divided into three groups according to percentage of target dose 6 months after implantation: 0 (no), 1–50% (low), and >50% (high). We defined adherence to medical therapy as the continued treatment during follow-up in patients receiving an HF medication 6 months after implantation, and reported proportion of those adherent each year after implantation.

Statistical analysis
Distributions were tested for normality using Q–Q plots and histograms. Continuous data are reported as mean and standard deviation (SD) if normally distributed and as median with 25th–75th interquartile range (IQR) if non-normally distributed. Categorical data were presented as number and percentage. When differences were assessed between implantation and 6 months after, data were analysed as paired data, based on paired Student’s t-test or McNemar’s test. If non-paired, differences between groups were assessed by χ² test, Student’s t-test, or a non-parametric test as appropriate.

Patients were followed from 225 days after implantation, which was defined as the index date, and until the date of death, heart transplantation, system downgrade to ICD or cardiac pacemaker, or the end of follow-up, whichever came first. Hazard ratios (HRs) and adjusted HR (aHR) of survival with 95% confidence intervals (CIs) were estimated, using Cox proportional hazard models. We adjusted for a priori selected confounders; gender, age, estimated glomerular filtration rate (eGFR) in the two groups (<60 vs. ≥60 mL/min/1.73 m²), QRS width, LVEF, heart rate, systolic blood pressure, NYHA functional class, the presence of coronary artery disease, ICD-backup, left bundle branch block (LBBB), chronic obstructive lung disease, diabetes mellitus and history of atrial fibrillation at the time of implantation, and diuretic treatment at 6 months. The survival curves represent the hazard estimates based on the adjusted Cox model. Owing to the long inclusion period, we choose to adjust for early or late implantation (implantation before or after January 2005). The proportional hazard assumption was evaluated for all variables by comparing estimated log-log survivor curves, and tests for interactions were performed by inclusion of an interaction term in the analysis. A P-value of <0.05 was considered significant. All statistical analyses were performed using the STATA software (STATA Inc. for Windows, version 12).

Results
A total of 826 patients were included in the study cohort. Reasons for exclusion were QRS width <120 ms (99 patients), LVEF >35% (66 patients), or follow-up for <225 days due to death, heart transplantation, or system downgrade (110 patients). No patients were lost to follow-up. Patient characteristics at CRT implantation are presented in Table 1. The median follow-up after implantation was 4.4 years (3.0–6.7), during which 324 patients (39%) died, 19 patients underwent heart transplantation, and 10 patients had their system downgraded to an ICD or cardiac pacemaker without CRT.

Change in heart failure medication after cardiac resynchronization therapy implantation
Six months after implantation, the proportion of patients who received BB had increased (88 vs. 75%; P < 0.001) with an increase
in daily dose (median 53 vs. 43%; P < 0.001) (Table 2), and a higher proportion of patients received high dose of BB (48 vs. 32%; P < 0.001) when compared with baseline. The proportion of patients treated with ACEi/ARB was unchanged at 6 months (91 vs. 90%; $P = 0.75$) as well as the proportion of patients who received high dose of ACEi/ARB (63 vs. 63%; $P = 0.96$). An increase in daily dose was however observed (median 78 vs. 74%; $P = 0.02$). Overall, the proportion of patients who reached doses equal to target doses of BB or ACEi/ARB at 6 months was 21 and 37%, respectively. The most commonly prescribed BBs were metoprolol (33%) and carvedilol (63%), while ramipril (35%), trandolapril (19%), and losartan (14%) were the most commonly used ACEi/ARBs. There was no difference in the proportion of patients treated with aldosterone antagonists (59 vs. 58%; $P = 0.28$) or daily doses (median 49 vs. 51%; $P = 0.46$) at 6-month follow-up compared with pre-implantation doses. More patients seemed to receive loop diuretics (82 vs. 79%; $P = 0.05$), but daily dose was unchanged (median 80 vs. 80 mg; $P = 0.22$) 6 months after implantation.

At baseline, patients who were uptitrated with BB within the first 6 months after CRT implantation were more likely to receive diuretics and an ICD, and those uptitrated with ACEi/ARB were younger and had better renal function. Otherwise, the patients’ baseline characteristics were similar.

In general, patients treated with high dose of BB and ACEi/ARB after 6 months had less co-morbidity than those who either received no or lower doses. Thus, patients who received high dose of BB were younger (67 (60–73) vs. 70 (63–76) years; $P < 0.001$), had higher systolic blood pressure (119 ± 17 vs. 116 ± 18 mmHg; $P = 0.004$), better renal function (eGFR: 66 ± 25 vs. 58 ± 27 mL/min/1.73 m²; $P < 0.001$), less symptomatic (NYHA class; 2.68 ± 0.54 vs. 2.81 ± 0.57; $P = 0.001$), higher body mass index (26 (24–30) vs. 25 (23–29) kg/m²; $P < 0.001$), and were less likely to have coronary artery disease (47 vs. 56%; $P = 0.008$) and a diagnosis of chronic obstructive lung disease (14 vs. 21%; $P = 0.013$). Similarly, patients treated with high dose of ACEi/ARB were younger (67 (59–73) vs. 71 (63–76) years; $P < 0.001$), had higher systolic blood pressure (119 ± 17 vs. 116 ± 17 mmHg; $P = 0.004$), better renal function (eGFR: 66 ± 25 vs. 57 ± 25 mL/min/1.73 m²; $P < 0.001$), and higher body mass index (26 (24–30) vs. 25 (23–29) kg/m²; $P < 0.001$). No difference was found in regard to LVEF, heart rate, history of atrial fibrillation, or diabetes mellitus between patients who received low vs. high dose of either ACEi/ARB or BB.

### Adherence to heart failure medication during follow-up

During the long-term follow-up, both the proportion of patients who received HF medication and the proportion of patients who received higher dose remained high after 4 years of follow-up (Figure 1). The adherence was 95% for BB and 94% for ACEi/ARB at 4 years. Mean daily dose for BB and ACEi/ARB remained stable at 1, 2, 3, and 4 years (BB: 58 (29–95)%; 56 (34–95)%; 63 (35–96)%; 59 (36–96)%; ACEi/ARB: 78 (45–100)%; 77 (41–100)%; 76 (43–99)%; and 82 (44–100)%, respectively). Adherence to aldosterone antagonist decreased within the first 2 years, and was 77% at 4 years.

### Long-term survival and heart failure medication

When compared with no medication, the intake of BB and ACEi/ARB in low or high dose after 6 months was associated with significantly better survival (Figure 2). After adjustment for a priori selected variables, both low and high doses of BB and ACEi/ARB were associated with prolonged survival (Table 3). The higher dose of both BB and ACEi/ARB was associated with prolonged survival when compared with the lower dose (BB: aHR, 0.76; 95% CI 0.59–0.99; $P = 0.04$ and ACEi/ARB: aHR, 0.82; 95% CI 0.63–1.06; $P = 0.13$), although the association was statistically significant only for BB. Patients not treated with diuretics had better survival than those who received diuretics, both in unadjusted and adjusted analyses. No association was observed between treatment with aldosterone antagonists and all-cause mortality in unadjusted or adjusted analysis.
Heart failure medication in responders to cardiac resynchronization therapy

In 791 of the patients (96%), NYHA functional class was available at 6-month follow-up and of those, 410 patients (52%) were classified as responders. The proportion of responders was higher in patients with LBBB or right ventricular pacing than in those who had right bundle branch block or non-specific intraventricular conduction delay at baseline (56 vs. 41%; \( P = 0.001 \)). More responders received treatment with ACEi/ARB at 6 months (94 vs. 84%; \( P = 0.01 \)), and there was a trend towards a higher mean daily dose in responders when compared with non-responders (85 (46–100) vs. 76 (44–99)); \( P = 0.09 \). Responders received a lower dose of diuretics when compared with non-responders (60 (40–120) vs. 90 (40–160) mg; \( P < 0.001 \)). There was no difference in the proportion of patients treated or the mean daily doses prescribed between responders and non-responders for BB and aldosterone antagonist.

Discussion

This study indicates that optimization of treatment with BB and ACEi/ARB is possible after CRT implantation in an unselected cohort of patients with HF, and that adherence to HF medication remains high with sustained mean doses during the 4-year follow-up. Treatment with higher doses of BB and ACEi/ARB at 6 months is associated with prolonged long-term survival after CRT implantation.
Medical therapy with BB and ACEi/ARB reduces mortality and morbidity in patients with left ventricular systolic dysfunction,\textsuperscript{16–18} and studies have indicated an increased benefit with higher doses.\textsuperscript{19,20} Current guidelines therefore recommend doses comparable with those used in the clinical trials or maximum tolerable doses.\textsuperscript{15} The addition of a CRT device to medical therapy improves

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**Table 3**  Long-term risk of all-cause mortality according to heart failure medication and doses of heart failure medication assessed at 6 months

|                  | Unadjusted |            |            |            |                |            |            |                |            |
|------------------|------------|------------|------------|------------|----------------|------------|------------|----------------|------------|
|                  | HR         | 95% CI     | P-Value    | HR         | 95% CI        | P-Value    |
| BB               |            |            |            |            |                |            |            |                |            |
| No treatment     | Reference  |            |            |            |                |            |            |                |            |
| Low              | 0.71       | 0.52–0.96  | 0.027      | 0.65       | 0.47–0.90     | 0.009      |
| High             | 0.43       | 0.31–0.59  | <0.001     | 0.50       | 0.35–0.70     | <0.001     |
| ACEi/ARB         |            |            |            |            |                |            |            |                |            |
| No treatment     | Reference  |            |            |            |                |            |            |                |            |
| Low              | 0.54       | 0.38–0.78  | 0.001      | 0.68       | 0.46–1.00     | 0.05       |
| High             | 0.39       | 0.28–0.55  | <0.001     | 0.55       | 0.38–0.80     | 0.002      |
| Aldosterone      | 0.88       | 0.71–1.10  | 0.27       | 1.05       | 0.82–1.34     | 0.70       |
| Loop diuretics   | 2.60       | 1.76–3.83  | <0.001     | 1.56       | 1.04–2.34     | 0.03       |

Beta-blockers and ACEis/ARBs were divided into three groups according to percentage of target dose; no treatment, low (1–50%), and high (>50%) doses. Aldosterone antagonists and loop diuretics were divided into two groups, according to the presence or absence of treatment.

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**Figure 2**  The survival estimates of all-cause mortality according to doses of heart failure medication 6 months after cardiac resynchronization therapy implantation. The curves represent the hazard estimate obtained from the adjusted Cox model described under the statistical analysis. Doses of beta-blocker and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker are divided into three groups: 0%, 1–50%, and >50% of target doses, and aldosterone antagonists and loop diuretics into two groups: patients with or without treatment. Follow-up started 225 days after implantation.
survival in a subgroup of these patients; however, patients with CRT are often treated with doses of HF medication below those recommended in guidelines. Treatment with CRT improves haemodynamics and clinical symptoms, and prevents bradycardia, which might allow further optimization of treatment with BB and ACEi/ARB. The present large-cohort study demonstrates that uptitration and initiation of HF medication is indeed possible after CRT implantation, supporting and strengthening the findings from prior studies. We have no detailed information regarding the plantation, supporting and strengthening the findings from prior ARB. The present large-cohort study demonstrates that uptitration might allow further optimization of treatment with BB and ACEi/ARB. The effect of loop diuretics on mortality is largely unknown, and thus diuretics are mainly prescribed to relieve symptoms of congestion. Treatment with diuretics should be adjusted to maintain lowest effective doses. Our findings that responders to CRT received lower doses of loop diuretics compared with non-responders, as well as shorter survival among patients treated with diuretics are similar to other studies, and likely reflect that diuretics are needed for the sickest patients with the worst prognosis.

This study has important implications for the clinical strategy of follow-up after CRT implantation. We found that higher doses of HF medication were associated with prolonged survival in patients with CRT. Therefore, optimization of medical therapy should be attempted after CRT implantation. Furthermore, this study indicates that patient’s compliance to these medications can be maintained at a high level during the long-term follow-up.

**Limitations**

The major limitations of the present study are those inherent for observational studies. Given the Danish healthcare system’s partially reimbursement of expenses for medication, all Danish pharmacies are required to register all dispensed drug prescriptions, which ensures complete registration of the HF medication data. The study was restricted to include only patients with more than 8 months of follow-up, and the findings regarding survival therefore are valid only beyond that period. The association observed between higher doses of medical therapy and survival might in part be caused by confounding-by-indication, as a number of poor prognostic patient factors were statistically associated with lower doses of BB and ACEi/ARB. Furthermore, the use of only one target dose for each drug might have led to a simplification when comparing drug doses, since individual patient characteristics could have made the physicians choose different target doses. We defined responders according to improvement in NYHA class, as an echocardiogram was available in only 57% of the patients within the first 12 months after implantation. Although our responder rate is lower than previously reported by observational studies, our percentage of responders are consistent with the numbers from the clinical trials. However, this study included a large cohort of consecutive CRT patients with a complete and long-term follow-up, and the point-estimates indicating beneficial effect of higher doses of ACEi/ARB and BB were quite robust and consistent in unadjusted and adjusted analyses.

**Conclusion**

This study indicates that optimization of treatment with BB and ACEi/ARB is possible after CRT implantation in a large unselected cohort of patients, and that the adherence to HF medication remains high with sustained daily doses during the 4-year follow-up. Treatment with higher doses of BB and ACEi/ARB at 6 months is associated with prolonged long-term survival after CRT implantation.
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