VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2017, Vol. 24, No. 4, 374–384
DOI: 10.5603/CJ.a2017.0019

ISSN 1897–5593

Cardiovascular drug utilization post-implant is related to clinical outcome in heart failure patients receiving cardiac resynchronization therapy

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Abstract

Background: *In select patients with heart failure, cardiac resynchronization therapy (CRT) is the most common complementary treatment besides medical treatment. We aimed to assess the association between post CRT-implant changes in cardiovascular medication and cardiovascular mortality and heart failure hospitalization.*

Methods: *211 patients on optimal medical therapy eligible for CRT were retrospectively included in this study (72 ± 7 years, 80% male, 66% left bundle branch block, 48% dilated cardiomyopathy and investigated at baseline and after 6 months. Follow-up with medication, biochemical markers and echocardiography was performed and 3-year mortality data was collected.*

Results: *At 6 months post-implant the cohort was divided into two groups; 157 patients had low dosage furosemide treatment (up to 40 mg) and 54 patients were treated with high dosage (> 40 mg). A composite endpoint of heart failure hospitalization and all-cause mortality was evaluated at 30 months (881 ± 267 days) after the 6-month visit. In multivariate Cox regression analysis, patients in the high dose diuretics group had a higher risk of the primary endpoint (HR 1.9 [1.1–3.4], p = 0.033), but treatment with high dose diuretics was not associated with improved clinical symptoms (r = 0.031, p = 0.64).*

Conclusions: *High dosage of loop-diuretics was associated with worse medium-term clinical outcome in CRT treated patients. It is unclear whether there is a direct causality between these associations, or if higher prescribed dosage of loop-diuretics is just a marker of more severe disease. Higher dose loop diuretics do not necessarily improve the symptoms and may be harmful to the patient. Prospective trials are warranted to further elucidate these findings.* (Cardiol J 2017; 24, 4: 374–384)

Key words: cardiac resynchronization therapy, heart failure, dilated cardiomyopathy, ischaemic heart failure, medical therapy, loop diuretics

Introduction

Heart failure (HF) is a common cause of death in developed countries [1]. In the last decade cardiac resynchronization therapy (CRT) has emerged as a complement to medical therapy in patients with wide QRS and impaired left ventricular ejection fraction [2, 3]. Large randomized trials have demonstrated the advantage of CRT, however 30–40% of the patients have no perceived benefit; so called non-responders. The reason for non-response seems to be multifactorial, and data from different trials suggest that patient selection, electrode placement, and optimization of therapy at follow-up all play a role [4–10]. Medical

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Received: 23.07.2016 Accepted: 23.11.2016

therapy with beta-blockers, angiotensin converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARBs) and aldosterone antagonists [11–13] are all important in HF treatment with proven long term benefits in terms of morbidity and mortality [14]. Aldosterone receptor inhibitors are also an important part of the medical therapy; however, they are less-tolerated mainly due to the elevated serum potassium level [15]. Angiotensin receptor blocker with neprilysin inhibitor (ARNI), as a new medical treatment is on the horizon for HF population, however the long-term effect of the treatment is unknown, and there are no data about this therapy in the CRT population [16]. The potential risks and benefits by changing the medication for CRT-treated patients are less documented, and it is still unclear to what extent changes in medical therapy can influence clinical outcome in this subpopulation. Data regarding medication changes and prognostic outcome is lacking for CRT-treated patients outside the clinical trial setting, but could add knowledge concerning clinical prognosis for these patients. A few studies have suggested that loop diuretic therapy is associated with higher mortality in non-CRT HF patients [17], but only one prospective study has evaluated this in a HF population with mild symptoms after CRT implantation [18]. The aim in this study was to assess the association between the efficacy and clinical outcome of CRT in relation to concurrent use of HF medications, more specifically loop-diuretic therapy due to its ambiguous effect on morbidity and mortality.

Methods

Consecutive patients receiving CRT in a tertiary Swedish centre between 2011 and 2014 were included retrospectively. All patients had indications for CRT according to the European Society of Cardiology (ESC) recommendations [19, 20]. Patients were on HF therapy with the highest tolerable dosage of beta-blocker and ACEI/ARB prior to implantation. Mortality data up to 4 years was extracted from the Swedish National Cause of Death Registry. Clinical data was evaluated at 6-month post-implant, and retrospectively collected for baseline parameters. Prior to implantation, all patients had an assessment of their preoperative functional clinical status. Subjective clinical improvement and New York Heart Association (NYHA) classification was assessed by the study physician 6 months after the implantation. A subset of patients had available preoperative and follow up data from standardized HF questionnaires (Minnesota living with heart failure questionnaires [MLHFQ]) and quality of life questionnaires (EQ5D). Medical information, 12-lead electrocardiogram (ECG), laboratory examinations and a standardized echocardiography protocol was extracted from the local electronic medical record system. Written informed consent was collected before the enrolment and the local ethics committee approved the study.

Medication

Information about beta-blockers, ACEI, ARBs, statins, diuretics, aldosterone inhibitors, thrombocyte aggregation inhibitors, oral anticoagulation drugs were collected at baseline and 6 months. Changes in dosages and between substances were recorded, which was initiated under the supervision of the treating physician. Optimal medical therapy was considered as the highest tolerable dosage of beta-blocker and ACEI or ARB as criteria for CRT treatment. Loop diuretic therapy was indicated according to the ESC recommendation [14] and the decision making about changes in medication over time was at the discretion of the treating physicians.

Heart failure symptom evaluation

Minnesota living with heart failure questionnaires (MLHFQ) [21–23] and standardized instrument for use as a measure of health outcome (EQ5D) [24] formularies and Self Rated Health (EQ VAS) questionnaires were filled in and collected at baseline and 6 months after the implantation. NYHA classification at baseline and at the 6 month visit was evaluated and the enrolled study subjects were directly asked about subjective improvement.

Echocardiography

Preoperative and at 6-month echocardiography was performed in all patients. Off-line analysis was performed with Echopac BT12 software (Echopac BT12, GE Medical, Hortens, Norway). Left ventricular (LV) volumes and ejection fraction (EF) were measured with Simpson's biplane method [25]. Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured, and LVESV index were calculated (LVESVi) [26–30]. Mitral regurgitation (MR) was graded 0–3 according to current guidelines [31]. Septal to posterior wall motion delay was measured as the shortest interval between the maximal displacement of the septum and the posterior wall in milliseconds using 2-dimensional papillary muscle level short axis view [32].

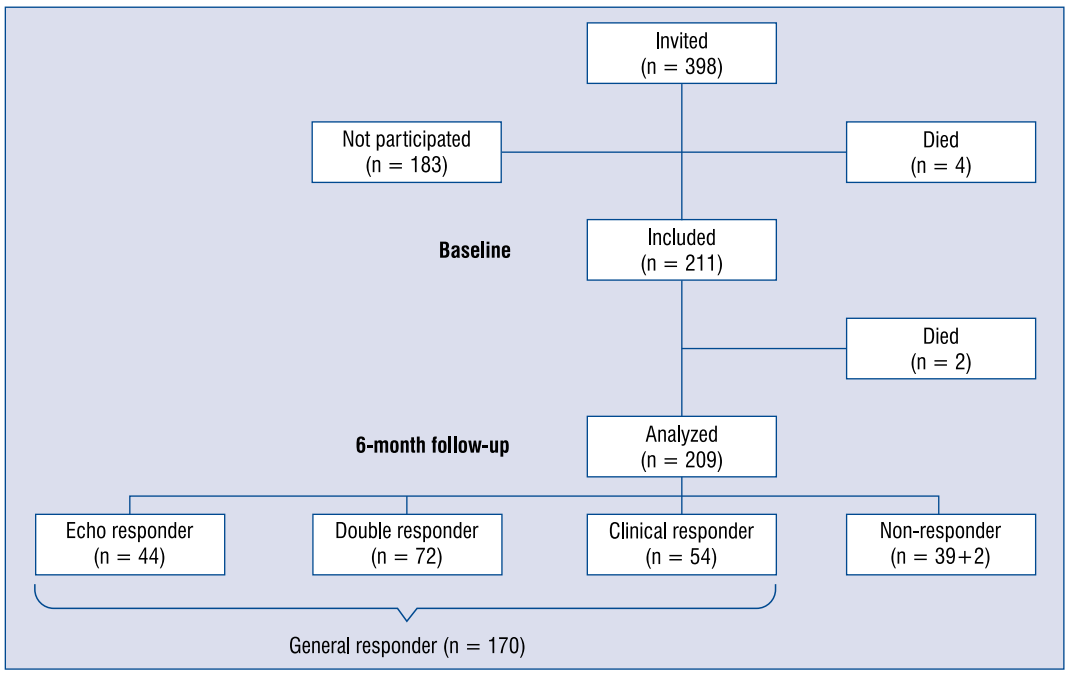

Figure 1. The flow chart demonstrates the inclusion process and the response to the cardiac resynchronization therapy. The different type of response are also represented on the figure.

Definition of positive response to CRT

At least 15% reduction or more of the LVESV [33] was considered as reverse remodeling and positive echocardiographic response to the therapy. Positive clinical response was defined as ≥ 1 NYHA class improvement.

Device implantation and follow up

Device implantation was performed using left subclavian vascular access. A lateral or posterolateral coronary sinus branch was targeted for the LV lead positioning. The majority of patients (n = 128) received a St. Jude Quickopt®-algorithm capable device using the algorithm recommended settings. The rest of the patients (n = 83) received a Medtronic device, with fixed atrio-ventricular delays of 120/150 ms and simultaneous VV-times.

End point of the study

The primary endpoint of the present study was death, and secondary endpoint was death or hospitalization for HF. The diagnosis of HF was based either on the medical records or on the record linkage with the national Swedish Patient Registry, if the primary cause of hospitalization was listed as HF.

Statistical analyses

SPSS statistical software was used for data analysis (IBM, SPSS ver.: 21. 2012). Continuous variables are expressed as means (± standard deviation [SD]), categorical variables are presented as frequencies and percentages. For non-normally distributed continuous variables the median value with interquartile range (IQR) is presented. Differences between groups were assessed using paired and unpaired Student t-tests for continuous variables, Mann-Whitney U test for variables with non-Gaussian distribution, and the χ^2 test for categorical variables, or the Fisher's exact test for unordered categorical variables as appropriate. For survival analysis Kaplan-Meier method with log-rank test were used to analyze the cumulative events. Cox regression analysis was used to determine the Hazard ratio (HR) with 95% confidence interval (CI) for clinical endpoints. The proportional hazards assumption was tested by log minus log curves and was met. Variables with a $p < 0.10$ were then entered into a multivariate model. Pearson's r test was performed to calculate the correlation coefficient. A two-sided p-value < 0.05 was considered statistically significant.

Results

Clinical characteristics of the overall study population

The group of 398 patients were invited and 211 of these were enrolled. The inclusion process is summarized in Figure 1. The included patients were divided in two subgroups, depending the dosage of

Table 1. Study population characteristics. The first column represents the whole study population. The second and third columns show the two groups with low and high dose diuretics. The last column shows the p-value for difference between the subgroups.

	Overall	Group I (n = 157)	Group II (n = 54)	P
Age [years] ± SD	71.6 ± 7	71.5 ± 8	71.6 ± 8	0.96
QRS duration [ms]	164	163	166	0.29
Male	80%	80%	85%	0.37
Ischemic cardiomyopathy	52%	47%	68%	**0.01**
Hypertension	59%	55%	74%	**0.02**
Presence of diabetes	23%	19%	35%	**0.02**
Renal failure	13%	11%	18%	0.16
History of AF	50%	48%	61%	0.12
History of CABG	29%	26%	41%	0.06
History of MI	52%	46%	68%	**0.01**
CRT-P	24%	24%	24%	1
LBBB/Non LBBB/PM	66%/18%/16%	67%/19%/14%	57%/20%/22%	0.31
Echo responder	62%	59%	65%	0.47
Clinical responder	58%	61%	54%	0.42

AF — atrial fibrillation; CABG — coronary artery bypass surgery; CRT-P — cardiac resynchronization therapy without defibrillator function; ICMP — ischemic cardiomyopathy; LBBB — left bundle branch block; MI — myocardial injury/infarction; PM — pacemaker rhythm; SD — standard deviation

Table 2. Medical therapy for the two groups at baseline and at 6 months (%). The last column shows the p-value for difference between the subgroups.

Medication (in %)	Group I (n = 157)	Group II (n = 54)	P
Baseline			
Beta-blocker	87	92	0.33
ACEI/ARB	96	93	0.28
Digoxin	12	13	0.76
Statin therapy	60	70	0.56
Aldosterone antagonist	49	65	0.09
Thiazide diuretics	4	5	0.65
6-month follow up			
Beta-blocker	86	92	0.41
ACEI/ARB	89	89	0.29
Digoxin	11	12	0.26
Statin therapy	56	72	0.40
Aldosterone antagonist	45	76	**0.01**
Thiazide diuretics	4	5	0.62

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker

the loop diuretics at 6-month follow up. Based on previous studies, the cut-off value between low and high dosage of furosemide was set at 40 mg [17]. In the low dose group (Group I) the patients had loop diuretic treatment with furosemide up to 40 mg (n = 157). Patients with > 40 mg furosemide were classified as high dose group (Group II, n = 54). The baseline characteristics of the whole cohort and the two subgroups are presented in Table 1.

The medical therapy initially included beta-blocker in 89%, ACEI/ARB in 96% and aldosterone blockade in 58% of the patients. At 6 months, 87% were on a beta-blocker, 92% on an ACEI/ARB and 53% were on aldosterone therapy. Table 2 shows

information about the HF therapy, comparing baseline and 6-month visit data: At baseline, 68% of the patients were on loop diuretic therapy, and at 6 months the corresponding percentage was 62% on loop diuretic therapy (p = 0.006). In Group I the percentage of patients with loop diuretic therapy decreased significantly (58% preoperatively vs. 49% at 6-month follow-up, p = 0.002), however similar changes were not observed in Group II (96% at baseline vs. 100% at 6-month follow-up, p = 0.32). The mean furosemide dose in Group I pre-implant was 42 ± 17 mg, which was decreased to 36 ± 7 mg (p = 0.01) at 6 months. In Group II the initial mean dosage of the furosemide was 100 ± 65 mg at baseline, and it increased to 115 ± ± 85 mg at 6 months (p = 0.11).

Biochemical markers

At baseline, slightly elevated creatinine in Group II was observed compared with Group I (124 ± 49 μmol/L vs. 103 ± 60 μmol/L, p = 0.09) and at 6 months, the difference became significant (126 ± 58 μmol/L vs. 108 ± 50 μmol/L, p = 0.03). However, the change of the creatinine level from baseline to 6-months within the respective groups did not differ significantly (p = 0.16, p = 0.44). The N-terminal pro B-type natriuretic peptide (NT-proBNP) in Group II improved significantly (from median 3848 ng/L [IQR: 3575] to 2039 ng/L [IQR: 2311], p = 0.03) as well as in Group I (from 3695 ng/L [3581] to 2740 ng/L [2427], p = 0.05). However, no significant difference at baseline (p = 0.73) or at follow-up (p = 0.69) was found in NT-proBNP levels, between the two groups.

Association between cardiovascular medication and clinical improvement

Self-assessed quality of life pre-implant (1–100 scale) was similar in the two groups (57 ± 21 vs. 59 ± 20, p = 0.78). However, at the 6-month follow-up, patients in Group I had a better overall subjective health assessment compared to patients in Group II (69 ± 18 vs. 62 ± 20, p = 0.03). The mean NYHA classification at baseline was similar in both subgroups. Sixty-six percent of the patients showed improvement in NYHA class and the improvement in both groups were similar during the 6-month follow-up, as presented in Table 3 (p < 0.01 in both group). Improvement of the NYHA class was neither correlated to aldosterone antagonist therapy (r = 0.08, p = 0.25), nor to loop diuretic treatment (r = 0.03, p = 0.64) or beta-blocker therapy (r = 0.001, p = 0.99) at 6-months. No correlation was observed between baseline beta-blocker (r = 0.03, p = 0.62), aldosterone inhibitor (r = 0.03, p = 0.61), or loop diuretic (r = 0.04, p = 0.54) therapy and clinical improvement. In contrast, clinical improvement did show a correlation with baseline ACEI/ARB therapy (r = 0.17, p = 0.01) and 6 month ACEI/ARB therapy (r = 0.15, p = 0.03).

Association between cardiovascular medication and reverse remodeling

Sixty-one percent of the patients (n = 128) showed more than 15% reduction in the LVESV (64% in Group I, 56% in Group II, p = 0.37). The overall mean LVEF improved in the whole population (from 27 ± 8% to 35 ± 13% p = 0.001). Correlations between reverse remodeling and HF medications were tested. Reduction in LVESV showed a positive trend in correlation with baseline beta-blocker (r = 0.117, p = 0.049) and ACEI (r = 0.283, p = 0.066) therapy. However, diuretic therapy with furosemide (r = 0.042, p = 0.58) or aldosterone inhibitors (r = 0.047, p = 0.54) was not associated with reverse remodeling. Improvement of the LVEF showed no correlation with the loop diuretic therapy (r = 1, p = 0.38) or with aldosterone antagonist treatment (r = 0.08, p = 0.3). The mitral regurgitation improved during this 6 month follow up (p < 0.01). Initially 28 patients had grade II and only 2 patients had grade III mitral regurgitation. At 6 month control the mitral regurgitation had improved, only 6 patients had grade II regurgitation, and only 1 patient had grade III regurgitation due to mitral prolapse. The improvement of the regurgitation was not correlated with the dose of the diuretic therapy (r = 0.02, p = 0.85).

Association between cardiovascular medication and clinical endpoints

During the whole follow up period (826 ± 331 days) 26 deaths and 27 hospitalizations for HF were observed. 14 patients were hospitalized due to HF and 2 patients died before the 6-month follow up visit in sudden cardiac death despite CRT-D, and these events were excluded from the outcome analyses. During the remainder of the follow-up, 13 deaths occurred in Group I and 11 deaths were observed in Group II. The effect on clinical outcome of medical therapy using ACEI/ARBs, beta-blockers or aldosterone antagonists was examined by univariate Cox regression analysis. In the univariate Cox regression analysis, high dose loop diuretic therapy was associated with a HR of 1.94 (95% CI 1.11–3.376). Accordingly, in Kaplan-Meier analysis a significant difference was found

Table 3. Biochemical marker levels, clinical symptoms and echocardiographic parameters for the two groups at baseline and at 6 months. The last column shows the p-value for difference between the subgroups. The Δ-values show the mean (± standard deviation) difference between the baseline and 6-month values of each parameter.

Variable	Group I (n = 157)	Group II (n = 54)	P
Biochemistry			
Baseline creatinine [μmol/L]	103 ± 89	124 ± 49	0.09
6-month creatinine [μmol/L]	108 ± 50	126 ± 58	**0.03**
Baseline hemoglobin [g/L]	136 ± 14	132 ± 16	0.12
6-month hemoglobin [g/L]	137 ± 13	135 ± 16	0.34
Baseline NT-proBNP [ng/L]	3615 ± 5617	3950 ± 5384	0.73
6-month NT-proBNP [ng/L]	2646 ± 5295	2314 ± 2950	0.69
Clinical markers			
Baseline MLWHF	40 ± 20	44 ± 25	0.55
6-month MLWHF	27 ± 20	39 ± 24	**0.001**
Baseline EQ5D	5.7 ± 3.7	5.4 ± 3.8	0.76
6-month EQ5D	6.1 ± 2.5	6.2 ± 3	0.75
Baseline EQ-VAS	57 ± 21	59 ± 20	0.78
6-month EQ-VAS	69 ± 18	62 ± 20	**0.03**
NYHA baseline	2.4 ± 0.8	2.4 ± 0.8	0.95
6-month NYHA	1.7 ± 0.6	1.7 ± 0.7	0.76
Echocardiography			
Baseline LVESV BP [mL]	141 ± 53	173 ± 81	**0.03**
Baseline LVEDV BP [mL]	196 ± 65	228 ± 92	**0.02**
Baseline LVEF BP [mL]	27 ± 8	25 ± 8	0.14
6-month LVESV BP [mL]	112 ± 52	141 ± 85	**0.03**
6-month LVEDV BP [mL]	164 ± 60	205 ± 97	**0.01**
6-month LVEF BP [mL]	36 ± 15	33 ± 8	0.23
Baseline mitral regurgitation	1 ± 0.57	1.1 ± 0.51	0.80
6-month mitral regurgitation	0.81 ± 0.51	0.86 ± 0.46	0.62
Difference between the baseline and 6-month values			
Δ LVESV BP [mL]	32 ± 40	32 ± 50	0.97
Δ LVEDV BP [mL]	32 ± 51	25 ± 58	0.40
Δ LVEF BP [mL]	8 ± 15	7 ± 9	0.48

BP — biplane view; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end diastolic volume; LVESV — left ventricular end systolic volume; MLFHQ — Minnesota living with heart failure questionaires; NT-proBNP — N-terminal pro B-type natriuretic peptide

between the two groups (p = 0.03; Fig. 2). Absence of beta-blocker or aldosterone antagonist therapy showed no influence on the primary endpoint using univariate analysis, but ACEI/ARB therapy significantly reduced risk (HR = 0.35, 95% CI 0.123–0.988, p = 0.04). In the multivariate Cox regression model, high dose diuretic therapy adjusted for age, sex, aetiology, renal disease, showed a HR of 2.1 (95% CI 1.0–4.2, p = 0.04) for the primary endpoint. None of the other variables, such as ischemic etiology of HF (p = 0.82, HR = 0.93, 95% CI 0.49–1.78), renal disease (p = 0.57, HR = 1.27, 95% CI 0.553–2.91), or echocardiographic response (p = 0.96, HR = 0.98, 95% CI 0.57–1.7) showed independent predictive value for clinical outcome.

Association between diuretic therapy and cardiac device type was noted. Fifty patients received CRT without defibrillator function (CRT-P) device and the majority of the population (n = 161) had CRT with defibrillator function (CRT-D) implanted. The distribution of CRT-D therapy was similar in Group I and Group II (75% vs. 74%, p = 0.9). As expected, the CRT-P patients were older (76 ± 9 vs. 70 ± 9 years, p = 0.001), but had sim-

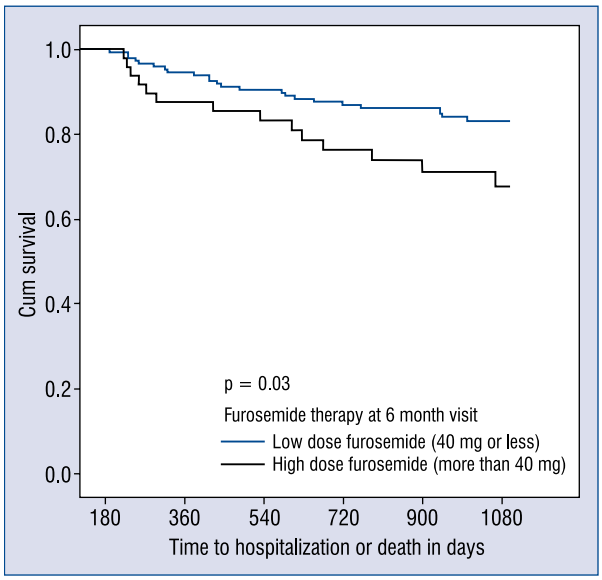

Figure 2. Kaplan-Meier curve is showing the event free survival in patients with low (Group I) and high (Group II) dose diuretics respectively. The curve is a landmark analysis reset at the 6-month follow-up visit.

ilar NYHA class (2.6 ± 0.5 vs. 2.5 ± 0.6, p = 0.07) at baseline. The NYHA class improvement was slightly better in the CRT-D treated patients at 6 months (1.8 ± 0.6 vs. 1.9 ± 0.6, p = 0.055). In patients with CRT-D devices, no prognostic difference was found when stratifying for diuretic therapy dosage (Group I: n = 120 vs. Group II: n = 41, p = 0.15) regarding composite clinical end points (Fig. 3A), but in patients with CRT-P devices low dose diuretic therapy (Group I: n = 37) patients had a better survival compared with higher dosages (Group II: n = 13), p = 0.02 (Fig. 3B).

Discussion

Our main finding in this observational study suggests that higher dosage loop diuretic therapy at follow up is independently associated with increased risk for medium term death or HF hospitalization. It is unclear whether the diuretic therapy itself creates an unfavourable circumstance or the lack of positive improvement leads to higher dosage treatment for symptom relief. Patients who required higher diuretic treatment were older and had higher prevalence of hypertension, ischemic heart disease and diabetes mellitus. This finding also supports, that more ill patients often require more diuretic therapy, mainly due to dyspnoea or fluid retention.

The survival and clinical benefit of the CRT is well studied, however the risk of unfavourable events with loop diuretics is less studied in this

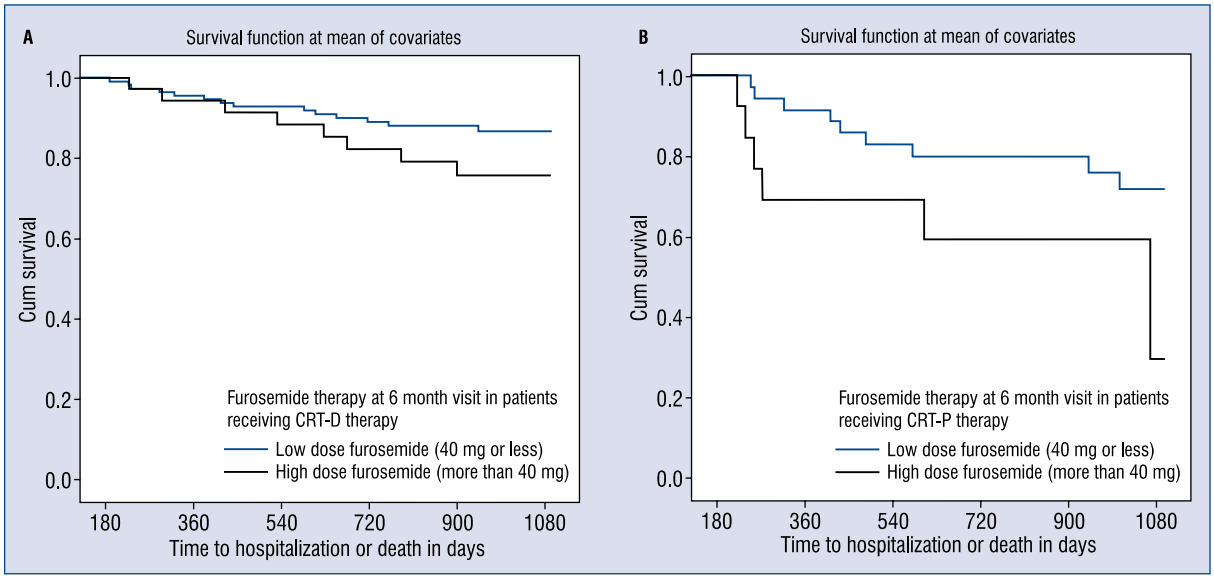

Figure 3. A. Kaplan-Meier demonstrates the event free survival in cardiac resynchronization therapy with defibrillator function (CRT-D) treated patients with low (Group I) and high (Group II) dose diuretics, respectively. The curve is a landmark analysis reset at the 6 month follow-up visit. The difference between the two groups is not significant, p = 0.15; **B.** Kaplan Meier curve demonstrates the event free survival in cardiac resynchronisation therapy without defibrillator function (CRT-P) treated patients with low (Group I) and high (Group II) dose diuretics. The curve is a landmark analysis reset at the six-month follow-up visit. Patients with high loop diuretic therapy has worse outcome, p = 0.02.

population. The major finding of this study suggests that the increased diuretic therapy with high dose loop diuretics may be associated with a negative influence on survival and risk of HF hospitalization. The risk for hospitalization/death were more pronounced in the group of CRT-P treated patients, who represented a slightly older population with more comorbidity, compared to the CRT-D treated patients. No positive correlation between loop diuretic dosages and clinical improvement or reverse remodeling was found, regardless of implanted device type.

In "real life", treating the failing heart might differ in some details compared to what is seen in the large clinical trials, even though the long--term benefits of medical and CRT therapy in terms of mortality have been well established by the prospective randomized trials. Depending on the local routines, experiences and possibilities, the optimal medical therapy including dosages may differ.

Routinely, many patients are started on loop diuretics at a time with decompensated HF before the CRT implantation, but over time — and especially post-CRT implant — many of them improve their symptoms including mitral regurgitation [34–37], but nevertheless continue on the same dose of diuretics and are thus treated with a higher dose than necessary. On the other hand, HF therapy is often made complicated by patient specific factors such as low blood pressure, renal dysfunction, and not least by patient preferences and compliance.

Loop diuretic therapy is one of the most commonly used complementary medications for symptom relief and for reducing fluid retention, but long-term data suggests potential harmful effect in higher dosages [17, 38]. Early experimental studies have suggested that in HF without congestion, furosemide therapy can activate the renin-angiotensin system and thus can influence the HF negatively [39]. An Italian study with 813 ambulatory patients with mild to moderate HF, and found that more than 50 mg furosemide daily increased the 3-year mortality [17]. A recent prospective study with 244 stable non-CRT treated HF patients also found that higher furosemide dose was associated with increased morbidity and mortality, and only 40 mg furosemide daily on top of the standard HF therapy resulted in 66% increased risk of adverse event [38]. That population was younger and had less comorbidity compared to this present one, but the medical therapy was comparable in both studies. Similar to findings herein, the high dose diuretic therapy also had slightly more comorbidity, higher frequency of renal impairment and more often had ischemic cardiomyopathy and also presented worse outcomes when compared with low dose treatment. Furthermore, Penn et al. [18] used the MADIT-CRT data for investigation and also found that in mild HF patients after CRT implantation, higher diuretic usage was correlated with increased risk of death and hospitalization [18]. However up to date there is no data to support a specific cut-off level for the potentially harmful effects of loop diuretic therapy, and the lack of reduction of the loop diuretic therapy itself can perhaps be considered a potential risk.

Thus, in harmony with other trials, this data also suggests that high dose furosemide therapy may be non-beneficial in the long term [17]. Independently from clinical improvement, renal function or reverse remodeling, higher dose diuretic therapy with furosemide appears to be unfavourable in terms of long term survival. High dose loop diuretic therapy was associated with larger LVESV and LVEDV, but reverse remodeling was similar in both groups and no significant difference in this regard was found between them. The negative influence of the loop diuretic therapy seems to be more prominent in CRT-P recipients who represent an older population with relatively more comorbidity within the CRT group. Loop diuretics may increase the risk of hypokalemia induced malignant arrhythmias and sudden cardiac death, which in theory may explain the difference in outcome for CRT-P treated patients compared to CRT-D. However, of the 26 deaths only two were classified as sudden cardiac death, and these patients both received a CRT-D device.

Together with previously published results, the present data suggest that a high awareness is warranted regarding cardiovascular medication changes for CRT-treated patients. CRT has the potential to induce substantial changes in the cardiac function [40], which in turn may influence blood pressure, renal function and fluid status of the patient. It is imperative to make a renewed assessment of fluid status and loop diuretic need, after the expected (potential) remodelling effect of CRT has taken place, in order to re-evaluate the indication and required dosages for the treatment. For patients where no diuretic reduction is possible, or where an increased dosage of diuretic is required, special attention is warranted. These patients are likely to be at increased risk of HF

related morbidity and mortality, and every effort should therefore be made for individual optimization of the CRT-settings and other cardiovascular medications for these patients.

Limitations of the study

We acknowledge that there are several limitations to this study. It is a single-centre retrospective study, based on registry data. From the invited 398 patients only 211 participated in this trial therefore selection bias cannot be ruled out. All efforts were made to reach the most optimal biventricular pacing, however full data on this was not available for the current analyses. Data about the medication was collected from the local medical database and from the participants but no verification was available for compliance on individual level. Medication changes during the study were at the discretion of the patient's treating physician and the study group had no influence on these changes. Clinical endpoints were collected from the validated Swedish national death and hospitalization registries, which ensures a high accuracy, even though no individual scrutiny of the electronic medical records was possible regarding mortality cause. The reduction of the NT-proBNP — which is an important HF marker — can also be secondary to the improvement of the fluid balance in some patients, this cannot be ruled out. However, all of the study subjects were on optimal medical therapy before the CRT implantation with stable HF status.

Conclusions

In this observational study, higher dosages of loop diuretic therapy were associated with worse medium-term clinical outcome in CRT treated patients. However, higher doses of loop diuretic therapy showed no influence on echocardiographic remodeling response, or on clinical improvement. It is unclear whether there is a direct causality between these associations, or if higher prescribed dosage of loop-diuretics is just a marker of more severe disease. Prospective trials are needed to further elucidate these findings, and it may be warranted to try to reduce the dosage of loop diuretics in the post-CRT implant phase. In cases, where the response to the treatment is poor and high dose diuretics are necessary, further interventions are desirable to prevent an unfavourable clinical outcome.

Conflict of interest: None declared

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