Effects of Long-Acting Loop Diuretics in Heart Failure With Reduced Ejection Fraction Patients With Cardiac Resynchronization Therapy  
A Crossover Study

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SUMMARY

There have been no reports evaluating the impact of long-acting loop diuretics (LLD) on the outcome of heart failure (HF) and arrhythmia treatment in HF with reduced ejection fraction (HFrEF) patients implanted with a cardiac resynchronization therapy (CRT) device.

This was a prospective, single-blind, randomized crossover study. We allocated 21 consecutive CRT implanted patients into 2 groups. The furosemide group received furosemide as a first treatment and azosemide as a second treatment. The azosemide group received this treatment in the reverse order. The first treatment was given to each group for 6 months and the second treatment continued for an additional 6 months. We combined the data of each medication regimen in each group and analyzed it at baseline, 6 months, and 1 year. The primary endpoints were the variation of fluid index and thoracic impedance measured by CRT at 6 months.

The baseline characteristics were similar for both groups. The difference in the primary endpoints was not statistically significant between the 2 medication arms (fluid index: -29.6 ± 64.4 versus 16.2 ± 48.2; \( P = 0.22 \), thoracic impedance: -0.49 ± 17.8 versus 2.45 ± 12.5; \( P = 0.56 \)). Likewise, the clinical outcome of HF and the CRT derived parameters in both arms were comparable.

HFrEF patients taking LLD after CRT implantation might be comparable to those taking short-acting loop diuretics in the treatment of HF and HF-associated arrhythmias.  (Int Heart J 2017; 58: 1-9)

Key words: Severe cardiac dysfunction, Cardiac implantable electrophysiological devices, Clinical outcome, Arrhythmia, Diuretics

Chronic heart failure (HF) is an increasingly prevalent public health problem with an incidence of more than 10% in patients over 70 years of age. Diuretics are widely used to reduce water retention caused by impaired cardiac function in chronic HF patients. However, several reports have shown that diuretics increase the risk of arrhythmic death, presumably because they alter the electrolyte balance. Loop diuretics activate the renin–angiotensin system and the sympathetic nervous system (SNS), and may therefore lead to poor prognosis in patients prescribed with these drugs. Recent reports have shown that long-acting loop diuretics (LLD) improve body weight, brain natriuretic peptide, atrial natriuretic peptide, SNS activation, quality of life, and clinical outcome in contrast to short-acting loop diuretics (SLD). However, there is limited data available on the effect of treatment with LLD in heart failure with reduced ejection fraction (HFrEF) patients. LLD have a long drug half-life compared with SLD. As such, patients who are taking LLD are less prone to fluctuations in total body fluid (ie, fluid losses or gains) during the day than those who are prescribed SLD. We therefore speculated that LLD would decrease some heart failure (HF) parameters or the frequency of HF-associated arrhythmias in comparison with SLD. This was also hypothesized to occur in HFrEF patients due to the fact that LLD are known to suppress the activation of the SNS due to small changes in body fluid during the day, which is not the case with SLD.

Furthermore, cardiac resynchronization therapy (CRT) has a well-documented positive effect on morbidity and mortality in chronic HF patients with wide QRS complexes and a low left ventricular ejection fraction (LVEF). The PARTNER-HF study showed that the Cardiac Compass (Medtronic plc., Minneapolis, MN, USA), which evaluated the severity of HF in subjects implanted with...
a CRT device, was useful to identify patients who were at higher risk of HF within a few months of their hospitalization. We quantitatively evaluated the effect of HF treatment and the frequency of arrhythmias, as well as the Cardiac Compass data in HFrEF patients with CRT. We subsequently compared the effect of SLD to LLD using the aforementioned parameters.

**METHODS**

**Patient population:** Twenty-one consecutive patients implanted with a CRT device who had previously taken loop diuretics were enrolled in this study between August 2013 and March 2014. The exclusion criteria were 1) any changes pertaining to medication use within 1 month, 2) patients planning an admission to a hospital within the next 3 month for any reason, and 3) patients undergoing haemodialysis. The study was in agreement with the guidelines of the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki. Each patient provided written informed consent.

**Study protocol:** This was a prospective, single-blind, randomized crossover study. We randomly allocated all patients into 2 groups using the envelope method. We used furosemide as SLD and azosemide as LLD. In the furosemide group, the patients were given furosemide as a first treatment and azosemide as a second treatment. In the azosemide group, the patients received the treatment in the reverse order. Each group was administered furosemide or azosemide for 6 months ± 35 days. After this period, the drugs were crossed over and the treatment was continued for an additional 6 months ± 35 days (Figure 1). There was no washout period at the crossover time because the patients needed to continue taking some diuretic drugs to relieve their symptoms. We conducted medical interviews pertaining to the New York Heart Association classification, chest X-rays, echocardiograms, and CRT interrogation from all patients at baseline, during medication crossover, and 1 year after enrollment. Furthermore, we simultaneously collected blood samples, information regarding body height, body weight, and specific activity scale questionnaire scores. A furosemide dose of 40 mg was considered equivalent to an azosemide dose of 60 mg, while a furosemide dose of 20 mg was considered equivalent to azosemide at a dose of 30 mg. We combined the data of medication used as the 1st drug or 2nd drug in each group and analyzed it as the respective medication arm. We prospectively compared quantitative evaluations of some HF parameters and the clinical outcome between HFrEF patients implanted with a CRT device taking SLD to those who were taking LLD.

**Evaluation of arrhythmia and HF:** The Cardiac Compass® diagnostic report enabled continuous monitoring, recording, and display of various HF diagnostic parameters and arrhythmia. The Cardiac Compass data, which we obtained from the CRT, were therefore used to evaluate arrhythmia and HF. These data included the arterial and ventricular pacing rate, average day and night heart rate, heart rate variability, level of physical activity, thoracic impedance, reference impedance, fluid index, the number of ventricular tachycardias (VT) or ventricular fibrillations (VF), non-sustained ventricular tachycardia (NSVT), atrial tachycardia (AT) or atrial fibrillation (AF), and time in AT or AF. The definition of all Cardiac Compass parameters has been previously described in detail. The average values of the parameters that were monitored by CRT during the consumption of furosemide were compared with those during the consumption of azosemide to evaluate the impact of LLD on arrhythmia and chronic HF. Furthermore, we evaluated the variation of all the CRT parameters during the consumption of each individual drug by analyzing the standard deviation of the average value of each parameter.

**Measurement of catecholamine:** Catecholamine fractions were collected from all subjects after they laid down for 30 minutes at baseline, during medication crossover, and 1 year after enrollment.

**Evaluation of chest X-ray and echocardiography:** The patient’s cardiothoracic ratio was evaluated by chest X-ray at baseline, after 6 months, and after 1 year. The variation of cardiac function, including LVEF, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, end-diastolic volume, and end-systolic volume were investigated by echocardiography at baseline and at the end of each drug intervention.

**Study endpoints:** The primary endpoints were the variation of fluid index and thoracic impedance by means of the Cardiac Compass. The secondary endpoints were all-cause mortality, cardiovascular death, unplanned admission to the hospital for HF exacerbation, any changes in cardiovascular medication, the frequency of arrhythmia, any variation in the Cardiac Compass parameters excluding primary endpoints, any variation in the levels of catecholamine and brain natriuretic peptide, and changes in the quality of life based on the specific activity scale questionnaire score. Cardiovascular death was defined as demise as a consequence of worsening of congestive HF, coro-

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**Figure 1.** Flow chart of this study that addressed the impact of long-acting loop diuretics on the effect of treatment of heart failure, and arrhythmia in heart failure with reduced ejection fraction patients with cardiac resynchronization therapy.
nary artery disease, cardiac arrest, cardiac arrhythmia, myocardial infarction, stroke, or sudden death. All suspected events were independently adjudicated by two expert doctors.

**Statistical analyses:** Continuous variables are presented as the mean ± standard deviation. We used a paired *t*-test to evaluate the effect of each drug intervention before and after the treatment, and an independent *t*-test was used to evaluate the variation of all parameters after each treatment. Categorical variables are expressed as numbers and percentages and compared using the chi-square or Fisher’s exact test. The variation of the

### Table I. Baseline Characteristic at Enrollment

| Variable                          | All patients (n = 21) | Furosemide group (n = 10) | Azosemide group (n = 11) | p  |
|-----------------------------------|---------------------|--------------------------|--------------------------|----|
| Age, years                        | 72.5 ± 8.9          | 69.5 ± 8.4               | 75.3 ± 8.3               | 0.15|
| Male gender, n (%)                | 18 (85.7)           | 10 (100.0)               | 8 (72.7)                 | NA |
| Body weight, kg                   | 61.7 ± 11.6         | 65.3 ± 10.6              | 58.5 ± 11.6              | 0.20|
| Body mass index kg/m²             | 23.5 ± 4.1          | 24.3 ± 4.3               | 22.8 ± 3.9               | 0.44|
| Systolic BP, mmHg                 | 107.4 ± 15.4        | 107.6 ± 16.1             | 107.3 ± 14.7             | 0.96|
| Diastolic BP, mmHg                | 66.6 ± 7.0          | 67.5 ± 8.6               | 65.7 ± 5.0               | 0.10|
| Heart rate, bpm                   | 75.6 ± 10.1         | 81.6 ± 8.7               | 70.2 ± 8.1               | 0.81|
| NYHA, n (%)                       |                     |                          |                          | 0.47|
| I                                 | 1 (4.8)             | 0 (0.0)                  | 1 (9.1)                  |    |
| II                                | 14 (66.7)           | 6 (60.0)                 | 8 (72.7)                 |    |
| III                               | 6 (28.6)            | 4 (40.0)                 | 2 (18.2)                 |    |
| IV                                | 0 (0.0)             | 0 (0.0)                  | 0 (0.0)                  |    |
| SAS questionnaire score, metz     | 4.3 ± 1.6           | 4.1 ± 1.9                | 4.4 ± 1.4                | 0.34|
| LVEF, %                           | 32.2 ± 10.0         | 30.4 ± 7.4               | 33.9 ± 11.6              | 0.19|
| LVDD, mm                          | 59.1 ± 8.9          | 61.0 ± 9.1               | 57.3 ± 8.4               | 0.36|
| LVDDs, mm                         | 50.2 ± 10.5         | 53.0 ± 9.7               | 47.7 ± 10.6              | 0.27|
| LVDS, mm                          | 142.3 ± 48.9        | 167.1 ± 47.5             | 119.8 ± 58.1             | 0.49|
| ESV, mL                           | 99.4 ± 43.1         | 119.9 ± 41.5             | 80.7 ± 35.8              | 0.64|
| CTR, %                            | 55.0 ± 4.3          | 56.3 ± 3.9               | 53.8 ± 4.3               | 0.21|
| eGFR, mL/minute/l.73m²            | 42.9 ± 16.7         | 47.1 ± 14.1              | 39.0 ± 17.9              | 0.29|
| Hemoglobin, g/dL                  | 12.7 ± 1.8          | 13.1 ± 1.4               | 12.4 ± 2.0               | 0.30|
| Potassium, mEq/L                  | 4.3 ± 0.4           | 4.2 ± 0.2                | 4.4 ± 0.5                | 0.37|
| BNP, pg/mL                        | 288.8 ± 219.5       | 391.3 ± 209.3            | 195.6 ± 184.1            | 0.68|
| Epinephrine, ng/mL                | 41.0 ± 31.1         | 37.8 ± 22.2              | 43.6 ± 36.7              | 0.18|
| Norepinephrine, ng/mL             | 521.3 ± 259.6       | 486.2 ± 142.3            | 550.0 ± 322.7            | 0.58|
| Dopamine, ng/mL                   | 21.3 ± 22.0         | 16.5 ± 5.4               | 24.8 ± 28.1              | 0.38|
| Ventricular pacing rate, %        | 96.8 ± 6.7          | 95.9 ± 9.5               | 97.7 ± 2.5               | 0.59|
| Etiology of heart failure, n (%)  |                     |                          |                          | 0.26|
| DCM                               | 11 (52.4)           | 4 (40.0)                 | 7 (63.6)                 |    |
| ICM                               | 6 (28.6)            | 5 (50.0)                 | 1 (9.1)                  |    |
| Valvular heart disease            | 3 (14.3)            | 0 (0.0)                  | 3 (27.3)                 |    |
| Myocarditis                       | 1 (4.8)             | 1 (10.0)                 | 0 (0.0)                  |    |
| Duration after device implantation, months | 27.4 ± 15.2 | 26.1 ± 17.5 | 28.6 ± 12.5 | 0.30 |
| History, n (%)                    |                     |                          |                          |    |
| Diabetes mellitus                 | 8 (38.1)            | 6 (60.0)                 | 2 (18.2)                 | 0.052|
| Hypertension                      | 13 (61.9)           | 6 (60.0)                 | 7 (63.6)                 | 0.94|
| Dyslipidemia                      | 13 (61.9)           | 7 (70.0)                 | 6 (54.5)                 | 0.49|
| Family history of CAD            | 5 (23.8)            | 1 (10.0)                 | 4 (36.4)                 | 0.18|
| Current smoker                    | 1 (4.8)             | 0 (0.0)                  | 1 (9.1)                  | NA |
| Chronic kidney disease            | 14 (66.7)           | 6 (60.0)                 | 8 (72.7)                 | 0.76|
| Chronic AF/AFI                    | 4 (19.0)            | 4 (40.0)                 | 0 (0.0)                  | NA |
| Medication, n (%)                 |                     |                          |                          |    |
| ACEI or ARB                       | 15 (71.4)           | 7 (70.0)                 | 8 (72.7)                 | 0.91|
| β-Blocker                         | 17 (81.0)           | 8 (80.0)                 | 9 (81.8)                 | 0.89|
| Aldosterone-antagonist            | 10 (47.6)           | 4 (40.0)                 | 6 (54.5)                 | 0.53|
| Statin                            | 14 (66.7)           | 7 (70.0)                 | 7 (63.6)                 | 0.77|
| Inotropic agent                   | 3 (14.3)            | 1 (10.0)                 | 2 (18.2)                 | 0.47|
| Anti-arrhythmic drug              | 5 (23.8)            | 3 (30.0)                 | 2 (18.2)                 | 0.55|
| Warfarin                          | 8 (38.1)            | 6 (60.0)                 | 2 (18.2)                 | 0.052|
| Anti-platelet drug                | 14 (66.7)           | 7 (70.0)                 | 7 (63.6)                 | 0.77|
| Diuretics                         |                     |                          |                          | 0.96|
| Furosemide                        | 20 (95.2)           | 10 (100.0)               | 10 (90.0)                |    |
| Azosemide                         | 1 (4.8)             | 0 (0.0)                  | 1 (9.1)                  |    |

Values are mean ± standard deviation where appropriate. NA indicates not available; BP, blood pressure; NYHA, New York Heart Association; SAS, specific activity scale; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter; LVDDs, left ventricular end-systolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; CTR, cardiothoracic ratio; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; CAD, coronary artery disease; AF/AFI, atrial fibrillation/atrial flutter; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and DPP, dipeptidyl peptidase.
CRT parameters was assessed by Bartlett’s test or the Levene test. The event-free survival rates were constructed using Kaplan–Meier curves. These curves were compared using the log-rank test. Hazard ratios (HR) and confidence intervals (CI) were calculated for each factor using Cox proportional hazards regression. For all analyses $P < 0.05$ was considered statistically significant. All analyses were performed using MedCalc version 14.12.0 (MedCalc Software BVBA, Ostend, Belgium).

**Results**

**Patient characteristics:** The furosemide group and the azosemide group were comprised of 10 patients and 11 patients, respectively. One patient died during the consumption of azosemide before switching medication, and another subject died while on the furosemide regimen after switching medication. Thus, a total of 19 patients were included in the furosemide arm and a total of 20 patients were included in the azosemide arm. The baseline characteristics were similar for both the furosemide and azosemide groups (Table I). The median duration of the follow-up was 189 days (interquartile range, 182-196 days) in the furosemide group and 189 days (interquartile range, 175-196 days) in the azosemide group ($P = 0.83$). The mean age of all patients was 72.5 ± 8.9 years. Most patients (95.2%) had New York Heart Association classification II or III symptoms, and the average LVEF was 32.2 ± 10.0%.

**Effect of each medication:** The data of all HF parameters before the drug intervention were compared with the data obtained after the treatment to assess the effect of each medication (Table II). Prior to and following the drug intervention we collected average CRT data for the duration of 1 month for 19 patients in the furosemide arm and a total of 20 patients in the azosemide arm. The baseline characteristics were similar for both the furosemide and azosemide groups (Table I). The median duration of the follow-up was 189 days (interquartile range, 182-196 days) in the furosemide group and 189 days (interquartile range, 175-196 days) in the azosemide group ($P = 0.83$). The mean age of all patients was 72.5 ± 8.9 years. Most patients (95.2%) had New York Heart Association classification II or III symptoms, and the average LVEF was 32.2 ± 10.0%.

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Values are mean ± standard deviation where appropriate. We collected 1-month average data before we started or finished treatment in both arms as all CRT parameter data at the start of treatment and after treatment. BP indicates blood pressure; NYHA, New York Heart Association; SAS, specific activity scale; LVEF, left ventricular ejection fraction; LVDs, left ventricular end-diastolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; CTR, cardiothoracic ratio; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; VT/VF, ventricular tachycardia/ventricular fibrillation; NSVT, non-sustained ventricular tachycardia; and AT/AF, atrial tachycardia/atrial fibrillation.

### Table II. Comparison of All Parameters Before and After Treatment in Each Arm

| Variable                        | Furosemide arm (n = 21) | Azosemide arm (n = 20) | P     |
|---------------------------------|-------------------------|------------------------|-------|
|                                 | At the start of treatment | After treatment       |       |
|                                 | Body weight, kg          | 63.0 ± 9.9             | 62.2 ± 10.2 | 0.17 |
|                                 | Body mass index, kg/m²   | 23.9 ± 3.9             | 23.6 ± 3.7 | 0.14 |
|                                 | Systolic BP, mmHg        | 109.9 ± 17.5           | 110.7 ± 15.9 | 1.00 |
|                                 | Diastolic BP, mmHg       | 66.7 ± 9.6             | 69.7 ± 8.8 | 0.28 |
|                                 | Heart rate, bpm          | 75.3 ± 10.7            | 73.3 ± 12.0 | 0.32 |
|                                 | NYHA, n (%)              | 2 (10.0)               | 2 (10.5) | 0.09 |
|                                 |                          | 13 (65.0)              | 12 (63.2) | 0.46 |
|                                 |                          | 5 (25.0)               | 5 (26.3) | 0.11 |
|                                 |                          | 0 (0.0)                | 0 (0.0) | 0.00 |
|                                 |                          | 3.9 ± 1.6              | 3.6 ± 1.6 | 0.30 |
|                                 |                          | 33.0 ± 9.9             | 33.7 ± 12.2 | 0.82 |
|                                 |                          | 58.3 ± 9.7             | 56.9 ± 8.7 | 0.17 |
|                                 |                          | 50.0 ± 10.6            | 47.7 ± 9.7 | 0.04 |
|                                 |                          | 143.6 ± 56.4           | 136.2 ± 61.9 | 0.46 |
|                                 |                          | 101.2 ± 48.2           | 93.8 ± 56.8 | 0.41 |
|                                 |                          | 0.0 (0.0)              | 0.0 (0.0) | 0.00 |
|                                 |                          | 3.9 ± 1.4              | 3.2 ± 1.2 | 0.03 |
|                                 |                          | 31.8 ± 9.9             | 33.9 ± 9.2 | 0.20 |
|                                 |                          | 58.5 ± 8.1             | 58.1 ± 9.5 | 0.66 |
|                                 |                          | 49.7 ± 9.3             | 49.7 ± 10.4 | 0.51 |
|                                 |                          | 137.0 ± 56.0           | 129.4 ± 55.3 | 0.24 |
|                                 |                          | 95.5 ± 50.5            | 93.7 ± 56.2 | 0.80 |
|                                 |                          | 55.4 ± 5.2             | 56.0 ± 6.6 | 0.38 |
|                                 |                          | 43.5 ± 17.8            | 40.4 ± 14.5 | 0.03 |
|                                 |                          | 12.5 ± 2.0             | 12.3 ± 2.1 | 0.27 |
|                                 |                          | 139.3 ± 2.8            | 138.3 ± 2.8 | 0.16 |
|                                 |                          | 4.4 ± 0.5              | 4.4 ± 0.5 | 0.32 |
|                                 |                          | 101.7 ± 3.4            | 101.6 ± 3.6 | 1.00 |
|                                 |                          | 283.9 ± 220.9          | 259.9 ± 237.5 | 0.51 |
|                                 |                          | 39.9 ± 24.7            | 38.6 ± 26.6 | 0.81 |
|                                 |                          | 479.9 ± 159.2          | 606.6 ± 414.3 | 0.27 |
|                                 |                          | 17.9 ± 8.6             | 19.9 ± 14.0 | 0.49 |
|                                 |                          | 93.6 ± 17.4            | 95.5 ± 9.6 | 0.46 |
|                                 |                          | 25.5 ± 33.4            | 26.7 ± 35.4 | 0.69 |
|                                 |                          | 272.5 ± 9.8            | 60.6 ± 8.5 | 0.13 |
|                                 |                          | 77.7 ± 9.9             | 77.4 ± 9.4 | 1.00 |
|                                 |                          | 51.3 ± 43.6            | 53.4 ± 42.9 | 0.93 |
|                                 |                          | 103.6 ± 66.3           | 117.3 ± 69.7 | 0.36 |
|                                 |                          | 61.0 ± 16.8            | 60.3 ± 22.9 | 0.91 |
|                                 |                          | 63.5 ± 17.0            | 60.8 ± 22.9 | 0.49 |
|                                 |                          | 35.0 ± 62.5            | 7.2 ± 9.9 | 0.07 |
|                                 |                          | 1.70 ± 4.94            | 3.42 ± 8.09 | 0.058 |
|                                 |                          | 0.55 ± 1.16            | 2.63 ± 7.46 | 0.25 |
both treatment arms. Almost all variables were similar before and after the medication regimen. However, the treatment with furosemide significantly aggravated renal function in contrast to azosemide (estimated glomerular filtration rate; furosemide arm; before treatment, 43.5 ± 17.8 versus after treatment, 40.4 ± 14.5; \( P = 0.03 \); azosemide arm; 40.1 ± 15.1 versus 38.7 ± 15.7; \( P = 0.06 \)). A slight improvement of LVEF and reduction of left ventricular end-systolic volume (LVESV) in both arms were observed, but they were not significant (LVEF; furosemide arm; before treatment, 33.0 ± 9.9 versus after treatment, 33.7 ± 12.2; \( P = 0.82 \); azosemide arm; 31.8 ± 9.9 versus 33.9 ± 9.2; \( P = 0.20 \), LVESV; furosemide arm; before treatment, 101.2 ± 48.2 versus after treatment, 93.8 ± 56.8; \( P = 0.41 \); azosemide arm; 95.5 ± 50.5 versus 93.7 ± 56.2; \( P = 0.80 \)).

**Table III.** Comparison of Variation of All Parameters After Treatment Between Furosemide and Azosemide Arms

| Variable | Furosemide arm \((n = 19)\) | Azosemide arm \((n = 20)\) | \(P\) |
|----------|-----------------------------|-----------------------------|------|
| Body weight, kg | -0.94 ± 2.80 | -0.29 ± 2.73 | 0.48 |
| Systolic BP, mmHg | 0.00 ± 10.7 | 2.75 ± 11.4 | 0.45 |
| Diastolic BP, mmHg | 2.05 ± 7.80 | -0.70 ± 8.44 | 0.31 |
| Heart rate, bpm | -1.47 ± 6.11 | 0.05 ± 5.78 | 0.44 |
| NYHA, n (%) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) | \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.5) 12 (63.2) 5 (26.3) 0 (0.0) \(\begin{array}{c} I \\ II \\ III \\ IV \end{array}\) 2 (10.0) 13 (65.0) 5 (25.0) 0 (0.0) |
| eGFR, mL/minute/1.73m\(^2\) | -4.40 ± 7.80 | -2.48 ± 5.40 | 0.12 |
| Hemoglobin, g/dL | -0.32 ± 1.19 | -0.66 ± 1.21 | 0.39 |
| Potassium, mEq/L | 0.10 ± 0.39 | 0.04 ± 0.43 | 0.69 |
| BNP, pg/mL | -28.0 ± 173.5 | 23.9 ± 174.4 | 0.37 |
| Epinephrine, ng/mL | 1.05 ± 25.5 | 6.60 ± 15.8 | 0.36 |
| Fluid index | -29.6 ± 64.4 | 16.2 ± 48.2 | 0.22 |

Values are mean ± standard deviation where appropriate. We collected 1-month average data before we finished treatment in both arms as all CRT parameter data after treatment. BP indicates blood pressure; NYHA, New York Heart Association; SAS, specific activity scale; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; CTR, cardiothoracic ratio; eGFR, estimated glomerular filtration rate; and BNP, brain natriuretic peptide.

**Table IV.** Clinical Endpoints

| Outcome | Furosemide arm \((n = 20)\) | Azosemide arm \((n = 21)\) | HR (95% CI) | \(P\) |
|---------|-----------------------------|-----------------------------|--------------|------|
| Composite outcome | Cardiovascular death, unplanned admission to hospital for HF exacerbation, or admission to hospital for arrhythmia | 4 (20.0) | 3 (14.3) | 0.63 (0.14-2.80) | 0.55 |
| Components of composite outcome | Cardiovascular death | 1 (5.0) | 1 (4.8) | 0.93 (0.06-14.9) | 0.96 |
| | Unplanned admission to hospital for HF exacerbation | 4 (20.0) | 2 (9.5) | 0.43 (0.09-2.14) | 0.32 |
| | Admission to hospital for arrhythmia | 0 (0.0) | 0 (0.0) | NA | NA |
| Other outcomes | All-cause mortality | 1 (5.0) | 1 (4.8) | 0.93 (0.06-4.87) | 0.96 |
| | Any change of cardiovascular medication | 3 (15.0) | 3 (14.3) | 0.96 (0.19-4.74) | 0.96 |

HR indicates hazard ratio; CI, confidence interval; HF, heart failure; and NA, not available.
There was no significant difference between the responder rates, which were defined as a reduction of LVESV, in both arms (furosemide arm versus azosemide arm; 9 patients (45.3%) versus 15 patients (75.0%); \( P = 0.08 \)).

**Study endpoints:** The variation in all HF parameters in response to both medication regimens is depicted in Table III. The clinical outcome is summarized in Table IV. Altogether, there were no statistically significant differences in the primary endpoints between both medication arms (fluid index; furosemide versus azosemide, -29.6 ± 64.4 versus 16.2 ± 48.2; \( P = 0.22 \), thoracic impedance; -0.49 ± 17.8 versus 2.45 ± 12.5; \( P = 0.56 \)) (Figures 2A, B). As to the secondary endpoints, there were also no significant differences between the furosemide and azosemide medication arms (Supplemental Figure A-F). Other parameters in the Supplemental Figure did not relate to either furosemide or azosemide treatments (Supplemental Figure G-J). For all clinical endpoints there were no significant differences between the furosemide and azosemide medication arms (Figure 3).

**Detailed analysis of CRT parameters:** The incidence of arrhythmia was analyzed in detail. Specifically, the daily frequency of VT/VF (furosemide versus azosemide, 0.26 ± 0.93 versus 0.14 ± 0.65; \( P = 0.13 \)), NSVT (5.74 ± 14.1 versus 4.43 ± 12.2; \( P = 0.54 \)) and AT/AF time (284.0 ± 553.9 versus 253.4 ± 523.5; \( P = 0.53 \)) were not significantly different between the furosemide and azosemide arms (Table V). Furthermore, we also compared other CRT parameters for each medication between the 2 arms and observed no significant differences. However, we showed that there was a significant difference between the standard deviation of the average value of thoracic impedance in the furosemide arm and the azosemide arm (4.38 ± 3.85 versus 3.00 ± 1.39; \( P = 0.03 \)) (Table VI).

**Discussion**

To the best of our knowledge, no previous report has evaluated the impact of LLD on the outcome of chronic HF and arrhythmia treatment in HFrEF patients implanted with a CRT device. Our results demonstrated that the subjects with a CRT device taking LLD were similar to those taking SLD in the fluid index and thoracic impedance. In addition, HF parameters, the clinical outcome, and the frequency of arrhythmia were also comparable in patients taking LLD to those taking SLD.

**Effect to heart failure:** Several reports have clearly demonstrated the advantage of LLD for patients suffering from chronic HF. In the COLD-CHF study,\(^{13}\) Miyata, et al showed that the use of LLD, rather than SLD, significantly decreased body weight, brain natriuretic peptide, and atrial natriuretic peptide levels. However, the present study did not show any statistically significant differences in the primary endpoints between HFrEF patients implanted with a CRT taking LLD and those taking SLD. In the J-MELODIC study,\(^{14}\) Masuyama, et al demonstrated that LLD improved the clinical outcome of HF in comparison with SLD. Conversely, the current study did not demonstrate an improvement in any clinical outcome parameters. However, the thoracic impedance read out showed a significant difference between the 2 treatment arms, which was in line with our hypothesis. The absence of any significant differences in the HF parameters and the clinical endpoints between both medication arms may have been due to the short follow-up term and the small sample size. In the J-MELODIC...
study, for example, the clinical endpoints of HF were evaluated for a period of 2 years, compared to a relatively short follow-up period of only 6 months in the current study. In addition, both the COLD-CHF and J-MELODIC studies included many HF populations with preserved ejection fraction (HFpEF) patients while our study population only comprised HFrEF patients. Several reports have shown that diuretics increase the risk of arrhythmia-induced death presumably because they alter the electrolyte balance. The potential of loop diuretics to activate the SNS may be associated with poor prognosis in patients consuming them. We hypothesized that HFrEF patients needed to take more LLD in order to receive any clinical benefit. The above-mentioned reasons may explain why there were no observable improvements in any of the primary endpoints in the LLD arm.

Previously, Hitakate, et al found that the use of 123I-metaiodobenzylguanidine suppressed the activation of the SNS in patients taking LLD compared with those taking SLD. Activation of the SNS is one of the fundamental pathophysiologic abnormalities in patients with chronic HF and is actually considered a cause of chronic HF. In our study we evaluated catecholamine levels as a measure for SNS activation instead of 123I-metaiodobenzylguanidine. However, we could not demonstrate that patients taking LLD had decreased catecholamine fractions in comparison with those taking SLD. HFrEF patients might not expect adequate effects of LLD due to the poor general condition of those patients activated SNS stronger than the suppression effect of LLD. Furthermore, we did not include a washout period before initiating the second drug treatment. This may have had an impact on the results because the data after taking the first drugs and at the start of taking the second drugs were the same data. However, LLD has a half-life of about 9 hours. We did not think that it was long enough to affect the clinical outcomes. The finding that LLD provided results similar to SLD in terms of some HF parameters and clinical outcomes in the present study that included many HFrEF patients may suggest that LLD are effective for both HFrEF and HFpEF patients. The SOLVD study showed that non-potassium-sparing diuretics are associated with cardiovascular death.
other hand, Cooper, et al did not show any increase in arrhythmias when a non-potassium-sparing diuretic was taken together with a potassium-sparing diuretic, angiotensin converting enzyme inhibitor (ACEI), or angiotensin II receptor blocker (ARB). In our population, the rate of taking an ACEI, ARB, or aldosterone-antagonist was 90.5%. Thus, it might not have increased the frequency of arrhythmia in both arms. In the present study, patients taking LLD were comparable to those taking SLD in terms of the frequency of arrhythmia. These results might suggest that sufficient evidence-based optimal medical therapy such as β-blockers, ACEI, ARB, or aldosterone-antagonist was fundamental to HFrEF patients with CRT for the prevention of sudden death and arrhythmia. Larger randomized trials are needed to evaluate the safety and efficacy of LLD in HFrEF patients.

Study limitations: There are several limitations to the present study. First, the sample size is small and all subjects were drawn from a single center. Therefore, the results should be merely considered exploratory and suitable for generating further hypotheses. Secondly, the drug furosemide had already been used by most patients before the start of the study. This means that the baseline data were similar to the data of the furosemide arm. This may have influenced the results of the azosemide group in comparison with the furosemide group because the azosemide group underwent an initial change of medication. Thirdly, we did not include a washout period in the study design. Fourthly, we chose 6 months as the observation period, which was not long enough to evaluate the seasonal effects. Seasonal effects, such as temperature or weather, may affect the outcomes. Finally, we excluded severe HF patients who made any changes to their medication regimen 1 month prior to the start of the trial, patients planning an admission to a hospital within the next 3 months for any reason, and patients undergoing haemodialysis. However, in this first report, we showed that the HF parameters, the clinical outcome, and arrhythmias were unaltered for HFrEF patients taking LLD in comparison with those taking SLD.

Conclusions: To the best of our knowledge, the present study is the first to compare HF parameters, the clinical outcome, and arrhythmias in HFrEF patients implanted with a CRT device taking LLD with those taking SLD. Our findings showed that the subjects taking LLD were comparable to those taking SLD in the treatment of HF and HF-associated arrhythmias. In HFrEF patients implanted with a CRT device, therefore, we might use LLD as with SLD for the treatment of HF under adequate evidence-based optimal medical therapy. Larger randomized trials are needed to evaluate the safety and efficacy of LLD in HFrEF patients.

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Disclosure

Conflicts of interest: All authors have no conflicts of interest to declare.
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**Supplemental File**

Supplemental Figure

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