

# openheart Comparative effects of long-acting and short-acting loop diuretics on cardiac sympathetic nerve activity in patients with chronic heart failure

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## ABSTRACT

**Objective:** Short-acting loop diuretics are known to enhance cardiac sympathetic nerve activity (CSNA) in patients with chronic heart failure (CHF). The effects of two loop diuretics—long-acting azosemide and short-acting furosemide—on CSNA were evaluated using <sup>123</sup>I-metaiodobenzylguanidine (MIBG) scintigraphy in patients with CHF.

**Methods:** The present study was a subanalysis of our previously published study, which had reported that serial <sup>123</sup>I-MIBG studies were the most useful prognostic indicator in patients with CHF. Patients with CHF (n=208, left ventricular ejection fraction <45%) but no history of cardiac events for at least 5 months prior to the study were identified according to their histories of acute decompensated heart failure requiring hospitalisation. Patients underwent <sup>123</sup>I-MIBG scintigraphy immediately before hospital discharge and at a 6-month follow-up. The delayed % denervation, delayed heart/mediastinum count (H/M) ratio and washout rate (WR) were determined using <sup>123</sup>I-MIBG scintigraphy. A total of 108 patients were selected, and propensity score matching was used to compare patients treated with either oral azosemide (n=54) or furosemide (n=54).

**Results:** After treatment, <sup>123</sup>I-MIBG scintigraphic parameters improved in both groups. However, the degree of change in % denervation was  $-13.8 \pm 10.5$  in the azosemide group and  $-5.7 \pm 12.7$  in the furosemide group ( $p < 0.01$ ), the change in H/M ratio was  $0.20 \pm 0.16$  in the azosemide group and  $0.06 \pm 0.19$  in the furosemide group ( $p < 0.01$ ), and the change in WR was  $-11.3 \pm 9.2\%$  in the azosemide group and  $-3.0 \pm 12.7\%$  in the furosemide group ( $p < 0.01$ ). Moreover, multivariate analysis showed an independent and significant positive relationship between furosemide and  $\delta$ -WR from hospital discharge to 6 months after treatment in patients with CHF ( $p = 0.001$ ).

**Conclusions:** These findings indicate that azosemide suppresses CSNA compared with furosemide in patients with CHF.

**Trial registration number:** UMIN000000626 (UMIN-CTR Clinical Trial).

## KEY QUESTIONS

### What is already known about this subject?

▶ Myocardial imaging with <sup>123</sup>I-metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, is useful for detecting cardiac sympathetic nerve activity (CSNA) abnormalities in patients with chronic heart failure (CHF). The treatment of CHF can improve CSNA, based on cardiac <sup>123</sup>I-MIBG scintigraphic findings.

### What does this study add?

▶ The long-acting loop diuretic, azosemide, can suppress CSNA compared with short-acting furosemide, in patients with CHF.

### How might this impact on clinical practice?

▶ Azosemide may be potentially effective for reducing cardiac events in stabilised patients with CHF, through improved CSNA.

The high prevalence and incidence of chronic heart failure (CHF) and the associated morbidity and mortality represent a financial burden on economies, and make CHF a major and growing public health concern. Advances in treatment notwithstanding, the mortality rates due to heart failure have recently increased.<sup>1–2</sup> Loop diuretics are widely used to treat CHF because they can reduce the build-up of body fluid caused by cardiac pulmonary oedema.<sup>1</sup> However, such drugs can worsen prognoses in patients with CHF by activating the renin-angiotensin-aldosterone system (RAAS) and cardiac sympathetic nerve activity (CSNA).<sup>3–5</sup>

The foremost pathophysiological abnormality associated with heart failure is stimulation of CSNA.<sup>6</sup> This means that plasma norepinephrine levels influence the prognosis of patients with CHF.<sup>7</sup> <sup>123</sup>I-metaiodobenzylguanidine

(MIBG) is a norepinephrine analogue that can be used in myocardial imaging to detect abnormalities in the myocardial adrenergic nervous system.<sup>8,9</sup> To support the theory that there is prognostic value in evaluating CSNA using one-time <sup>123</sup>I-MIBG scintigraphy in patients with CHF, previous studies have evaluated CSNA during stable periods.<sup>9–11</sup> Changes in washout rate ( $\delta$ -WR=follow-up WR—baseline WR) determined by serial <sup>123</sup>I-MIBG scintigraphic studies are, according to a previous report by our group, currently the best available tool for evaluating prognosis in patients with CHF.<sup>12</sup>

Azosemide, a long-acting loop diuretic, has a milder effect on the RAAS and CSNA than does furosemide, a short-acting loop diuretic.<sup>4</sup> In a comparison study using a Dahl rat heart failure model, azosemide was positively associated with a better outcome compared with furosemide.<sup>13</sup> In a study measuring the plasma concentrations of norepinephrine in patients with CHF receiving azosemide treatment or furosemide treatment, norepinephrine levels were higher in patients receiving furosemide treatment.<sup>14</sup>

However, differences in the effects of long-acting and short-acting loop diuretics on CSNA have not yet been fully clarified. In the present retrospective study, we aimed to compare the effects of azosemide with those of furosemide on CSNA in patients with CHF, based on our previous work.<sup>12</sup>

## METHODS

### Study patients and protocol

Four hundred fifty-nine patients presenting with their first instance of acute decompensated heart failure with a left ventricular ejection fraction (LVEF) of less than 45% were admitted to our institution from February 2000 through August 2005. These 459 patients were enrolled in the current study following inclusion criteria that have been published elsewhere.<sup>12</sup> All patients underwent standard electrocardiography, chest radiography and echocardiography. All acute-phase patients were treated according to standard heart failure treatment protocols. Forty-two patients who presented with acute coronary syndrome or with active ischaemia (including effort angina) were excluded from the study. (Since active ischaemia can influence <sup>123</sup>I-MIBG scintigraphic findings, we evaluated coronary angiography or stress perfusion scintigraphy for almost all patients) Twenty-nine patients with active cancer, primary hepatic failure or renal failure were also excluded. Thirty-eight patients requiring mechanical support (cardiac resynchronisation therapy, intra-aortic balloon pumping or left ventricular assist devices) or heart transplantation because of severe heart failure, were also excluded. The patient selection process is shown in figure 1.

During the stable period, oral medications were used to treat heart failure in all patients. These medications included  $\beta$ -adrenergic blocking agents, diuretics, ACE inhibitors and angiotensin receptor blockers (ARBs). No

patient received alternative serotonin reuptake inhibitors or tricyclic antidepressants. <sup>123</sup>I-MIBG scintigraphy and echocardiography were performed just before patients were discharged from hospital. (An additional 52 patients, in whom neither procedure was performed, were excluded from this study) Patients were managed medically by either a cardiologist or institutional internist, and <sup>123</sup>I-MIBG scintigraphic and echocardiographic results were provided to facilitate their treatment decisions. A further 18 patients were excluded because of serious events (10 cardiac events, 5 cerebral events and 3 events classified as other) that occurred within 5 months of enrolment.

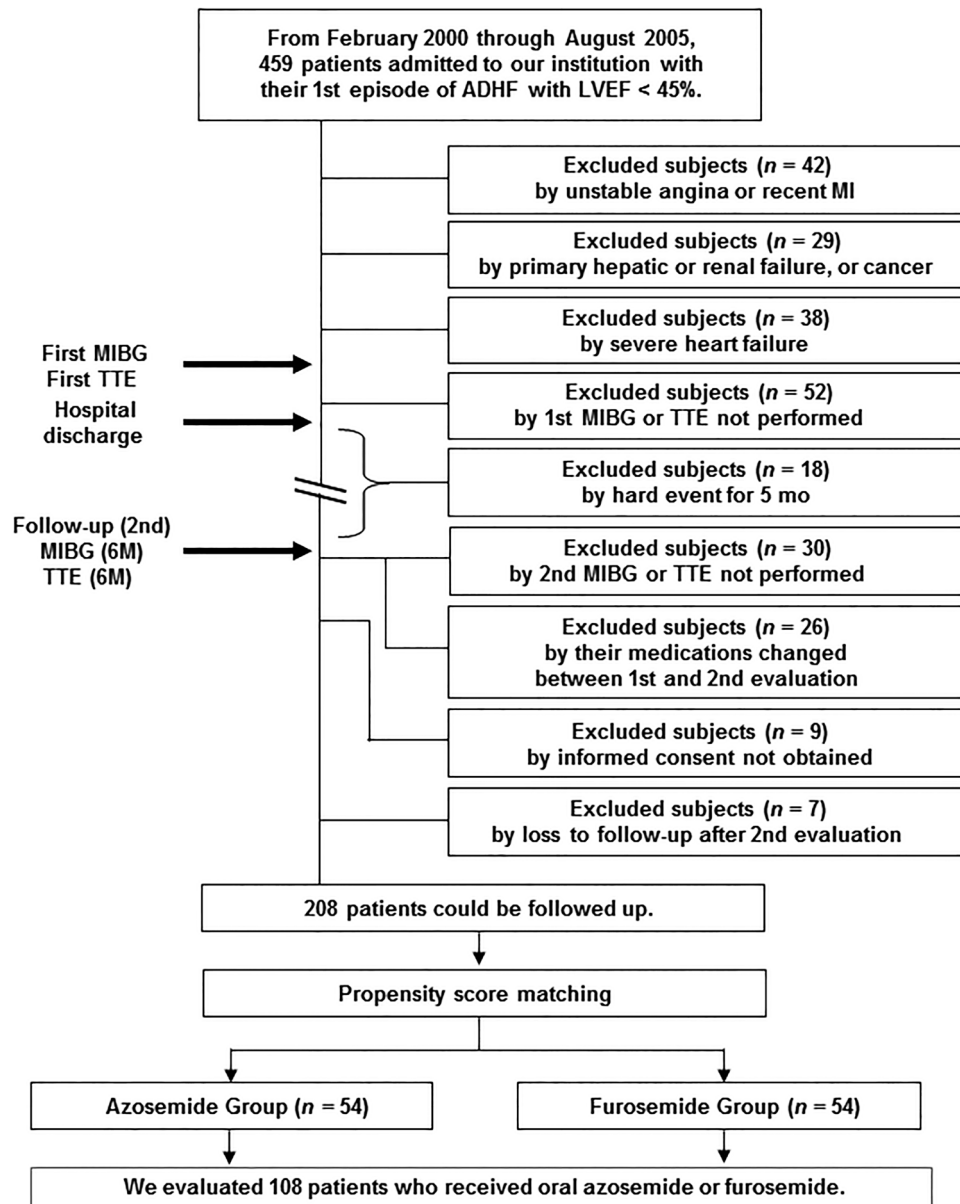
Approximately 6 months after patients were discharged from hospital (mean time: 6.4 months), repeat <sup>123</sup>I-MIBG scintigraphy and echocardiography were carried out. Thirty patients in whom this second follow-up evaluation was not performed and 26 patients in whom medication protocols were changed at any point between the first and second evaluation were also excluded from the study. All procedures relating to human participants performed for this retrospective study adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki, its later amendments or comparable ethical standards. All participants included in the study gave their informed consent. Nine patients who did not give their informed consent were excluded, as were seven additional patients who did not attend the follow-up evaluation.

A total of 208 patients with CHF underwent follow-up evaluations, and this population provided highly reliable data. The study group was made up of 130 men and 78 women aged between 35 and 87 years (mean age: 68.6 years). Using propensity score matching, patients were included in either the azosemide treatment group (n=54) or the furosemide treatment group (n=54), as presented in figure 1, to evaluate the effects of long-acting loop diuretics on the CSNA.

### <sup>123</sup>I-MIBG imaging

The <sup>123</sup>I-MIBG imaging method used in this study has been described previously.<sup>12,15</sup> Briefly, at 15 min and at 4 h after injection with commercially available <sup>123</sup>I-MIBG (FUJIFILM RI Pharma Co, Ltd, Tokyo, Japan), a single-head  $\gamma$  camera (Millennium MPR, GE Medical Systems, Waukesha, Wisconsin, USA) was used to obtain anterior planar and single photon emission CT (SPECT) images.

The anterior planar delayed <sup>123</sup>I-MIBG image was used to evaluate the heart/mediastinum count (H/M) ratio by the standard method. The WR was calculated from early and delayed planar images. As recommended by the American Heart Association,<sup>16</sup> assessment of regional tracer uptake was performed semiquantitatively in 17 segments on the delayed SPECT image using a 5-point scoring system (0: normal to 4: no uptake). The total defect score (TDS, maximum score=4 $\times$ 17=68) was



**Figure 1** Flow diagram of participants in current study. ADHF, acute decompensated heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MIBG, metaiodobenzylguanidine scintigraphy; TTE, transthoracic echocardiography; 6M, after 6 months of hospital discharge.

evaluated as the sum of all defect scores and was converted to the percentage of the total denervated myocardium (% denervation) as follows:  $\text{TDS}/68 \times 100$ . As previously reported, in our laboratory, the reference range for % denervation is 6–18; the delayed H/M ratio range is 2.18–2.70 and the normal WR range is 20–30%.<sup>12 15</sup>

### Echocardiography

Two experienced echocardiography technicians were blinded with respect to independently performed standard echocardiography measurements made by them for this study. The LV end-diastolic volume (EDV), the LV end-systolic volume (ESV) and LVEF were evaluated using the two-dimensional biplane method, as reported previously.<sup>12</sup>

### Changes between the first and second echocardiographic and scintigraphic parameters

Changes between the first and second echocardiographic parameters (EDV, ESV and LVEF) and <sup>123</sup>I-MIBG scintigraphic parameters (% denervation, H/M ratio and WR) were calculated using the following formula:  $\delta\text{-}(X) = ((X) \text{ value after 6 months}) - (\text{baseline value of } (X))$ , in which (X) represents the <sup>123</sup>I-MIBG echocardiographic or scintigraphic parameters.

### Statistical analysis

Data were analysed using the Statistical Analysis System V.9.1 (SAS Institute Inc, Cary, North Carolina, USA) or the Statistical Package for the Social Sciences V.16.0 (SPSS Inc, Chicago, Illinois, USA). Results are expressed

**Table 1** Univariate and multivariate linear model of  $\delta$ -WR

	Univariate Correlation coefficient	p Value	Multivariate $\beta$ -Coefficient	p Value
Age	0.226	0.019	0.185	0.025
Gender (male=1)	0.169	0.081		
Ischaemic aetiology	0.080	0.411		
Diabetes mellitus	0.116	0.231		
NYHA	0.095	0.329		
ACE inhibitor	-0.109	0.263		
$\beta$ -Blocker	-0.384	<0.001	-0.363	<0.001
Furosemide	0.364	0.001	0.314	0.001
LVESV	0.131	0.177		
LVEF	-0.087	0.373		

LVEF, left ventricular ejection fraction; LVSDV, left ventricular end-systolic volume; NYHA, New York Heart Association; WR, washout rate.

as the mean $\pm$ SD or number (%). In all analyses, p values of less than 0.05 were considered statistically significant. A propensity-matched analysis was carried out to minimise the selection bias for azosemide administration.<sup>17</sup> The propensity score for the probability that azosemide would be administered was established by multivariate logistic regression analyses. The propensity score was evaluated using the following variables: age; sex; heart rate; blood pressure; tobacco usage; ischaemic aetiology; renal function; the New York Heart Association (NYHA) functional classes;<sup>123</sup> I-MIBG scintigraphic and echocardiographic parameters; acute phase treatments; and the presence of dyslipidaemia, diabetes and hypertension. Patients in the azosemide and furosemide groups were matched one to one to an accuracy of two digits, using the estimated propensity score for treatment with oral azosemide or furosemide. In our database, 54 patients were treated with azosemide, so 54 matched patients were selected from the furosemide group.

Categorical group data were compared using a two-sided  $\chi^2$  test, and differences between continuous variables were evaluated using a paired t test according to propensity score matching. Fisher's test was used to compare NYHA functional classes within the groups, and Fisher's permutation test was used between groups.

Deviations from the group baseline were evaluated using a paired t test, and differences between the two groups were analysed using two-way analysis of variance ANOVA.

Additionally, stepwise multiple linear regression was carried out to examine the variable of interest to evaluate the contribution to  $\delta$ -WR (table 1). Variables with p values of less than 0.1 on univariate analysis underwent multivariate analysis. To evaluate the effects of  $\beta$ -blockers in our patients with CHF, patients treated with  $\beta$ -blockers and those not treated with  $\beta$ -blockers were evaluated separately using the same analysis (tables 2 and 3, respectively).

## RESULTS

### Clinical characteristics

One-to-one propensity score matching was used on the 208 patients with CHF in our database to select 54 patients treated with furosemide to match the 54 patients treated with azosemide;<sup>12</sup> consequently, 108 patients were included in the present analysis. The baseline clinical characteristics, including those used for propensity score matching of the two groups, are shown in table 4. After 6 months of treatment, the dose of azosemide was 45 $\pm$ 18 mg/day, and that of furosemide was 31 $\pm$ 12 mg/day. (According to the results of a clinical study,

**Table 2** Univariate and multivariate linear model of  $\delta$ -WR in the patients treated with  $\beta$ -blocker

	Univariate Correlation coefficient	p Value	Multivariate $\beta$ -Coefficient	p Value
Age	0.226	0.031	0.183	0.058
Gender (male=1)	0.186	0.075		
Ischaemic aetiology	0.088	0.405		
Diabetes mellitus	0.023	0.824		
NYHA	0.020	0.850		
ACE inhibitor	-0.151	0.180		
Furosemide	0.413	<0.001	0.393	<0.001
LVESV	0.164	0.118		
LVEF	-0.118	0.262		

LVEF, left ventricular ejection fraction; LVSDV, left ventricular end-systolic volume; NYHA, New York Heart Association; WR, washout rate.



**Table 3** Univariate and multivariate linear model of  $\delta$ -WR in the patients treated without  $\beta$ -blocker

	Univariate Correlation coefficient	p Value	Multivariate $\beta$ -Coefficient	p Value
Age	0.431	0.096	0.364	0.113
Gender (male=1)	0.151	0.330		
Ischaemic aetiology	0.029	0.915		
Diabetes mellitus	0.384	0.113		
NYHA	0.200	0.764		
ACE inhibitor	-0.381	0.146		
Furosemide	0.461	0.018	0.441	0.021
LVESV	0.144	0.594		
LVEF	-0.120	0.659		

LVEF, left ventricular ejection fraction; LVSDV, left ventricular end-systolic volume; NYHA, New York Heart Association.

20 mg and 40 mg of furosemide were equivalent to approximately 30 mg and 60 mg of azosemide, respectively.<sup>14)</sup>

Systolic and diastolic blood pressure and heart rate tended to decrease in both groups after 6 months of treatment (table 5). However, the differences between these parameters were not significant. In addition, there were no significant differences between the baseline and 6-month-post-treatment values in either group with

respect to blood urea nitrogen, potassium level or estimated glomerular filtration rate (table 5).

### Comparison of cardiac <sup>123</sup>I-MIBG scintigraphic findings before and 6 months after treatment

Figure 2 summarises the changes in % denervation, H/M ratios and WR values. After 6 months of treatment, the % denervation had significantly decreased relative to baseline values in both groups (azosemide group: 58.1

**Table 4** Clinical characteristics of the patients

	Azosemide (n=54)	Furosemide (n=54)	p Value
Age (year)	67±13	68±11	0.567
Systolic pressure (mm Hg)	121±18	122±20	0.785
Diastolic pressure (mm Hg)	71±12	72±13	0.679
Heart rate (bpm)	70±8	71±10	0.567
Gender (male)	31 (57%)	35 (65%)	0.554
Ischaemic aetiology	21 (39%)	20 (37%)	0.843
Diabetes mellitus	25 (46%)	23 (43%)	0.847
Hypertension	28 (52%)	31 (57%)	0.699
Dyslipidaemia	22 (41%)	20 (37%)	0.844
Current smoker	13 (24%)	10 (19%)	0.639
BUN (mg/dL)	22.0±8.2	21.7±7.9	0.847
eGFR (mL/min/1.73 m <sup>2</sup> )	55±16	54±14	0.730
Potassium (mEq/L)	4.4±0.5	4.3±0.6	0.349
NYHA functional class II/III/IV	16/32/6	14/34/6	0.765
I-123 MIBG Scintigraphy			
Per cent denervation	58.1±11.9	60.8±9.8	0.155
H/M ratio	1.64±0.19	1.63±0.20	0.986
WR	48.9±9.7	49.1±10.8	0.875
Echocardiography			
LVEDV (mL)	187±42	186±42	0.902
LVESV (mL)	126±38	128±45	0.790
LVEF (%)	33±8	31±9	0.194
Medical treatment			
ACE inhibitor	41 (76%)	35 (65%)	0.292
ARB	22 (41%)	27 (50%)	0.440
$\beta$ -blocker	45 (83%)	46 (85%)	0.792
MR-antagonist	20 (37%)	24 (44%)	0.557

Values are mean±SD or number (%).

ARB, angiotensin-receptor blocker; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; H/M, heart/mediastinum count; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVSDV, left ventricular end-systolic volume; MIBG, meta-iodobenzylguanidine; MR, mineralocorticoid receptor; NYHA, New York Heart Association; WR, washout rate.

**Table 5** Changes in blood pressure, heart rate, BUN, eGFR and potassium in both groups

	Azosemide		Furosemide	
	Baseline	6 months	Baseline	6 months
Systolic pressure (mm Hg)	121±18	120±17	122±20	121±18
Diastolic pressure (mm Hg)	71±12	70±10	72±13	70±11
Heart rate (bpm)	70±8	69±8	71±10	70±9
BUN (mg/d)	22.0±8.2	22.3±8.4	21.7±7.9	22.0±8.2
eGFR (mL/min/1.73 m <sup>2</sup> )	55±16	55±19	54±14	53±18
Potassium (mEq/L)	4.4±0.5	4.4±0.5	4.3±0.6	4.3±0.5

Values are means± SD.

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

±11.9 to 44.3±13.2;  $p<0.001$ ; furosemide group: 60.8±9.8 to 55.1±15.7;  $p<0.01$ ). However, the  $\delta$ -% denervation was significantly lower in the azosemide group than that in the furosemide group ( $-13.8\pm10.5$  vs  $-5.7\pm12.7$ ;  $p<0.01$ ). H/M ratios had increased significantly after 6 months in both groups compared to those at baseline (azosemide group: 1.64±0.19 to 1.84±0.23;  $p<0.001$ ; furosemide group: 1.63±0.20 to 1.70±0.26;  $p<0.05$ ). However, the  $\delta$ -H/M ratio was significantly higher in the azosemide group than that in the furosemide group

( $0.20\pm0.16$  vs  $0.06\pm0.19$ ;  $p<0.01$ ). The WR in the azosemide group decreased significantly after 6 months relative to baseline values ( $48.9\pm9.7\%$  to  $37.6\pm10.2\%$ ;  $p<0.001$ ). However, no significant differences were observed between the baseline and 6-month-post-treatment values in the furosemide group ( $49.1\pm10.8\%$  to  $47.1\pm14.0\%$ ;  $p=NS$ ). The decrease in  $\delta$ -WR was significantly larger in the azosemide group than in the furosemide group ( $-11.3\pm9.2\%$  vs  $-2.0\pm12.7\%$ ;  $p<0.01$ ).

### Comparison of echocardiographic findings before and 6 months after treatment

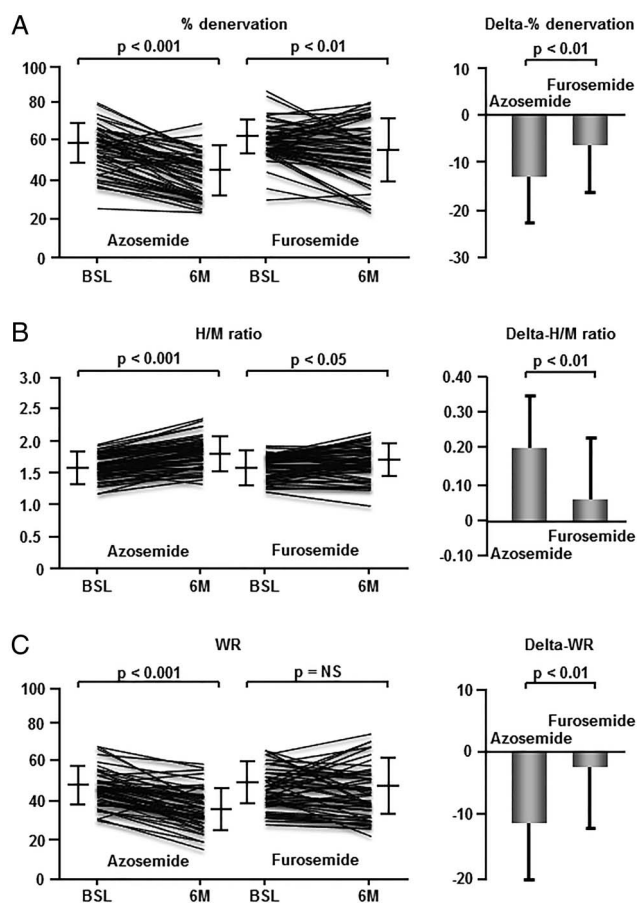
Table 6 summarises LVEDV, LVESV and LVEF. After 6 months of treatment, relative to baseline values, LVEDV and LVESV had decreased significantly, and LVEF had increased significantly in both groups. The sizes of the changes in these LV parameters in the azosemide group tended to be more favourable than those in the furosemide group, but the differences were not statistically significant.

### Comparison of NYHA functional class before and 6 months after treatment

Figure 3 and table 6 show the NYHA functional class status of patients. Patients from both groups showed improvement after 6 months of treatment relative to baseline values. After 6 months, the NYHA functional class status of patients receiving azosemide had improved more than it had in patients receiving furosemide.

### Evaluation of factors predicting increased $\delta$ -WR

Table 1 shows the results of the univariate and stepwise multiple linear regression model analyses assessing factors that predict an increase in  $\delta$ -WR. Univariate analysis indicated that age and not being treated with  $\beta$ -blockers, alongside furosemide treatment, were predictive factors. Stepwise multiple linear regression model analysis also showed that age and not being treated with  $\beta$ -blockers, alongside furosemide treatment, were significant independent predictors that increased  $\delta$ -WR in this group of patients with CHF. According to the  $\beta$ -coefficient (regression coefficient) results, furosemide



**Figure 2** Comparison of cardiac <sup>123</sup>I-metaiodobenzylguanidine scintigraphic findings for % denervation (A), H/M ratio (B) and WR (C) in the two groups. H/M, heart/mediastinum count; WR, washout rate; BSL, baseline; 6M, after 6 months of therapy.

**Table 6** Changes in left ventricular volume, ejection fraction and NYHA functional class

In both groups	Baseline	Azosemide 6 months	$\delta$	Baseline	Furosemide 6 months	$\delta$
Echocardiography						
LVEDV (mL)	187±42	160±44*	-26±32	186±42	165±47†	-21±28
LVESV (mL)	126±38	99±40*	-27±28	128±45	106±48*	-22±27
LVEF (%)	33±8	38±10*	6±9	31±9	36±11*	5±10
NYHA functional class I/II/III/IV	0/16/32/6	13/28/13/0*		0/14/34/6	6/23/24/1*‡	

Values are means±SD.

\*p < 0.001 vs Baseline, †p < 0.01 vs Baseline, ‡p < 0.01 vs Azosemide Group.

LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVSDV, left ventricular end-systolic volume; NYHA, New York Heart Association.

treatment was the second most reliable predictor of increasing  $\delta$ -WR.

In patients treated with  $\beta$ -blockers, age and furosemide treatment were predictive factors of increasing  $\delta$ -WR in the univariate analysis. The stepwise multiple linear regression model analysis identified only furosemide treatment as a significant independent predictor of increasing  $\delta$ -WR (table 2). In patients not treated with  $\beta$ -blockers, only furosemide treatment was a predictive factor in the univariate analysis. The stepwise multiple analysis identified furosemide treatment as the sole significant independent predictor of increasing  $\delta$ -WR (table 3).

## DISCUSSION

Patients were allocated by propensity score matching to groups treated with either the long-acting loop diuretic azosemide or the short-acting loop diuretic furosemide. Both groups showed improvement of  $^{123}$ I-MIBG scintigraphic parameters, with more favourable effects observed in the azosemide group. Stepwise analysis with a multiple linear regression model showed an independent and significant relationship between furosemide treatment and increasing  $\delta$ -WR in patients with CHF.

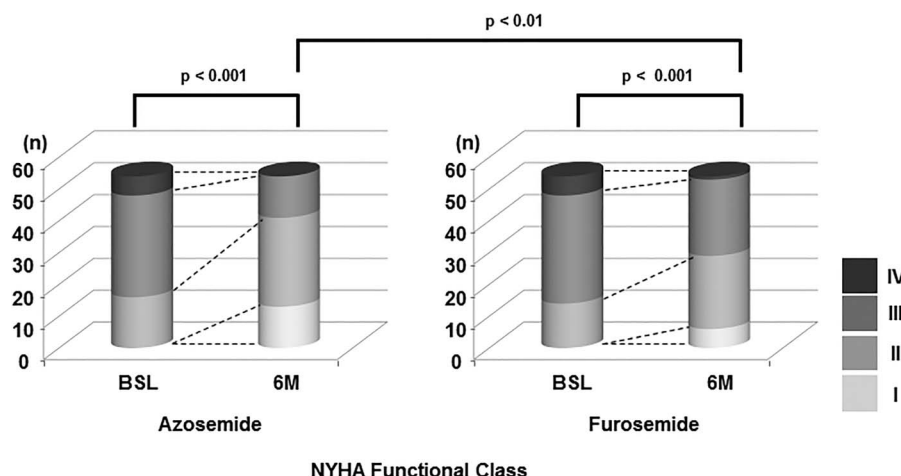
Loop diuretics exert powerful effects because they increase sodium and water excretion along the ascending limb of the loop of Henle. This class of drugs plays an essential role in the treatment of patients with CHF.<sup>1</sup> Administration of loop diuretics to patients with CHF activates the RAAS<sup>3,4</sup> and CSNA,<sup>5</sup> both of which play a principal role in the development of heart failure. Loop diuretics can be divided into two classes: short-acting vasodilators and long-acting vasodilators. Previous reports have shown increased mortality in patients with ischaemic heart disease treated with short-acting vasodilators.<sup>18,19</sup> This increase in mortality may be caused by short-acting vasodilators increasing the reflex in the sympathetic nerve system, because long-acting vasodilators do not appear to elicit such adverse effects.<sup>13</sup> Short-acting vasodilators are not indicated for the long-term treatment of patients with ischaemic heart disease.<sup>13</sup> The same adverse effects on the sympathetic

nerve system are caused by the short-acting loop diuretic furosemide and by short-acting vasodilators, and these adverse effects accelerate the progression of left ventricular systolic dysfunction in the failing heart.<sup>3</sup>

Azosemide exerts its diuretic action more slowly and has fewer adverse effects on the RAAS or CSNA than does furosemide.<sup>13</sup> The Japanese Multicenter Evaluation of Long-acting versus short-acting Diuretics In Congestive heart failure (J-MELODIC) study established that, compared to furosemide treatment, azosemide treatment reduces the risk of unplanned hospital admissions and cardiovascular death resulting from heart failure in patients with CHF.<sup>20</sup> In the current study, azosemide treatment ameliorated symptoms of heart failure as evidenced by enhanced improvements in NYHA functional classes compared to furosemide treatment. However, the long-term prognoses of the two groups could not be compared because of the small number of patients enrolled in this study. Further studies are needed to compare the effects of azosemide and furosemide on the long-term prognosis of a larger group of patients.

$^{123}$ I-MIBG is an analogue of the adrenergic neuron-blocking agent guanethidine, and likely uses the same myocardial uptake and release mechanisms as norepinephrine.<sup>21</sup> Consequently, cardiac  $^{123}$ I-MIBG imaging in patients with CHF is useful for identifying abnormalities in the myocardial adrenergic nervous system.<sup>8,9</sup> Many studies based on cardiac  $^{123}$ I-MIBG scintigraphic findings have suggested that treatment of CHF with ACE inhibitors,<sup>22,23</sup> ARBs,<sup>24-26</sup>  $\beta$ -blockers<sup>23,27,28</sup> or spironolactone<sup>29-31</sup> may improve CSNA. However, very few studies have used  $^{123}$ I-MIBG scintigraphy to evaluate the effects of azosemide on CSNA in patients with CHF. The current study focused on  $^{123}$ I-MIBG scintigraphic parameters to assess the effect of azosemide and furosemide therapy in patients with CHF; more improvement in these parameters was observed in the azosemide group compared to the furosemide group. In addition, furosemide therapy had an independent and significant positive relationship with  $\delta$ -WR in patients with CHF on stepwise multiple linear regression model analysis. We previously reported that  $\delta$ -WR is the best currently available prognostic indicator for patients with CHF.<sup>12</sup>

**Figure 3** Changes in New York Heart Association functional class during treatment in the two groups. NYHA, New York Heart Association; BSL, baseline; 6M, after 6 months of therapy.



Consequently, the current findings demonstrate for the first time that azosemide therapy may be more favourable than furosemide for attenuating the activated CSNA and for improving the long-term prognoses of patients with CHF. Also, multiple linear regression model analysis showed that furosemide therapy had an independent and significant relationship with increasing  $\delta$ -WR in those treated with  $\beta$ -blockers as well as in those not treated with  $\beta$ -blockers. This finding suggests that furosemide therapy may have adverse effects on CSNA even if  $\beta$ -blockers are administered.

In patients with heart failure, changes in cardiac function and LV volume have been associated with adverse cardiac events, including cardiac deaths.<sup>32</sup> Yoshida *et al*<sup>13</sup> reported that, in an experimental animal model, azosemide administration not only prevented LV remodelling, but also further attenuated sympathetic activity when compared to the effects of furosemide administration. The advantageous effects of azosemide may improve outcomes.<sup>13</sup> In the present study, the extent of changes in cardiac function and LV volume tended to be more favourable in the azosemide group than in the furosemide group, although this difference was not statistically significant. This absence of statistical significance could have resulted from the small sample size of the current study; the effects of azosemide and furosemide on LV remodelling must be assessed in a larger group of patients.

## CONCLUSION

The <sup>123</sup>I-MIBG scintigraphic parameters improved in both treatment groups, but more favourable changes were evident in the azosemide group than in the furosemide group. Furosemide therapy was an independent predictor of increasing  $\delta$ -WR in patients with CHF, according to stepwise multivariate analysis and this finding suggests that azosemide therapy effectively attenuates the activated CSNA in patients with CHF. Our findings show that azosemide therapy is potentially more effective in reducing the incidence of cardiac events than furosemide therapy is.

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**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** This study was conducted with the approval of UMIN-CTR Clinical Trial. <https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000756&type=summary&language=E>

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