Rationale and Design of a Randomized Trial to Assess the Effects of Diuretics in Heart Failure
— Japanese Multicenter Evaluation of Long- vs Short-Acting Diuretics in Congestive Heart Failure (J-MELODIC) —

The J-MELODIC Program Committee*

Background Diuretics are the most prescribed medication for heart failure (HF) patients, but clinical evidence of the long-term effects of diuretics are lacking. The present study was designed to compare the therapeutic effects of furosemide, a short-acting loop diuretic, and azosemide, a long-acting one, in patients with HF to test the hypothesis that long-acting diuretics are superior therapy.

Methods and Results The Japanese Multicenter Evaluation of LOng- vs short-acting Diuretics In Congestive heart failure (J-MELODIC) is a multicenter, prospective, randomized trial enrolling a total of 300 patients (150 patients in each group). The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive HF. Other outcomes include all-cause mortality, worsening of the symptoms of HF, or a need for modification of therapy. Serial assessment of echocardiographic and neurohumoral parameters will be conducted over a minimum follow-up period of 2 years.

Conclusions The study results will provide important evidence for the treatment of chronic HF. (Circ J 2007; 71: 1137–1140)

Key Words: Azosemide; Diuretics; Furosemide; Heart failure

Heart failure (HF) continues to be prevalent, particularly in the elderly population, and mortality and morbidity are still high, despite emerging evidence of the beneficial effects of angiotensin-converting enzyme inhibitors, Î±-blockers, angiotensin II type 1 receptor blockers and aldosterone-receptor antagonists.

Diuretics are the most prescribed drugs for HF and there is no question of their necessity for attenuating symptoms related to fluid retention, and they are recommended as essential in patients with HF symptoms and/or fluid retention. However, the effects of long-term administration on morbidity and mortality have not been adequately assessed in a prospective clinical study, and retrospective analysis does not necessarily indicate diuretic-induced improvement of mortality.

Loop diuretics are more widely used in the treatment of HF than thiazide diuretics and can be divided into 2 classes: short-acting and long-acting. In clinical practice, furosemide, a short-acting loop diuretic, is the most commonly used in the treatment of HF. McCurley et al demonstrated adverse effects of furosemide in a tachycardia-induced HF model and Yoshida et al demonstrated that administration of furosemide did not improve mortality rate in a hypertensive HF model, despite a significant reduction in blood pressure. Thus, a lack of improvement in the mortality rate of HF patients with prescription of diuretics may be partly explained by the wide-spread use of short-acting loop diuretics.

Yoshida et al also reported that the administration of azosemide, a long-acting loop diuretic, improved mortality rate in their hypertensive HF model. If the effects on mortality and/or morbidity of HF patients are different among the classes of diuretics, we should choose a class that provides a better prognosis. Thus, we designed a multicenter prospective study, J-MELODIC (Japanese Multicenter Evaluation of LOng- vs short-acting Diuretics In Congestive HF) to obtain clinical evidence of the effects of diuretics in HF.

Aims
The aim of this trial is to test our hypothesis that long-acting diuretics give a better prognosis for HF patients than short-acting ones, and we will compare the effects of furosemide, a short-acting loop diuretic, and azosemide, a long-acting one.

Study Design
The study uses a multicenter, prospective, randomized, open, blinded endpoint (PROBE) design.

Ethical Issues
The study will be conducted in accordance with the principles stated in the Declaration of Helsinki, 1964, as revised
in South Africa in 1996. The Ethical Committee in Hyogo College of Medicine approved this study on October 18, 2005 (No. 298). The study protocol was also submitted to the ethics committee of each participating hospital. Written informed consent will be given by all patients before entry to the study.

### Outcome Measures

The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive HF. The secondary outcomes are: all-cause mortality; worsening of symptoms (defined by either a decrease by $\geq 1$ Mets in the SAS questionnaire score or an increase by $\geq 1$ class in the NYHA functional class for at least 3 months as compared with the baseline); an increase in brain natriuretic peptide (BNP) by $\geq 30\%$ of the value at randomization in patients with BNP $\geq 200$ pg/ml at randomization; unplanned admission to hospital for congestive HF, or a need for modification of the treatment for HF (changes in oral medicine for at least 1 month or addition of intravenous drug(s) for at least 4 h). Outcomes will be assessed by the endpoint committee where the allocated group is blinded to all the committee members.

### Eligibility

**Inclusion Criteria**
1. 20 years or older; clinical diagnosis of HF based on a slight modification of the Framingham criteria as previously described within 6 months before the entry (Table 1); current status of HF is NYHA II or III.
2. Currently, loop diuretic(s) is (are) administered.

**Exclusion Criteria**
1. Diabetes mellitus that has not been well controlled (fasting blood glucose $>200$ mg/dl, hemoglobin A1c $>9\%$).
2. Current symptomatic hypotension.
3. Hypertension that has not been controlled to the satisfaction of the investigator.
4. Serum creatinine $>2.5$ mg/dl.
5. Serious liver disease; acute coronary syndrome; any life-threatening acute disease.
6. Other diseases likely to cause death or serious disability during the period of the study.
7. Patients with implantable cardiac defibrillator.
8. Hemodynamically significant (in the investigators opinion) left ventricular (LV) outflow tract obstruction (caused by either aortic stenosis or ventricular hypertrophy).
9. History of serious chronic obstructive pulmonary disease or restrictive lung disease.
10. Primary pulmonary hypertension or pulmonary hypertension not caused by LV dysfunction.
11. Acute myocardial infarction, cerebrovascular accident, percutaneous coronary intervention or open heart surgery within the last 3 months.
12. On a waiting list for percutaneous coronary intervention or open heart surgery.
13. Any change in cardiovascular drug therapy within the month prior to randomization.
14. Malignancy; surgery to resect malignant tumor within past 5 years.
15. Patients unable to walk without personal aid.
16. Serious cerebrovascular disease.
17. Patients who require intravenous inotropes.
18. Pregnancy.
19. Patients who were judged not to be suitable for entry by physicians.

**Randomization and Maintenance Phase**

After screening for eligibility and obtaining written informed consent, patients will be randomized to either azosemide or furosemide treatment in a 1:1 ratio (Fig 1). In any arm, patients will be treated with standard therapy including digitalis, mineralocorticoid receptor blockers, thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, Î²-blockers, and calcium-channel blockers.

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**Table 1 Definition of Heart Failure**

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
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<tbody>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Edema</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>Night cough</td>
</tr>
<tr>
<td>Abnormal jugular venous distention</td>
<td>Dyspnea on exertion</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Tachycardia (&gt;120 beats/min)</td>
</tr>
<tr>
<td>Presence of a third heart sound</td>
<td>Weight loss of $\geq 4.5$ kg in 5 days (considered a major criterion if it occurs during therapeutic interventions for heart failure)</td>
</tr>
<tr>
<td>Central venous pressure $&gt;16$ cmH$_2$O</td>
<td>Heptalojugular reflux</td>
</tr>
</tbody>
</table>

A patient is considered to have heart failure if 2 major criteria are present or if 1 major and 2 minor criteria are present concurrently.

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**Fig 1. J-MELODIC study design.**
Patients will discontinue previously prescribed loop diuretic(s) and will be directly rolled over to 1 of the 2 arms with either azosemide 30–60 mg/day or furosemide 20–40 mg/day, without a placebo run-in period. The dose of each diuretic will be appropriately adjusted according to the symptoms of each patient, and patients will be maintained on that dosage for the rest of the study. If it is difficult to stabilize the symptoms of HF, azosemide will be increased up to 120 mg/day, and furosemide up to 80 mg/day. Loop diuretics other than the study drugs are not allowed to be prescribed.

Thereafter, patients are reviewed every 2–8 weeks. The planned minimum follow-up period for each patient is 2 years, and electrocardiography, echocardiography, chest X-ray and blood sampling will be conducted at study entry and every 12 months after randomization.

**Statistical Analysis**

**Sample Size Determination** As the short-acting loop diuretic, furosemide has produced the data of a 2-year incidence of the primary endpoint of 35%, whereas the 2-year incidence by use of a long-acting loop diuretics, torasemide, has been demonstrated to be 15%.10 It suggests that the hazard ratio of azosemide, another long-acting loop diuretic, might be 0.38 against furosemide. However, the 2-year incidence in Japan will be probably lower than the data shown above based on previous clinical experience. The combined incidence of death and hospitalization for HF in Japanese patients who were treated with standard therapy was reported to be 15% for 1 year (30% for 2 years) in EPOCH11 and 5% for 6 months (20% for 2 years) in ARCH-J.12 Therefore, the 2-year incidence was assumed to be 25% for furosemide and the hazard ratio was conservatively set at 0.5. Assuming a 2-year recruitment and a maximum of 4-years follow-up, a total of 132 per group is required to detect statistical significance between groups using the log-rank test, with a power of 80% according to the method of Lakatos and Lan.13 Taking a small proportion of attritions, we ended up with a total of 150 per group.

**Methods** Cumulative event-free curves are constructed by the Kaplan-Meier method, and differences between treatment groups are evaluated by log-rank test. The Cox proportional hazards regression model is used to examine the effect of treatment in the presence of pre-specified covariates. All analyses are conducted in accordance with the intention-to-treat principle. Proportions such as worsening BNP and symptoms are compared with either the chi-square test or Fisher exact test. Continuous variables, such as blood pressure, are compared by repeated measures analysis of variance adjusted by baseline values. Statistical significance is defined by 2-sided 5% and the analyses will be performed using SAS statistical software version 9.1. Interim analyses will be planned after the end of recruitment and 1 year later in an ad hoc fashion using the Peto-Haybittle criterion.

**Status of the Study**

The first patient was enrolled in June 2, 2006 and the study is expected to finish in 2010.

**Discussion**

Diuretics are clearly effective in relieving HF symptoms and loop diuretics are widely used in the treatment of HF; however, retrospective studies have reported increased risks of the use of non-potassium-sparing diuretics including loop diuretics in patients with HF.14,15 Loop diuretics can be divided into short- and long-acting ones, and furosemide, a short-acting one, is the most widely used.6 Recent animal experiments suggest that the wide-spread use of short-acting loop diuretics partly explains the lack of improvement in the mortality of patients treated with loop diuretics.6,7

Vasodilators are also widely used in the treatment of HF and are divided into short- and long-acting ones. Previous clinical studies reported adverse effects of short-acting vasodilators in patients with coronary artery disease, despite their antihypertensive effects.16,17 Currently, short-acting vasodilators are not used in the long-term treatment of patients with cardiovascular diseases. A probable mechanism is a reflex increase in sympathetic activity. Yoshida et al suggested the same mechanism as an explanation of the lack of improvement in the mortality rates with HF treatment using furosemide, despite a reduction in both preload and afterload.7

Previous clinical studies have shown the superiority of torasemide, a long-acting loop diuretic, to furosemide.17,18 Torasemide inhibits aldosterone binding to its receptor19,20 and several clinical studies have demonstrated the usefulness of aldosterone blockers in patients with HF.21,22 Thus, it is unclear whether the benefits of torasemide are provided through its longer half-life and longer duration of action or through its aldosterone blockade. The current study will address this issue.

In spite of recent progress in the treatment of HF following a number of prospective clinical trials during the past decades, the prognosis of HF patients is still poor.23 This study confirms our hypothesis, diuretic therapy should be switched to long-acting ones for the treatment of HF, leading to an improvement in the prognosis of HF patients. This clinical study will contribute to advances in the treatment of HF.

**Acknowledgments**

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**References**

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**Appendix 1**

**The J-MELODIC Program Committee**

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**Data Safety and Monitoring Committee:** Akira Kitabatake, Japanese Circulation Society; Hirohito Matsuo, Shikoku Electric Power Co Inc; Toshihiko Morikawa, Kurume University.

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http://www.escardio.org/knowledge/guidelines/Chronic_Heart_Failure.htm

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