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ORIGINAL ARTICLE
Heart Failure

Clinical Efficacy of Cardiac Resynchronization Therapy With an Implantable Defibrillator in a Japanese Population

– Results of the MIRACLE-ICD Outcome Measured in Japanese Indication (MOMIJI) Study –

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Background: Cardiac resynchronization therapy (CRT) is effective in reducing morbidity and mortality in systolic heart failure patients with cardiac dyssynchrony as demonstrated in studies with primarily Western populations. Although CRT devices with a defibrillator (CRT-D) became available in Japan since 2006, their efficacy remains uncertain in Japanese patients. In this prospective, multicenter study, the efficacy of CRT-D therapy in an all-Japanese population was compared with the study conducted in the US, Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD).

Methods and Results: Ninety-three patients were evaluated according to the subject selection criteria of the MIRACLE-ICD study, and 80 patients were enrolled. Results at baseline and 6-month post-CRT-D implantation were compared in terms of composite clinical response (CCR) and other secondary endpoints. Quality of life (QOL) was assessed with a validated Japanese version of the Minnesota Living with Heart Failure questionnaire. CCR was improved in 55 patients (68.8%), unchanged in 14 (17.5%), and worsened in 11 patients (13.7%) (MIRACLE-ICD general phase: 62.0%, 13.4% and 24.6%, respectively). Non-inferiority was verified by 1-sided test with 10% equivalence margin. QOL score improved significantly (50.0±26.2 vs. 23.6±20.2, P<0.01).

Conclusions: The MOMIJI study demonstrated that CRT-D effectiveness as assessed with CCR was non-inferior to the trials conducted outside Japan, thus suggesting that the benefits of CRT-D are similar between Japanese and non-Japanese patients. (*Circ J* 2012; **76:** 1911–1919)

Key Words: Biventricular pacing; Cardiac resynchronization therapy; Defibrillators; Heart failure; Minnesota Living with Heart Failure

A number of large-scale randomized clinical studies demonstrated that cardiac resynchronization therapy (CRT) with or without an implantable cardioverter defibrillator (CRT-D) could improve symptoms, quality of life (QOL), functional status, exercise capacity, and mortality in patients with moderate to severe heart failure (HF), a wide QRS, and life-threatening arrhythmias.[1–3] More recent studies suggested that long-term CRT-D therapy could prevent the progression of disease and reduce the mortality also in patients with asymptomatic or mild HF.[4–8] CRT-D devices have been available since 2006, and their use is gradually gaining acceptance in Japan. Japanese patients have been included in multinational studies of CRT[9] and the results for Japanese patients have been reported in single-center studies, registries, and case reports.[10–13] However, clinicians have been uncertain as to whether the prognosis of Japanese patients with HF is compa-

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Table 1. Inclusion and Exclusion Criteria

Inclusion

1. Age ≥20 years
2. Heart failure patients whose symptoms have not improved despite optimal pharmacological therapy and who meet all the criteria listed in (A) below as well as the criteria in either (B) or (C) with the exception of patients with disease of transient or reversible cause.
   (A) Indicated heart failure patients:
   - NYHA class III or IV
   - LVEF ≤35%
   - Intrinsic QRS duration ≥130 ms

   (B) Patients with one of the following risks for sudden cardiac death:
   - History of resuscitation from cardiac arrest following fatal arrhythmia (clear loss of consciousness)
   - VT or VF that disrupts hemodynamics
   - Confirmed NSVT, as well as VT or VF induced by electrophysiological testing

   (C) Patients who meet the Japanese criteria for implantation of an ICD
3. Patients signed the informed consent and permission for access to and use of health information.
4. Patients who are willing to visit the hospital in accordance with the follow-up schedule

Exclusion

1. Estimated survival <6 months
2. Bradycardia requiring pacemaker
3. Unstable angina, myocardial infarction, coronary angioplasty, cerebral vascular accident, or transient ischemic attack within the previous 3 months
4. >2 infusions of inotropic drug per week
5. Systolic blood pressure <80 mmHg or >170 mmHg
6. Resting heart rate >140 beats/min
7. Serum creatinine >3 mg/dl (265 μmol/L)
8. Hepatic enzymes >3-fold upper normal values
9. Severe lung disease
10. Chronic AF defined using the following classification:
    - Permanent: long-standing episode for which cardioversion did not take effect.
    - Persistent: recurrent episodes that are sustained but could be cardioverted.
    - Paroxysmal: recurrent episodes that stopped spontaneously.
11. Heart transplant recipient
12. Severe valvular heart disease (decision on severity made by a medical doctor)
13. Existing CRT or CRT-D device

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; CRT, cardiac resynchronization therapy; CRT-D, CRT with an implantable cardioverter defibrillator.

rable to that seen in the large-scale clinical trials conducted in Western countries.[14,15]

Editorial p1830

We conducted the MIRACLE-ICD Outcome Measured in Japanese Indication (MOMIJI) Study to compare the efficacy of CRT-D therapy in a population of Japanese patients with advanced HF, an intraventricular conduction delay, and an indication for implantable cardioverter defibrillator (ICD) therapy. The aim of the study was to examine the non-inferiority to the results of the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) general phase study conducted in the United States with regard to a composite clinical response (CCR) that classified patients as being improved, unchanged, or worsened. The MOMIJI study is the first prospective multicenter clinical trial of CRT-D therapy in an all-Japanese population seeking to evaluate equivalency of therapy to that in Western countries and the first usage of the officially validated Japanese language version of the Minnesota Living with Heart Failure (MLHF) questionnaire.

Methods

Study Population

The MOMIJI study was conducted at 22 centers in Japan between March 12, 2007 and March 31, 2009. Enrollment criteria were similar to those of the MIRACLE-ICD study,[1] except for left ventricular end-diastolic diameter (LVEDD) ≥55 mm and 6-min walk distance >450 m, which were an inclusion and an exclusion criterion, respectively, for MIRACLE-ICD. **Table 1** lists the inclusion and exclusion criteria. No particular medications were required, and the medication status of patients was collected at baseline. The study protocol was approved by the institutional review board/medical ethics committee of each participating center, and all patients provided signed informed consent.

Patients meeting the enrollment criteria underwent a baseline evaluation prior to implant that included New York Heart Association (NYHA) class assessment, echocardiography, most recent documented intrinsic QRS interval, and B-type natriuretic peptide (BNP) measurement. Patients were also asked to complete 2 QOL assessment tools: the MLHF questionnaire in the Japanese language and the Specific Activity Scale (SAS) questionnaire. Patients then underwent implantation of a com-

mercially available CRT-D device manufactured by Medtronic, Inc (Minneapolis, MN, USA) and a right atrial pacing lead, a right ventricular pacing/defibrillator lead, and a left ventricular lead. A variety of leads not limited to those manufactured by Medtronic were used in the study.

Device Programming

General device programming was left to physician discretion. However, optimization of the sensed and paced atrioventricular (AV) delays was required. Use of the Ritter Method[16] was encouraged though other methods were allowed. Interventricular (V-V) timing optimization was recommended, and was required to be performed prior to AV delay optimization. Additionally, programming antitachycardia pacing (ATP) according to the PainFREE Rx II algorithm was recommended.[17]

Study Design and Endpoints

The MOMIJI study was a prospective, multicenter, observational study characterizing outcomes of CRT-D therapy in a Japanese population. The primary endpoint was non-inferiority to the CCR seen in the general phase of the MIRACLE-ICD study. The CCR was a secondary endpoint in both the intensive and general phases of the MIRACLE-ICD study. The CCR, which assesses patients more globally, is an accepted outcome measure in HF trials and has been used as an endpoint in studies such as the MIRACLE-ICD II and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) studies.[4–6,18]

Patients in the MOMIJI study were classified as worsened, improved, or unchanged using definitions of those in the MIRACLE-ICD study. In the MOMIJI study, a patient was classified as worsened if he or she died, was hospitalized due to or associated with worsening HF, permanently discontinued CRT-D due to or associated with worsening HF, treatment failure, or lack of/insufficient therapeutic response, withdrew or was withdrawn from study and had worsening HF at the time of study withdrawal; demonstrated worsening in NYHA class at last observation carried forward (LOCF) or moderate-marked worsening of patient global assessment score at LOCF. Only hospitalizations that were due to worsening HF and would have resulted in the patient being hospitalized under standard medical practice were included in the CCR analysis. To minimize bias in comparison of hospitalization data between the MOMIJI and MIRACLE-ICD studies, a hospitalization events review committee composed of Japanese and US HF physicians adjudicated hospitalizations to determine if a Japanese admission would have been managed on an outpatient basis had the case been managed in the USA or if the patient would have been hospitalized. A patient was classified as improved if he or she had not worsened (as defined above) and demonstrated improvement in NYHA class at LOCF and/or moderate to marked improvement in patient global assessment score at LOCF. A patient was unchanged if he or she was neither improved nor worsened.

Secondary outcomes in the MOMIJI study included QOL assessment using the MLHF and SAS. The MLHF questionnaire is a validated[19,20] and well established assessment tool that has been used to assess patient QOL in a number of major trials of CRT.[1,5,6,21,22] The Japanese translation of the MLHF questionnaire was validated linguistically by the Health Outcome Group (San Francisco, CA, USA) with permission from Minnesota University (Minneapolis, MN, USA). The SAS assessment tool[23] is recommended by the Japanese Circulation Society and is widely used in Japan. Other secondary outcomes included characterization of the effectiveness of ATP in terminating ventricular tachycardia (VT) episodes and plasma BNP levels, echocardiographic parameters, and HF hospitalizations. The mitral regurgitant fraction was assessed by calculating the percentage of the color-Doppler area relative to the left atrial area in the apical 4-chamber view. Patients were followed at 1, 3, and 6 months. Full interrogation of the CRT-D device and NYHA assessment were performed at each visit. QOL evaluation using the MLHF and SAS questionnaires and echocardiography were performed at 6-month follow-up only.

MIRACLE-ICD General Phase

The general phase of the MIRACLE-ICD study was a continuation of the intensive phase which evaluated the safety and efficacy of the Medtronic Model 7272 InSync ICD system. All patients were programmed to CRT ON and both physicians and patients were unblinded to therapy delivery. Study inclusion and exclusion criteria were the same as in the intensive phase.[1] The general phase of the MIRACLE-ICD study was chosen as a comparative reference point for the therapeutic efficacy of CRT-D in the MOMIJI study because the inclusion criteria were similar to the CRT-D indication in Japan and because the study was unblinded. The intensive phase of the MIRACLE-ICD study was a prospective randomized double-blind study during which both physicians and patients were unaware of whether CRT was turned ON or OFF.[1] Results of the general phase of the MIRACLE-ICD study have not been published previously. However, the study authors have granted the MOMIJI investigators full access to the data and permission to publish the results of the general phase of the MIRACLE-ICD study as needed.

Statistical Analysis

All successfully implanted patients were included in the analysis. In terms of the primary endpoint, 62% (88/142) of the patients with NYHA class III or IV in the MIRACLE-ICD study had a response of improved on the CCR. We evaluated the non-inferiority with an equivalent margin of 10% on the CCR and a P-value <0.05 using an exact proportion test. An odds ratio analysis with and without a propensity score was also performed. The propensity score was computed using logistic regression with the study (MIRACLE-ICD or MOMIJI) as a response variable and 13 baseline parameters (sex, age, NYHA class (III or IV), QRS duration, left ventricular ejection fraction (LVEF), LVEDD, non-ischemic or ischemic etiology, hypertension, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, and diuretic) as explanatory variables. The odds ratio and 95% confidence interval (CI) of improved CCR between both studies were calculated directly and with the adjusted quintile propensity score.

For the secondary endpoints, descriptive statistics were used. The paired t-test was used to compare changes from baseline to 6 months. The success rate of ATP therapy was analyzed using detected VT/ventricular fibrillation (VF) episodes treated by ATP. ATP was considered successful if the episode terminated prior to a cardioversion or defibrillation shock. Geometric means were used for the analysis of BNP.

Adverse events were not collected. However, centers were required to report events in the same manner required for any commercially available device in Japan. The study was coordinated by Medtronic Japan. All data were collected on case report forms. Information was forwarded via a DataFax system and automatically stored into a database. Device interrogation data were saved to disk and forwarded to Medtronic Japan.

Table 2. Baseline Characteristics of the MIRACLE ICD and MOMIJI Study Groups*

Characteristic	MIRACLE ICD General phase (n=142)	MOMIJI (n=80)	P value
Age, (years) (SD)	67.3 (10.2)	64.7 (13.2)	0.10
Male sex, n (%)	109 (76.8)	63 (78.8)	0.87
NYHA class, (%)			0.65
III	126 (88.7)	73 (91.3)	
IV	16 (11.3)	7 (8.8)	
QRS interval, (ms) (SD)	166.4 (25.0)	160.9 (27.6)	0.13
BNP, pg/ml (SD)	–	626.8 (713.8)	–
LVEF, (%) (SD)	21.2 (6.5)[a]	23.0 (6.4)	0.04
LVEDD, (mm) (SD)	68.2 (8.6)	70.2 (10.3)[b]	0.13
MLHF score (SD)	56.9 (23.7)	51.8 (26.2)[c]	0.14
Underlying heart disease, n (%)			
Ischemic	82 (58.6)	24 (30.0)	<0.01
Non-ischemic	58 (41.4)	56 (70.0)	
Hypertension, n (%)	19 (13.4)	23 (28.8)	<0.01
Atrial tachyarrhythmias, n (%)			
Atrial flutter	5 (3.6)	3 (3.8)	>0.99
Paroxysmal AF	19 (13.6)	16 (20.0)	0.25
Ventricular tachyarrhythmias, n (%)			
Non-sustained VT	42 (30.0)	47 (58.8)	<0.01
Sustained VT	50 (35.7)	20.0 (25.0)	0.13
VF	14 (10.0)	7 (8.8)	0.82
Indication for ICD, n (%)			
Cardiac arrest*	–	9 (11.3)	–
Sustained VT*	–	22 (27.5)	–
Induced VF and SVT*	–	24 (30.0)	–
Low EF and advanced NYHA class alone	–	39 (48.8)	
Baseline medications, n (%)			
ACE inhibitor or ARB	126 (88.7)	64 (80)	0.11
β-blocker	91 (64.1)	58 (72.5)	0.23
Diuretic	137 (96.5)	76 (95.0)	0.73
Antiarrhythmic	46 (32.4)	42 (52.5)	<0.01

[a]n=141, [b]n=79, [c]n=76.
*More than 1 per patient possible.
P values were calculated by Fisher exact test or Student's t-test. All differences between the MIRACLE ICD and MOMIJI groups are not statistically significant, except categories with P<0.05.
MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; MOMIJI, MIRACLE-ICD Outcome Measured in Japan Indication; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic dimension; MLHF, Minnesota Living with Heart Failure; EF, ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker. Other abbreviations as in Table 1.

Results

Through August 31, 2008, 93 patients were enrolled in the MOMIJI study. Of these patients, 13 were withdrawn (7 patients did not meet the eligible criteria for this study; 3 patients underwent an implant attempt but a device was not implanted; 2 patients had their device explanted; and 1 patient died prior to implantation). The remaining 80 patients comprise the MOMIJI study population described in this report. The baseline characteristics of the patients in the MOMIJI and the MIRACLE-ICD general phase are summarized in **Table 2**. There was a significant difference (P<0.05) between the 2 populations in terms of LVEF and the percentage of patients with an ischemic etiology, hypertension, non-sustained VT, and antiarrhythmic drugs. For all other baseline categories, the clinical characteristics of patients in both studies were similar.

Primary Endpoint

CRT-D treatment exerted favorable effects on the CCR. At 6-month follow-up, CCR was improved in 68.8% (n=55), unchanged in 17.5% (n=14), and worsened in 13.8% (n=11). These results demonstrated the non-inferiority compared with the MIRACLE-ICD general phase data (**Figure 1**). The difference in the percentage of patients improved at 6-month follow-up was 6.78 (95% CI: −6.14 to 19.70). Non-inferiority was verified by 1-sided test with the equivalent margin of 10% (P=0.01).

Non-inferiority with the MIRACLE-ICD CCR was also confirmed in the odds ratio analysis to adjust for the differences in the baseline characteristics between 2 studies. For improved CCR, the unadjusted odds ratio between MIRACLE-ICD and MOMIJI was 1.350 (95% CI: 0.755 to 2.415, P=0.3119). The odds ratio adjusted by propensity score was 1.309 (95% CI: 0.684 to 2.507, P=0.42). These odds ratios were comparable, and both lower interval values were greater than 0.668 dem-

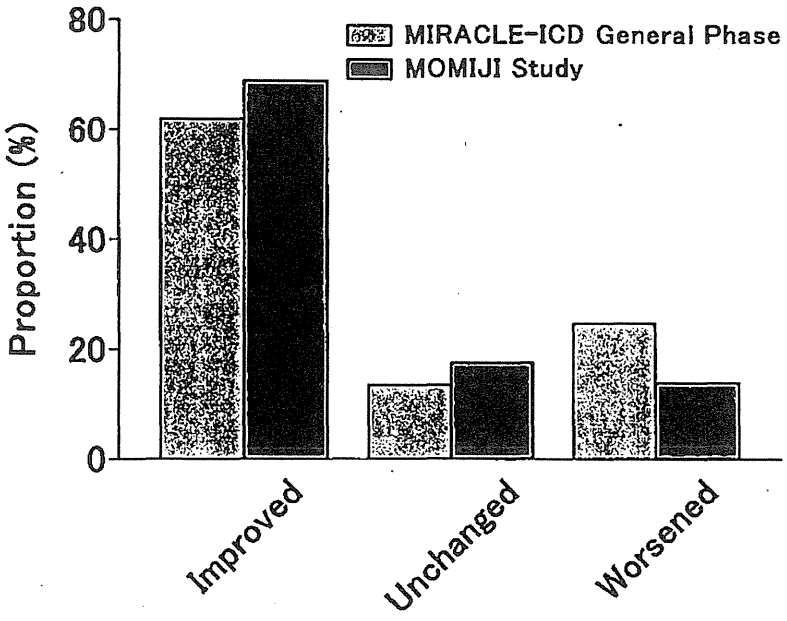

Figure 1. Clinical composite response in MOMIJI (n=80) and MIRACLE-ICD general phase (n=142) patients. There was a 6.8% (SD 6.59%) difference in the proportion that improved between the MOMIJI study and the MIRACLE-ICD general phase study. The 95% confidence interval was −6.14 to 19.70, demonstrating a non-inferiority margin of more than −10%.

Table 3. Secondary Endpoint Analysis Between Baseline and 6-Month Follow-up

	n	Baseline (mean±SD)	6 months (mean±SD)	P value
MLHF	67	50.0±26.2	23.6±20.2	<0.01
SAS	67	2.8±1.9	4.0±2.0	<0.01
LVEF (%)	54	23.6±6.4	31.6±12.0	<0.01
LVESV (ml)	49	163.1±81.1	135.0±78.8	<0.01
MRF (%)	32	24.8±14.8	18.4±14.9	0.03
BNP (pg/ml)	75	383.2±302.0	176.4±132.8	<0.01

SAS, Specific Activity Scale; LVESV, left ventricular end-systolic volume; MRF, mitral regurgitant fraction. Other abbreviations as in Tables 1,2.

onstrating lower limit corresponding to the non-inferiority margin of 10%.

Secondary Endpoints

The results of the secondary endpoints are summarized in Table 3. The improvement with MLHF scores between the baseline visit and 6-month follow-up were comparable to those seen with MIRACLE-ICD study (Figure 2). SAS scores also improved significantly confirming that the QOL of the patients were enhanced. Significant improvements were also observed with echocardiographic parameters as well as with the BNP level.

Arrhythmic Events

During the 6-month study period, a total of 80 episodes of VT (cycle length (CL): >320 ms) or fast VT (FVT, CL: 240–320 ms) were detected in 11 patients. Of these episodes, 50 were appropriate detections and 30 were inappropriate detections. Atrial tachycardia (AT) or atrial fibrillation was the reason for inappropriate detections in 15 (50%) of the total inappropriate detections, and the remaining supraventricular tachycardia was the reason for the other 15 (50%). A total of 5 patients experienced inappropriate detections with 3 patients experiencing 20 shocks. Considering the appropriate detections, 8 patients experienced a total of 50 episodes of VT or FVT. Of these episodes, 48 (96.0%) were VT and 2 were FVT (4%). Two FVT episodes occurred in 1 patient and were terminated with a total of 3 shocks.

The efficacy of ATP is shown in Figure 3. ATP was attempted in a total of 48 VT episodes and successfully terminated 79.2% (n=38) on the first attempt. In all, ATP was successful in 93.8% of the episodes (n=45) (Figure 3). The efficacy of ATP by CL is shown in Figure 4. ATP was successful in 100% of episodes with CLs >360 ms and in 81% of episodes with CLs from 320 to 360 ms.

HF Hospitalization and Deaths

There were 12 HF-related hospitalizations in 10 patients during the study. Adjudication by the Hospitalization Events Review Committee composed of 3 Japanese and 2 US HF specialists concurred that 4 (33.3%) of the HF hospitalizations would not have occurred if US practice guidelines had been applied. A total of 4 patients died during the follow-up period: 3 patients died due to progressive HF and 1 due to pneumonia.

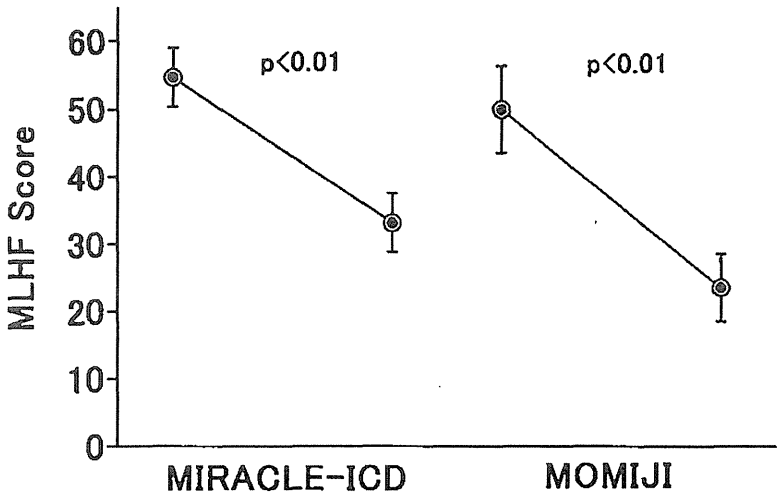

Figure 2. Minnesota Living with Heart Failure (MLHF) score at baseline and after treatment in MOMIJI (n=67) and MIRACLE-ICD general phase (n=120) patients. There was a significant decrease in MLHF scores, showing an improvement of quality of life in both the MOMIJI and the MIRACLE-ICD general phase studies. At 6-month follow-up, there was a 26.4 point decrease in the MOMIJI study compared with a 21.5 point decrease in the MIRACLE-ICD general phase compared with baseline.

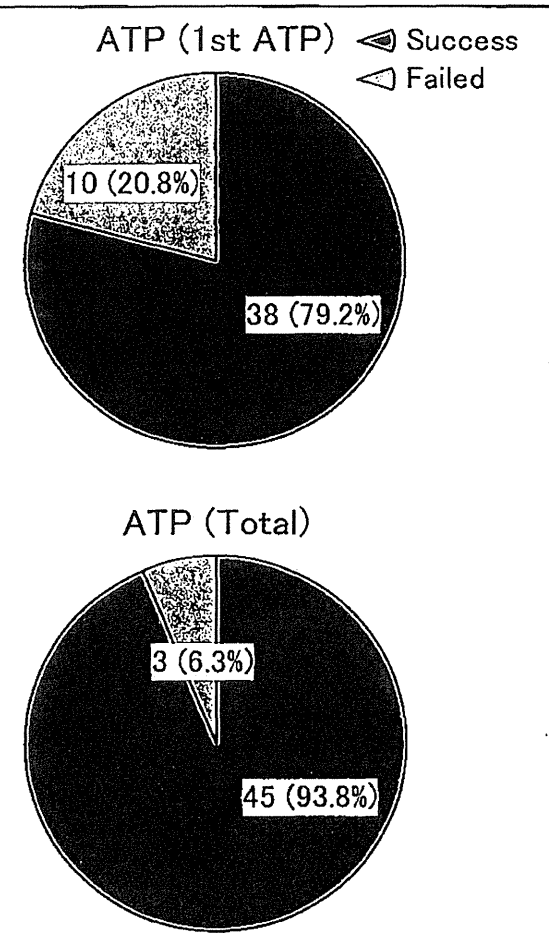

Figure 3. Terminating therapy for ventricular tachycardia (VT) episodes for first antitachycardia pacing (ATP) and total ATP. The number of episodes and percentages are shown.

Discussion

The improvements in the CCR observed in the MOMIJI study were non-inferior to those in the MIRACLE-ICD general phase. Compared with the patients in the MIRACLE-ICD study, those in the MOMIJI study had a higher LVEF, a higher proportion of non-ischemic cardiomyopathy and history of hypertension, and a higher rate of antiarrhythmic drug prescription. However, non-inferiority of the CCR was confirmed in the MOMIJI study after adjustment of these differences of baseline characteristics between the studies with propensity score analysis.

The results in the CCR score in the MOMIJI study were also similar to those in the PROSPECT study, which also assessed the performance of CRT in a predominately NYHA class III population (96% in the PROSPECT vs. 88.7% in the MOMIJI study) conducted in 53 centers in Europe, Hong Kong, and the USA.[18] In the PROSPECT study, the clinical composite score improved in 69% of 426 patients at 6-month follow-up compared with 68.8% in MOMIJI. This finding strengthens the evidence that the benefits of CRT observed in Western patients are transferable to Japanese patients with similar indications.

The morbidity and mortality benefits of CRT have been documented in prior large-scale landmark trials, however, Japanese patients were not included in the creation of this clinical evidence. The randomized controlled Cardiac Resynchronization-Heart Failure (CARE-HF) study, which included 813 patients with NYHA III or IV HF at 82 centers in Europe and a mean follow-up of 29.4 months, established the mortality benefit of CRT.[3] The CARE-HF study supported the recommendation that CRT devices should be considered in indicated patients to improve their prognosis. More recently, the efficacy of CRT and CRT-D has been studied in patients with less severe HF (NYHA class I and II). The European cohort of the REVERSE study demonstrated that CRT improved the CCR in a total of 287 patients from 35 European centers at 24 months.[5] The Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) of 1,798 patients in Canada, Europe, Turkey, and Australia with NYHA class II or III HF and a mean follow-up of 40 months found that CRT-D therapy resulted in a 25% reduction in the relative risk of death and in

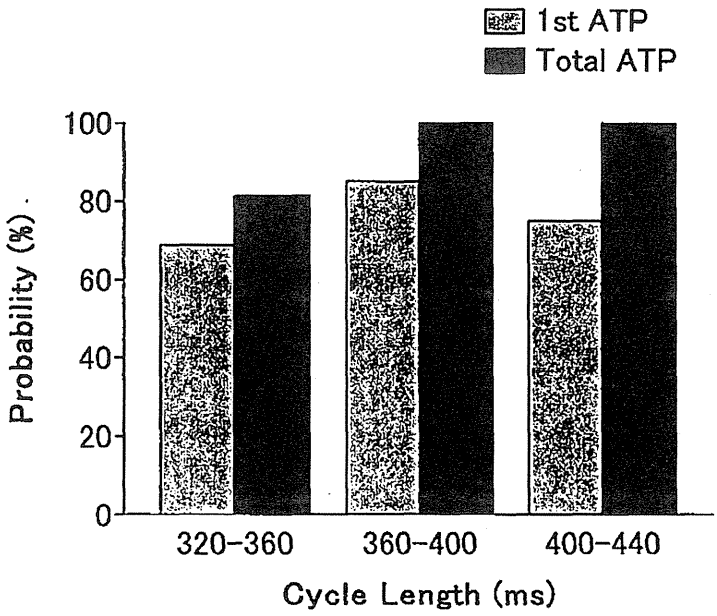

Figure 4. Distribution of ventricular tachycardia (VT) episodes by cycle length successfully terminated by antitachycardia pacing (ATP).

the composite endpoint of mortality or HF hospitalization compared with ICDs and optimal medical therapy.[8] These findings support the use of CRT-D in patients with mild to moderate HF, left ventricular dysfunction, and a wide QRS. In light of the favorable results in the MOMIJI study, the results of these landmark large-scale randomized controlled studies of CRT and CRT-D therapy may merit consideration when developing treatment strategies for Japanese patients with similar HF characteristics.

In terms of QOL evaluation, the MOMIJI study represents the first use of the MLHF questionnaire validated for Japanese patients. As such it provides a valuable assessment tool in studies examining the effects on patient QOL of various therapeutic modalities including CRT and CRT-D. MLHF score, a secondary endpoint in the MOMIJI and MIRACLE-ICD general phase, decreased in both studies, demonstrating improved QOL by CRT-D. MLHF score was a primary endpoint in the MIRACLE study, and patients receiving CRT demonstrated improvements at 6-month follow-up compared with the control group (median changes −18 vs. −9, P=0.001).[21] In the PATH-HF study, QOL score was unchanged in patients receiving CRT compared with univentricular pacing (25.2±3.3, 28.1±3.5, P=0.069); however, the follow-up period was very short.[22]

The MOMIJI study also evaluated cardiac functional parameters, which significantly improved as in the Western studies (Table 3). Although we could not perform statistical comparisons between them, the change in LVEF appeared to have improved more in the present patient population when compared with patients enrolled in the MIRACLE-ICD intensive phase[1] (median LVEF absolute change at 6 months +6.0% vs. +2.1%, respectively). This might be due to the higher proportion of non-ischemic patients among the MOMIJI study patients than that of the MIRACLE-ICD intensive phase (70.0 vs. 36.0%, P<0.01). Of note, the degree of LV reverse remodeling has been shown to be greater in non-ischemic than ischemic patients.[24,25] On the other hand, the mean changes in BNP at 3 months were comparable between the MOMIJI and the CARE-HF[3] studies: −186 pg/ml (95% CI: −366 to −7 pg/ml) and −225 pg/ml (95% CI: −705 to 255 pg/ml), respectively.

Among other secondary endpoints, the MOMIJI study examined the efficacy of ATP to terminate VT and prevent unnecessary defibrillation shocks. There were 50 episodes of ventricular tachyarrhythmia in 8 patients in the MOMIJI study, and the incidence rate was lower than that of MIRACLE-ICD intensive phase (10 vs. 22%, P=0.02).[1] One explanation could be that the patients in the MOMIJI study were prescribed antiarrhythmic drug more frequently than those in the MIRACLE-ICD intensive phase (52.5 vs. 32.4%, P<0.01). In the MOMIJI study, 93.8% of treated VT or FVT episodes were successfully terminated with ATP without the need for shocks. A lower incidence of shocks could improve QOL and increase the acceptability and tolerability of ICD therapy without compromising efficacy. Several studies have found that patients receiving defibrillation shocks have rather an increased mortality risk even though ICDs could terminate life-threatening ventricular arrhythmias.[26–28] Defibrillation shocks may cause myocardial damage and have negative inotropic effects, and those patients may be more susceptible to harm from shocks.[29–31] A combination of known and unknown factors may be involved, requiring further study to elucidate.

The MOMIJI study, which confirmed the therapeutic noninferiority to the MIRACLE-ICD study conducted in North America, advances the need of CRT-D therapy based on the broader clinical experience.

Study Limitations

First, the number of analyzed patients was as few as 80 in the MOMIJI study. In addition, the non-inferiority of the present analysis was based on a comparison between the MOMIJI and MIRACLE-ICD general phase populations. Therefore, the differences in baseline characteristics between them may have introduced bias into the results. However, non-inferiority was confirmed by the propensity score. Therefore, we consider that

the non-inferiority was meaningful in this study. Second, the prescription rate of β-blockers might be relatively low in light of current clinical practice and may have affected the results of this study;[32] however, there were no statistical difference between the MIRACLE-ICD study and the MOMIJI study with respect to the prescription rate. Third, the MOMIJI study was not designed or powered to detect mortality or morbidity difference and the follow-up period of 6 months may have been too short to detect the effects of CRT-D on cardiac function and QOL.

Conclusions

The MOMIJI study demonstrated the non-inferiority of the clinical efficacy of CRT-D in Japanese patients compared with a similar trial conducted in the USA. The results suggest that the benefits of CRT-D previously demonstrated in Western patient populations can be extrapolated to Japanese patients.

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Disclosures

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Conflict of Interest: Shin-ichi Momomura is the principal investigator of this study supported by Medotronic Japan.

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Appendix

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Additional Contributions

Harriet Guthertz, Medical Marketing and Communications, St. Paul, MN, USA assisted with the preparation of the manuscript.

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ORIGINAL ARTICLE
Heart Failure

Loop Diuretic Use at Discharge Is Associated With Adverse Outcomes in Hospitalized Patients With Heart Failure

– A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) –

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Background: Loop diuretics are commonly used in patients with heart failure (HF) to remove retained fluid and improve symptoms. However, they may potentially worsen outcomes in HF. It remains unknown whether the use of loop diuretics is associated with adverse HF outcomes in routine clinical practice. We thus determined the effects of loop diuretic use at discharge on long-term mortality and rehospitalization among patients hospitalized with HF.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments of a broad sample of patients hospitalized with worsening HF and followed for 2.1 years. Among a total of 2,549 HF patients, loop diuretics were used by 2,015 patients (79%), but not 534 patients (21%). The mean age was 70.7 years and 60% were male. Etiology was ischemic in 32% and mean left ventricular ejection fraction was 42%. After adjustment for covariates, discharge use of loop diuretics was associated with significant adverse risks of cardiac death (adjusted hazard ratio [HR] 2.348, 95% confidence interval [CI] 1.246–4.423, P=0.008) and rehospitalization (adjusted HR 1.427, 95% CI 1.040–1.959, P=0.027).

Conclusions: Among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with long-term adverse outcomes, which suggests that routine chronic use of loop diuretics may be harmful for patients with HF. (*Circ J* 2012; **76:** 1920–1927)

Key Words: Diuretics; Heart failure; Outcomes; Prognosis

Loop diuretics are the only drugs that can effectively control fluid retention in patients with heart failure (HF) and fluid overload.[1,2] However, loop diuretics can reduce the glomerular filtration rate (GFR), further worsen neurohormonal activation, and cause electrolyte disturbances.[3,4] Furthermore, they increase myocardial fibrosis,[5,6] which may be associated with disease progression and poor prognosis of HF. There have been no randomized clinical trials to determine the chronic effects of loop diuretics on HF outcomes. Previous subanalyses of randomized clinical trials demonstrated that the use of diuretics was associated with adverse outcomes in patients with HF and reduced left ventricular ejection fraction (LVEF).[4,7,8] In the Studies Of Left Ventricular Dysfunction (SOLVD), baseline use of a non-potassium-sparing diuretic was associated with an increased risk of arrhythmic death, after controlling for other variables of disease severity.[4] Similarly, analysis of the data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial demonstrated that higher doses of diuretics were associated with increased mortality over 6 months of follow-up among patients hospitalized with advanced HF.[7] However, these analyses used the data for HF patients enrolled in randomized clinical trials, clearly different from those in the "real world" under current standard practice for HF treatment, who are more elderly and have more comorbidities. In fact, in those trials, patients with HF and preserved LVEF or renal dysfunction were excluded. Thus, the effect of loop diuretics on long-term outcomes needed to be assessed in an unselected population of HF patients.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics, treatments and outcomes, including death and rehospitaliza-

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Table 1. Patients' Characteristics

Characteristics	Total (n=2,549)	Loop diuretic use (n=2,015)	No loop diuretic use (n=534)	P value
Age, years (mean±SD)	70.7±13.3	70.9±13.2	69.8±13.7	0.090
Male, %	60.0	60.9	56.6	0.066
BMI, kg/m²	22.4±4.1	22.4±4.1	22.2±4.1	0.262
Causes of HF, %				
Ischemic	32.0	33.1	28.1	0.029
Valvular	27.7	28.8	23.6	0.016
Hypertensive	24.2	23.5	26.8	0.118
Dilated cardiomyopathy	18.4	18.4	18.4	0.975
Medical history, %				
Hypertension	52.8	52.7	53.4	0.778
Diabetes mellitus	30.0	31.4	24.6	0.002
Dyslipidemia	25.1	26.1	21.4	0.028
Hyperuricemia	46.2	48.3	37.9	<0.001
Prior stroke	14.4	14.9	12.7	0.211
COPD	6.5	6.7	5.9	0.545
Smoking	38.1	38.8	35.6	0.191
Prior myocardial infarction	27.0	28.7	20.9	<0.001
Atrial fibrillation	35.2	36.8	29.1	0.001
Sustained VT/VF	6.0	6.3	4.7	0.163
Procedures, %				
PCI	17.8	18.4	15.2	0.085
CABG	9.5	10.2	6.8	0.020
Valvular surgery	6.7	7.2	4.9	0.061
PPM	0.9	1.0	0.6	0.349
ICD	2.0	1.9	2.6	0.285
CRT	1.6	1.6	1.5	0.820
Vital signs at discharge				
NYHA functional class, %				0.043
1	36.5	35.3	41.2	
2	57.2	58.0	53.9	
3	6.2	6.5	4.9	
4	0.2	0.2	0	
Heart rate, beats/min	70.3±11.8	70.2±11.6	70.7±12.6	0.652
SBP, mmHg	117.3±18.3	116.7±18.1	119.2±19.2	0.017
DBP, mmHg	66.2±10.4	66.0±11.6	66.9±11.3	0.138
Laboratory data at discharge				
eGFR, ml·min^{-1}·1.73m^{-2}	51.5±24.7	50.8±24.1	54.2±26.8	0.005
Serum uric acid, mg/dl	7.4±2.9	7.4±2.3	7.0±4.5	<0.001
Hemoglobin, g/dl	12.1±3.3	12.1±3.3	12.3±2.9	0.240
Plasma BNP, pg/ml	375±474	377±411	369±658	0.010
Echocardiographic data				
LVEDD, mm	56.3±10.4	56.8±10.4	54.6±10.3	<0.001
LVESD, mm	53.0±9.4	54.0±9.4	52.2±9.3	<0.001
LVEF, %	42.2±17.5	41.8±17.6	43.3±17.1	0.059

Data are percent or means±SD.
BMI, body mass index; HF, heart failure; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

tion, in a broad sample of patients hospitalized with HF in Japan.[9–20] The JCARE-CARD enrolled 2,675 patients admitted with HF and an average of follow-up of 2.2 years at 164 participating hospitals in a web-based registry.

The aim of the present study was to analyze the prognostic value of loop diuretics on mortality and rehospitalization rates by evaluating the relationship between the drugs' use at discharge and clinical outcomes among patients hospitalized with HF and registered in the JCARE-CARD database.

Table 2. Medication Use at Hospital Discharge

	Total (n=2,549)	Loop diuretic use (n=2,015)	No loop diuretic use (n=534)	P value
ACEI, %	37.4	38.6	32.8	0.013
ARB, %	44.4	43.7	47.2	0.146
ACEI or ARB, %	76.5	76.8	75.5	0.511
ACEI and ARB, %	5.3	5.5	4.5	0.374
β-blocker, %	48.6	47.8	51.9	0.093
ACEI or ARB and β-blocker, %	39.9	39.8	40.6	0.710
Thiazide, %	3.6	2.9	6.4	<0.001
Spironolactone, %	41.6	47.6	18.7	<0.001
Digitalis, %	30.9	31.7	27.7	0.075
Calcium-channel blocker, %	25.2	24.2	28.8	0.029
Nitrates, %	23.3	24.4	19.1	0.010
Antiarrhythmics, %	16.6	16.9	15.5	0.463
Aspirin, %	47.2	47.6	45.5	0.390
Warfarin, %	40.8	41.5	37.8	0.121
Statin, %	19.9	20.4	17.6	0.143

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Methods

Patients

The details of the JCARE-CARD have been described previously.[9,10,14,15,19] Briefly, eligible patients were those hospitalized with worsening HF as the primary cause of admission. The study hospitals were encouraged to register the patients as consecutively as possible. For each patient, baseline data included (1) age, sex, and body mass index; (2) cause of HF; (3) medical history; (4) prior procedures; (5) vital signs at discharge; (6) laboratory data; (7) echocardiographic data; and (8) medication use at discharge. The data were entered using a web-based electronic data capture (EDC) system licensed by the JCARE-CARD (www.jcare-card.jp).

From the database of a total cohort of 2,675 patients registered in JCARE-CARD, the present analysis used the data of 2,549 patients for whom information of the loop diuretic use could be obtained. The patients were divided into 2 groups according to loop diuretic use (n=2,015; 79.1%) or no loop diuretic use (n=534; 20.9%) at the time of discharge from the index hospitalization.

Outcomes

The status of all patients was surveyed and the following information about outcomes was obtained from participating cardiologists using the web-based EDC system: (1) all-cause death, (2) cardiac death, defined as death due to HF, myocardial infarction or other causes such as pulmonary embolism, (3) rehospitalization due to an exacerbation of HF that required more than continuation of the patient's usual therapy on prior admission, and (4) a composite endpoint of all-cause death and rehospitalization due to HF. The endpoints were adjudicated by the cardiologists in each participating hospital. Of the 2,549 patients, 244 (9.6%), missed during follow-up, were excluded from the follow-up analysis. Follow-up data could be obtained for 2,305 of the 2,549 patients (90.4%). Of these 2,305 patients, 1,814 were in the group of loop diuretic use and 491 were in that of no loop diuretic use. Mean postdischarge follow-up was 781±315 days (2.1±0.9 years).

The hypothesis being tested was whether loop diuretic use at hospital discharge would be associated with higher mortality and rehospitalization rates during the follow-up compared with no loop diuretic use.

Statistical Analysis

Patients' characteristics and treatments were compared using χ^2 test for categorical variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. We analyzed the data excluding the patients with missing data. Only patients who survived the index hospitalization were included in the follow-up analysis. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between loop diuretic use at discharge and outcome was evaluated among patients with multivariable adjustment. The covariates of age, sex, estimated GFR (eGFR) at discharge, systolic blood pressure (SBP) at discharge, LVEF, B-type natriuretic peptide (BNP), New York Heart Association (NYHA) functional class at discharge, cause of HF (ischemic, valvular), medical history (diabetes, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation) and medication use (angiotensin-converting enzyme inhibitor [ACEI], β-blocker, spironolactone, thiazide, calcium-channel blocker (CCB), nitrate, and statins), were used in developing the postdischarge Cox proportional hazard models. The same variables were included in a multivariable logistic regression model and the propensity score (PS) for loop diuretic use was estimated for each patient. Using a greedy matching protocol, we matched each patient with no loop diuretic use to a patient with loop diuretic use who had a very similar PS; thus we used 465 pairs matched with PS for PS matching. We performed a formal sensitivity analysis for unmeasured confounding factors.[21]

The results were reported as hazard ratio (HR), 95% confidence interval (CI), and P value. HR for outcomes when loop diuretics were used was compared with no use of diuretics. A P value of <0.05 was used as the criterion for variables to stay in the model. SPSS version 16.0J for Windows was used for all statistical analyses (Chicago, IL, USA).

Table 3. Unadjusted and Adjusted HRs for Outcomes According to Loop Diuretic Use

Outcome	n (%)		HR	95% CI	P value
	Loop diuretic use (n=1,814)	No loop diuretic use (n=491)			
All-cause death	399 (22.0%)	75 (15.3%)			
Unadjusted			1.501	1.171–1.925	0.001
Adjusted for covariates			1.545	0.986–2.420	0.058
Adjusted for matching with propensity score			1.510	1.113–2.048	0.008
Cardiac death	251 (13.8%)	41 (8.4%)			
Unadjusted			1.703	1.224–2.370	0.001
Adjusted for covariates			2.348	1.246–4.423	0.008
Adjusted for matching with propensity score			1.719	1.155–2.560	0.008
Rehospitalization	690 (38.0%)	146 (29.7%)			
Unadjusted			1.360	1.137–1.627	0.001
Adjusted for covariates			1.427	1.040–1.959	0.027
Adjusted for matching with propensity score			1.194	0.953–1.495	0.124
All-cause death or rehospitalization	834 (46.0%)	182 (37.1%)			
Unadjusted			1.326	1.129–1.558	0.001
Adjusted for covariates			1.363	1.022–1.816	0.035
Adjusted for matching with propensity score			1.236	1.010–1.511	0.040

A Cox regression model was used in the analysis adjusted for the following covariates: age, sex, eGFR at discharge, SBP at discharge, LVEF, BNP, NYHA functional class at discharge, cause of HF (ischemic, valvular), medical history (diabetes mellitus, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation) and medication use (ACEI, β-blocker, spironolactone, thiazide, calcium-channel blocker, nitrate, statin). The same variables were used to determine the propensity score for loop diuretic use, and 465 pairs were matched. The no loop diuretic use group was the reference group.
HR, hazard ratio; CI, confidence interval. Other abbreviations as in Tables 1,2.

Results

Patients' Characteristics

The present study included 2,549 patients with a mean age of 70.7±13.3 years and 60.0% were men (**Table 1**). The causes of HF were ischemic heart disease in 32.0%, valvular heart disease in 27.7%, hypertensive heart disease in 24.2%, and dilated cardiomyopathy in 18.4%. The mean LVEF was 42.2±17.5%.

The characteristics of patients prescribed loop diuretics at discharge and those not prescribed are compared in **Table 1**. Those discharged with loop diuretics had significantly more ischemic and valvular HF etiologies; more comorbidities, such as diabetes, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation; significantly more cases of coronary artery bypass grafting; severe HF symptoms by NYHA functional class at discharge; and SBP at discharge was significantly lower. However, diastolic blood pressure did not differ between groups. eGFR was significantly lower, and serum uric acid and plasma BNP levels were higher in patients with loop diuretics. LV end-diastolic and end-systolic diameters were significantly greater in patients with loop diuretics and LVEF tended to be lower, although this did not reach statistical significance (P=0.059).

Use of medications other than loop diuretics was compared between groups (**Table 2**). The use of ACEIs was slightly, but significantly, higher in patients with loop diuretic use (38.6% vs. 32.8%, P=0.013). However, the use of ACEI or angiotensin-receptor blocker (ARB) did not differ between groups (76.8% vs. 75.5%, P=0.511). Importantly, the combination of ACEI or ARB and β-blocker was similar between groups. However, spironolactone and nitrate were more often prescribed for the patients with loop diuretic use. On the other hand, thiazide diuretic and CCBs were more used by the patients with no loop diuretic use.

Postdischarge Clinical Outcomes According to Loop Diuretic Use

During follow-up of 2.1 years after hospital discharge, the rates of adverse outcomes were as follows: all-cause death 20.6%, cardiac death 12.7%, rehospitalization due to the worsening HF 36.3%, and all-cause death or rehospitalization 44.1%. The unadjusted rates of all-cause death, cardiac death, rehospitalization due to the worsening HF, and all-cause death or rehospitalization were significantly higher in patients with loop diuretic use (**Table 3, Figure**).

Even after adjustment for covariates in the multivariable Cox proportional hazard models, discharge use of loop diuretics, when compared to no use, was associated with an increased risk of cardiac death (HR 2.348, 95% CI 1.246–4.423, P=0.008), rehospitalization (HR 1.427, 95% CI 1.040–1.959, P=0.027), and all-cause death or rehospitalization (HR 1.363, 95% CI 1.022–1.816, P=0.035) (**Table 3**). Patients taking loop diuretics tended to have a higher risk of all-cause death, which, however, did not reach statistical significance after adjustment (P=0.058).

Furthermore, when we matched by PS, the same variables shown in **Table 1** and **Table 2** were comparable between groups. Even after adjustment for matching with PS, loop diuretic use was associated with all-cause death (HR 1.510, 95% CI 1.113–2.048, P=0.008), cardiac death (HR 1.719, 95% CI 1.155–2.560, P=0.008), and all-cause death and rehospitalization (HR 1.236, 95% CI 1.010–1.511, P=0.040). Sensitivity

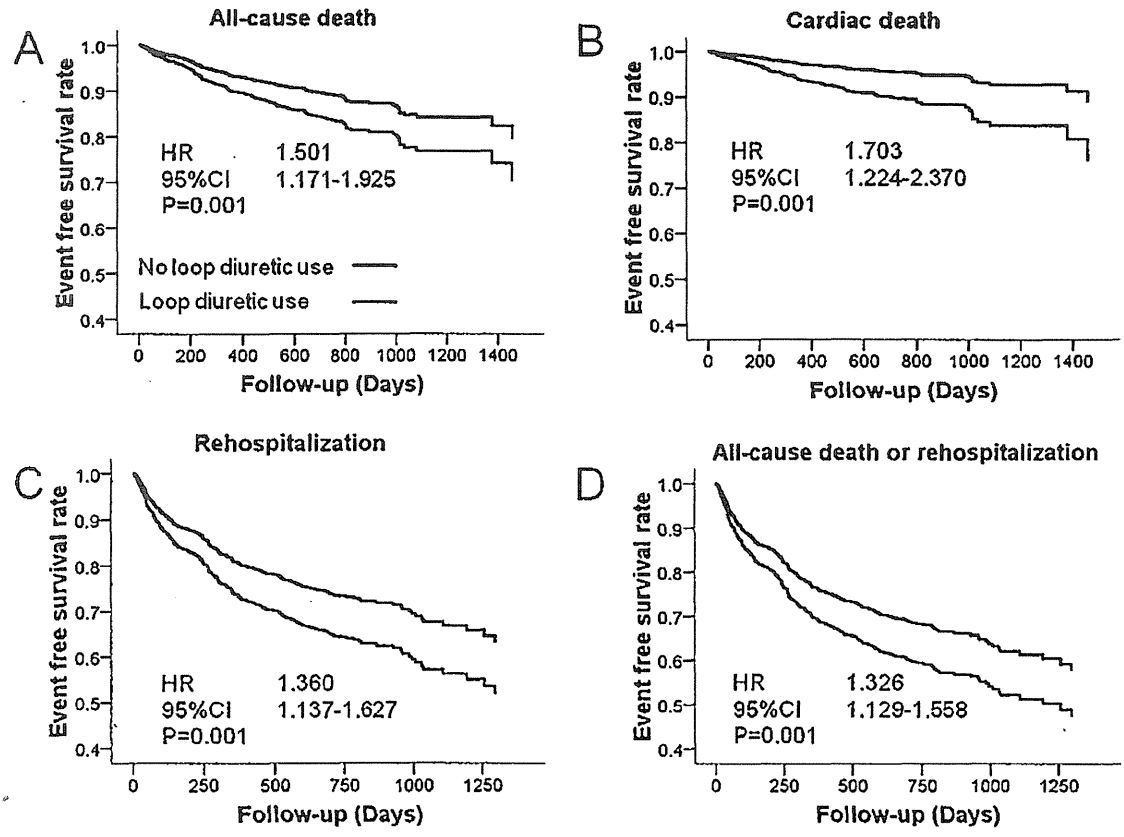

Figure. Kaplan-Meier survival curves for free from all-cause death (**A**), cardiac death (**B**), rehospitalization due to worsening heart failure (**C**), and all-cause death or rehospitalization (**D**) in hospitalized patients with loop diuretic use (red lines, n=1,814) vs. no loop diuretic use (black lines, n=491) at discharge. HR, hazard ratio; CI, confidence interval.

analysis for unmeasured confounding factors was performed. In the absence of unmeasured confounding factors, a binomial test for matched pair provides strong evidence (P=0.003) that loop diuretic use increases cardiac death, even after adjustment by PS matching. To attribute the higher rate of cardiac death to unmeasured confounding factor rather than to an effect of loop diuretic use, that unmeasured confounding factor would need to produce a 27% increase in the odds of loop diuretic use, and it would need to be a strong predictor of cardiac death.

Subgroup Analyses

The association of loop diuretic use with cardiac death was noted across a wide spectrum of HF patients (**Table 4**). Loop diuretic use was associated with increased cardiac death in HF patients who were elderly (≥70 years), with a non-ischemic etiology, no hypertension, no diabetes, and LVEF ≥40%. In any subgroup, there were no significant interactions between groups.

Discussion

The present study using the JCARE-CARD database demonstrated that among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with adverse outcomes during long-term follow-up up to 2.1 years.

These findings confirm and extend the results of previous studies that suggested an association between diuretic use and worse outcomes in patients with HF.[4,7,8,22] In the SOLVD trial, use of a diuretic was associated with a 37% increase in the risk of arrhythmic death after controlling for multiple other variables of disease severity.[4] The Digitalis Investigation Group Study also found a 31% increased risk of death associated with diuretic use when using propensity matching to control for baseline differences in patients with and without diuretic use.[8] The ESCAPE trial demonstrated a linear relationship between loop diuretic dose and mortality over 6 months of follow-up in patients hospitalized with HF.[7] Moreover, in a cohort of 1,354 patients with advanced HF and reduced LVEF referred to a single center, there was a dose-dependent association between loop diuretic use and impaired survival during 2-year follow-up.[22] However, those previous studies were performed with data from patients enrolled in clinical trials or cohort studies of patients with HF and reduced LVEF, thus excluding patients with HF and preserved LVEF. In contrast, the present study included patients hospitalized due to worsening HF as the primary cause of admission independent of LVEF data. Therefore, our findings confirm the association between loop diuretic use and poor outcomes in the "real world" under current standard medical practice. Furthermore, the present results

Table 4. Subgroup Analyses of Cardiac Death According to Loop Diuretic Use

Subgroup	n	HR	95% CI	P value	P value for Interaction
Age <70 years	936	1.812	0.927–3.542	0.082	
Age ≥70 years	1,369	1.599	1.094–2.338	0.015	0.759
Male	1,376	1.604	1.042–2.471	0.032	
Female	929	1.842	1.102–3.078	0.020	0.679
Ischemic	727	1.670	0.934–2.985	0.084	
Non-ischemic	1,578	1.691	1.131–2.528	0.010	0.975
Hypertension	1,203	1.620	0.967–2.712	0.067	
No hypertension	1,087	1.758	1.143–2.705	0.010	0.803
Diabetes	675	1.370	0.726–2.584	0.331	
No diabetes	1,626	1.826	1.239–2.690	0.002	0.443
LVEF ≥40%	1,020	2.484	1.394–4.428	0.002	
LVEF <40%	1,000	1.207	0.761–1.913	0.425	0.055

No loop diuretic use group was a reference.
Abbreviations as in Tables 1,3.

were consistent with our own previous study, in which the use of diuretics was independently associated with higher mortality in elderly patients.[9]

There are several potential mechanisms by which loop diuretics may be associated with adverse outcomes in HF patients. First, administration of diuretics to patients with HF may activate the renin-angiotensin-aldosterone system, as well as the sympathetic nervous system, both of which play a detrimental role in HF progression.[23–25] Neurohormonal activation is known to occur in patients with HF before overt symptoms appear. Plasma renin activity and norepinephrine levels have been shown to be significantly higher in HF patients with symptoms than in those without them.[25] Moreover, plasma renin activity is normal in HF patients without symptoms and who are not using diuretics and is significantly increased in patients on diuretic therapy.[25] In a tachycardia-induced animal model of HF, loop diuretic use significantly accelerated LV systolic dysfunction, elevated the serum aldosterone level, and increased basal sodium-calcium exchanger currents.[6] Activation of the renin-angiotensin-aldosterone system induces myocardial fibrosis, oxidative stress, stimulation of proinflammatory cytokines, and myocardial fibrosis.[26–29] Second, loop diuretics may also decrease intravascular volume and the GFR, which may also be caused by neurohormonal activation. Previous studies, including our own, have demonstrated that renal dysfunction is a common and independent risk for cardiovascular adverse outcomes in HF patients.[11,30–39] Finally, loop diuretics cause electrolyte imbalances, such as decreases in potassium and magnesium,[40,41] which may increase the risk of fatal arrhythmias and sudden cardiac death.[40–44]

Clinical Implications

Based on findings suggesting an association between diuretic use and worsening outcomes in patients with HF, guidelines from the European Society of Cardiology recommend that diuretics be used for HF patients with clinical symptoms or signs of volume overload and congestion.[45] The practice guideline from the Heart Failure Society of America also recommends loop diuretics at doses needed to produce diuresis sufficient to achieve an optimal volume status.[46] Therefore, routine chronic use of loop diuretics for HF patients without fluid retention needs to be avoided.

Study Limitations

Several limitations inherent in the design of the registry should be considered. First, the documentation of loop diuretic use at hospital discharge might not accurately reflect continuation over time or start after discharge. Moreover, we did not collect information regarding the dose and type of loop diuretic, such as furosemide and torsemide, and whether loop diuretics were initiated during or before hospitalization. Therefore, we could not assess the dose-effect relation in the study patients. However, higher doses are associated with higher mortality, based on the results of the ESCAPE trial.[7] Second, information regarding the serum electrolyte concentration was not obtained in this database, so we could not assess the impact of hypokalemia, hyponatremia, and hypomagnesemia on outcomes. Third, the present study was not a prospective randomized trial and, despite covariate adjustment and adjustment for matching by PS and sensitivity analysis, other measured and unmeasured factors may have influenced the outcomes. Renal dysfunction, hyperuricemia and electrolyte imbalances commonly associated with loop diuretic use might affect the outcomes. Specifically, patients who received loop diuretics might do so because of greater disease severity compared to those who did not. However, the present study demonstrated an adverse effect of loop diuretics, even after extensive multivariable adjustment of other known predictors and adjustment for PS matching, and it was consistent among the different subgroups studied. Moreover, this has been persistently reported in most prior studies.[4,7,8,22] Even though the present finding that use of loop diuretics was associated with worse outcomes is consistent with similar previous reports, unmeasured or unanalyzed factors that motivated the physicians caring for HF patients to give loop diuretics could have also put these patients at higher risk for death and subsequent hospitalization. It is difficult, even impossible, to account for these factors and the conclusion of the present study could be considered as "hypothesis generating". Finally, data were dependent on the accuracy of documentation and abstraction by the individual medical centers that participated in this study.

Conclusions

Among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with adverse outcomes during a long-term follow-up of up to 2.1 years. The potential risk of

loop diuretics for the larger numbers of HF patients encountered in routine clinical practice was suggested.

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Activation of Natural Killer T Cells Ameliorates Postinfarct Cardiac Remodeling and Failure in MiceNovelty and Significance

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Activation of Natural Killer T Cells Ameliorates Postinfarct Cardiac Remodeling and Failure in Mice

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Rationale: **Chronic inflammation in the myocardium is involved in the development of left ventricular (LV) remodeling and failure after myocardial infarction (MI). Invariant natural killer T (iNKT) cells have been shown to produce inflammatory cytokines and orchestrate tissue inflammation. However, no previous studies have determined the pathophysiological role of iNKT cells in post-MI LV remodeling.**

Objective: **The purpose of this study was to examine whether the activation of iNKT cells might affect the development of LV remodeling and failure.**

Methods and Results: **After creation of MI, mice received the injection of either α-galactosylceramide (αGC; n=27), the activator of iNKT cells, or phosphate-buffered saline (n=31) 1 and 4 days after surgery, and were followed during 28 days. Survival rate was significantly higher in MI+αGC than MI+PBS (59% versus 32%, $P<0.05$). LV cavity dilatation and dysfunction were significantly attenuated in MI+αGC, despite comparable infarct size, accompanied by a decrease in myocyte hypertrophy, interstitial fibrosis, and apoptosis. The infiltration of iNKT cells were increased during early phase in noninfarcted LV from MI and αGC further enhanced them. It also enhanced LV interleukin (IL)-10 gene expression at 7 days, which persisted until 28 days. AntienIL-10 receptor antibody abrogated these protective effects of αGC on MI remodeling. The administration of αGC into iNKT cell-deficient $J\alpha18^{-/-}$ mice had no such effects, suggesting that αGC was a specific activator of iNKT cells.**

Conclusions: **iNKT cells play a protective role against post-MI LV remodeling and failure through the enhanced expression of cardioprotective cytokines such as IL-10. (*Circ Res.* 2012; 111:1037-1047.)**

Key Words: natural killer T cells ■ myocardial infarction ■ inflammation ■ heart failure ■ cytokines

Myocardial infarction (MI) leads to the development of heart failure (HF), which is the major cause of death in post-MI patients. The changes in left ventricular (LV) geometry, such as cavity dilatation associated with myocyte hypertrophy and interstitial fibrosis, referred to as remodeling, contribute to the development of depressed cardiac function in HF after MI.[1] It has been reported that monocytes and lymphocytes are infiltrated in noninfarcted area as well as infarcted area of LV after MI.[2,3] Chemokines, monocyte chemoattractant protein-1 (MCP-1), and RANTES (regulated on activation normally T-cell expressed and secreted), are essential factors in the recruitment and activation of monocyte and lymphocyte. These chemokines are also increased in noninfarcted LV after MI and contribute to local inflammation through the release of inflammatory cytokines including tumor necrosis factor-α (TNF-α).[2,4] Targeted deletion of CC chemokine receptor 2 or anti–MCP-1 gene therapy has been shown to attenuate LV remodeling after MI.[2,5] Thus, chronic tissue inflammation plays an important role in LV remodeling process.

Invariant natural killer T (iNKT) cells are innate-like T-lymphocyte population coexpressing NK markers and an αβ T-cell receptor that recognize glycolipid antigens. They can rapidly and robustly produce a mixture of T-helper type 1 (T_H1) and T_H2 cytokines, such as TNF-α, interferon-γ (IFN-γ), interleukin (IL)-10, and IL-4, and also a vast array of chemokines in shaping subsequent adaptive immune response.[6] Thus, iNKT cells can function as a bridge between the innate and adaptive immune systems, and orchestrate

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Non-standard Abbreviations and Acronyms	
αGC	α-galactosylceramide
HF	heart failure
IFN-γ	interferon-γ
IL	interleukin
iNKT	invariant natural killer T
LV	left ventricle
MCP-1	monocyte chemoattractant protein-1
MI	myocardial infarction
MMP	matrix metalloproteinase
NK	natural killer
PBS	phosphate-buffered saline
qRT-PCR	quantitative reverse transcriptase–polymerase chain reaction
RANTES	regulated on activation normally T cell expressed and secreted
T_H1	T-helper type 1
T_H2	T-helper type 2
TNF-α	tumor necrosis factor-α

tissue inflammation. Indeed, we have shown that iNKT cells activate vascular wall inflammation in atherogenesis and adipose tissue inflammation in obesity-induced glucose intolerance.[7,8] On the other hand, iNKT cells play a protective role against autoimmune and inflammatory diseases such as type 1 diabetes,[9,10] allergic encephalomyelitis,[9,11] and rheumatoid arthritis.[12] These findings suggest that iNKT cells may have bidirectional effects on tissue inflammation. However, no previous studies have examined the changes of iNKT cells and their pathophysiological role in LV remodeling and failure after MI.

Therefore, the purpose of the present study was to determine whether iNKT cells might affect the development of LV remodeling and failure after MI. We demonstrated that the activation of iNKT cells by α-galactosylceramide (αGC), a specific activator for iNKT cells,[13] attenuated the development of LV remodeling and failure after MI in mice. The enhanced gene expression of IL-10 might be involved in these beneficial effects of iNKT cells on this disease process.

Methods

All procedures and animal care were approved by our institutional animal research committee and conformed to the animal care guideline for the Care and Use of Laboratory Animals in Hokkaido University Graduate School of Medicine.

Experiment 1: Time-Dependent Changes of iNKT Cell Receptors in Post-MI Hearts

Animal Models

MI was created in male C57BL/6J mice, 6 to 8 weeks old and 20 to 25 g body weight, by ligating the left coronary artery as described previously.[14] Sham operation without ligating the coronary artery was also performed as control. MI mice were euthanized and the hearts were excised at days 3, 7, 14, and 28 for quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) measurements.

Quantitative RT-PCR

Quantitative PCR for Vα14Jα18 (a specific marker of iNKT cells) was performed, as described previously.[8]

Experiment 2: Effects of iNKT Cell Activation on Post-MI Heart Animal Models

Sham and MI mice were created in male C57BL/6J as described in experiment 1. Each group of mice was randomly divided into 2 groups; either αGC (0.1 μg/g body weight; Funakoshi Company, Ltd, Tokyo, Japan), the activator of iNKT cells, or phosphate-buffered saline (PBS) was administered via intraperitoneal injection 1 and 4 days after surgery. The concentration of αGC was chosen based on the previous study of its efficacy.[8] Thus, the experiment was performed in the following 4 groups of mice; sham+PBS (n=10), sham+αGC (n=10), MI+PBS (n=31), and MI+αGC (n=27).

Survival

The survival analysis was performed in all 4 groups of mice. During the study period, the cages were inspected daily for dead animals. All dead mice were examined for the presence of MI as well as pleural effusion and cardiac rupture.

Echocardiographic and Hemodynamic Measurements

Echocardiographic and hemodynamic measurements were performed under light anesthesia with tribromoethanol/amylene hydrate (avertin; 2.5% wt/vol, 8 μL/g ip), as described previously.[14]

Myocardial Histopathology, Infarct Size, Myocardial Apoptosis, and Matrix Metalloproteinase Zymography

Myocyte cross-sectional area, collagen volume fraction, infarct size, myocardial apoptosis, and zymographic matrix metalloproteinase (MMP) levels were determined as described previously.[14,15]

Isolation of Cardiac Mononuclear Cell and Flow Cytometry

Cardiac mononuclear cells from 3 mice were isolated, pooled, and subjected to flow cytometric analysis as previously described.[7,16]

Quantitative RT-PCR

Quantitative PCR for Vα14Jα18, CD11c (a marker of M1 macrophages), arginase-1 (a marker of M2 macrophages), MCP-1, RANTES, IFN-γ, IL-4, IL-6, TNF-α, and IL-10 was performed, as described previously.[8]

Immunohistochemistry

LV sections were immunostained with antibody against mouse MAC3 (a macrophage marker), mouse CD3 (a T-cell marker), or mouse myeloperoxidase (a leukocyte marker), followed by counterstaining with hematoxylin.

Plasma Cytokine Concentration

Plasma IL-10, TNF-α, IFN-γ, IL-6, and IL-4 levels were measured by commercially available ELISA kit (R&D systems, Inc) in all groups.

Experiment 3: Effects of IL-10 Neutralization on αGC-Treated Post-MI Hearts

MI mice were divided into the following 3 groups; MI+αGC (n=18), MI+anti–IL-10 receptor antibody (n=12), and MI+αGC+anti–IL-10 receptor antibody (n=19). αGC was administered identically as in experiment 2. Anti–IL-10 receptor antibody (500 μg/mouse, BD Pharmingen, San Diego, CA) was administered via