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Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials

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Summary

Background Patients who have acute myocardial infarction remain at major risk of cardiovascular events. We aimed to assess the effects of either human atrial natriuretic peptide or nicorandil on infarct size and cardiovascular outcome.

Methods We enrolled 1216 patients who had acute myocardial infarction and were undergoing reperfusion treatment in two prospective, single-blind trials at 65 hospitals in Japan. We randomly assigned 277 patients to receive intravenous atrial natriuretic peptide (0·025 μg/kg per min for 3 days) and 292 the same dose of placebo. 276 patients were assigned to receive intravenous nicorandil (0·067 mg/kg as a bolus, followed by 1·67 μg/kg per min as a 24-h continuous infusion), and 269 the same dose of placebo. Median follow-up was 2·7 (IQR 1·5–3·6) years for patients in the atrial natriuretic peptide trial and 2·5 (1·5–3·7) years for those in the nicorandil trial. Primary endpoints were infarct size (estimated from creatine kinase) and left ventricular ejection fraction (gauged by angiography of the left ventricle).

Findings 43 patients withdrew consent after randomisation, and 59 did not have acute myocardial infarction. We did not assess infarct size in 50 patients for whom we had fewer than six samples of blood. We did not have angiographs of left ventricles in 383 patients. Total creatine kinase was 66459·9 IU/mL per h in patients given atrial natriuretic peptide, compared with 77878·9 IU/mL per h in controls, with a ratio of 0·85 between these groups (95% CI 0·75–0·97, p=0·016), which indicated a reduction of 14·7% in infarct size (95% CI 3·0–24·9%). The left ventricular ejection fraction at 6–12 months increased in the atrial natriuretic peptide group (ratio 1·05, 95% CI 1·01–1·10, p=0·024). Total activity of creatine kinase did not differ between patients given nicorandil (70520·5 IU/mL per h) and controls (70852·7 IU/mL per h) (ratio 0·995, 95% CI 0·878–1·138, p=0·94). Intravenous nicorandil did not affect the size of the left ventricular ejection fraction, although oral administration of nicorandil during follow-up increased the left ventricular ejection fraction between the chronic and acute phases. 29 patients in the atrial natriuretic peptide group had severe hypotension, compared with one in the corresponding placebo group.

Interpretation Patients with acute myocardial infarction who were given atrial natriuretic peptide had lower infarct size, fewer reperfusion injuries, and better outcomes than controls. We believe that atrial natriuretic peptide could be a safe and effective adjunctive treatment in patients with acute myocardial infarction who receive percutaneous coronary intervention.

Lancet 2007; 370: 1483–93

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Introduction

Despite availability of effective medical treatments, chronic heart failure remains a major cause of morbidity and mortality worldwide.[1–3] Ischaemic heart disease, in turn, is one of the main causes of chronic heart failure.[4] The most important treatment objectives are prevention of acute myocardial infarction, and, in individuals who have an acute myocardial infarction, reduction in infarct size and ischaemia or reperfusion injury.[5] Only a few medications have been shown to decrease ischaemia or reperfusion injury.[6–8]

Reperfusion of ischaemic myocardium reduces infarct size and improves left ventricular function, both of which contribute to better clinical outcomes in patients with acute myocardial infarction.[9–11] However, reperfusion can also cause tissue damage.[12] Several drugs have been trialled for the prevention or amelioration of such injuries, but results have not been consistently satisfactory.[13–15] Recently, human atrial natriuretic peptide and nicorandil have both been shown to be effective for reduction of myocardial damage after acute myocardial infarction in basic and clinical studies.[16–25] Atrial natriuretic peptide is a candidate for adjunctive treatment after acute myocardial infarction, because it has been shown to suppress the renin–angiotensin–aldosterone system and endothelin-1, both of which which modulate infarct size and cardiac remodelling.[19] Nicorandil is a combined adenosine triphosphate (ATP)-sensitive potassium channel opener and nitrate preparation that has also shown promise as an adjunctive treatment for acute myocardial infarction. In the clinical setting, however,

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the beneficial effects of atrial natriuretic peptide and nicorandil have only been tested in single-centre studies with small sample sizes.[20-25] The Japan working group studies on acute myocardial infarction for the reduction of necrotic damage by human atrial natriuretic peptide or nicorandil (J-WIND-ANP and J-WIND-KATP, respectively) aimed to assess the value of these drugs as adjuncts to percutaneous coronary intervention for patients with acute myocardial infarction.

Methods

Patients

We have described the protocols for the two trials previously.[26,27] In brief, we recruited patients to two independent, investigator-initiated, investigator-led, multicentre, prospective, randomised, single-blind, controlled trials at 65 hospitals. 27 hospitals participated in the atrial natriuretic peptide trial, and 38 separate hospitals in the nicorandil trial (table 1); the two studies were completely independent. We initially planned to include fewer hospitals, but we increased the number to promote enrolment of sufficient patients.

Eligibility criteria were age between 20 and 79 years; chest pain for more than 30 min; at least 0·1 mV of ST segment elevation in two adjacent ECG leads; admission to hospital within 12 h of the onset of symptoms; and one instance of acute myocardial infarction. Exclusion criteria were a history of myocardial infarction; left main trunk stenosis; severe liver or kidney dysfunction or both; suspected aortic dissection; previous coronary artery bypass grafting; and a history of drug allergy.

All patients gave written informed consent immediately after admission to hospital, and were asked to sign the same consent form again after 2 weeks when they had more time to decide. This system was applied on the recommendation of the institutional review boards. Only one patient, who was in the nicorandil group, withdrew their consent at their second opportunity. We enrolled patients from Oct 24, 2001, to Dec 13, 2005. The study protocol was approved by the institutional review boards and ethics committees of all participating hospitals, and was in accordance with the Declaration of Helsinki.

Procedures

An independent statistician generated our randomisation lists with a computer, by the permuted-block method. Within each centre, the block length was eight. Treatment allocations were concealed in opaque sealed envelopes until patients were enrolled. Physicians were not aware of the random assignments of patients until the follow-up stage; patients and those who analysed the data were unaware of the treatment assignment for the duration of the study. Both trials were designed as single-blind studies.

277 patients who were enrolled in the atrial natriuretic peptide trial were randomly assigned to receive an intravenous infusion of this drug after reperfusion treatment, at 0·025 μg/kg per min for 3 days, and 292 a placebo of 5% glucose solution by the same method. 276 patients in the other trial were randomly assigned to intravenous nicorandil, infused at 1·67 μg/kg per min for 24 h after bolus injection of nicorandil at a dose of 0·067 mg/kg, and 269 were assigned to 0·9% saline solution, by the same method. Previous studies have shown substantial cardiovascular protection with atrial natriuretic peptide and nicorandil at these doses.[20,22] Of the 276 patients assigned to receive nicorandil, 61 were given nicorandil orally, at the discretion of individual investigators, during the follow-up period.

We planned to stop the administration of treatment drugs in case of severe hypotension, which was defined as systolic blood pressure of less than 90 mm Hg, because of the vasodilator effect of these drugs. The study protocol did not restrict or specify any other diagnostic or therapeutic methods in the acute phase (2–8 weeks after acute myocardial infarction) or chronic phase (6–12 months).

We obtained data on baseline characteristics, emergent catheterisation, and medication at discharge after 1 month; data on follow-up catheterisation and medication after 6 months; and data on medication after 24 months. We also followed up all patients for cardiovascular events (ie, cardiac death, readmission to hospital due to heart failure, new onset of acute coronary syndrome, or revascularisation of new lesions) until the end of August, 2006. We took blood samples to measure concentrations of creatine kinase at a central laboratory, before the procedure and at 1, 3, 6, 9, 12, 18, 24, 36, 48, and 72 h after the onset of reperfusion.[14] We analysed total creatine kinase for all patients with at least six blood samples. We obtained right anterior oblique views with angiography of the left ventricle once in the acute phase (2–8 weeks), and once in the chronic phase (6–12 months).

Our primary endpoints were infarct size (which was estimated as the area under the concentration versus time curve for creatine kinase)[14] and ventricular ejection fraction (which was assessed by angiography of the left ventricle at 6–12 months after hospital admission).[15] The prespecified secondary endpoints were survival rate; cardiovascular events (such as cardiac death, readmission to hospital for heart failure, new onset of acute coronary syndrome, or revascularisation of new lesions); incidence of cardiac death or readmission to hospital for

	J-WIND-ANP study	J-WIND-KATP study
1–4 patients	7 hospitals	9 hospitals
5–9 patients	3 hospitals	13 hospitals
10–19 patients	7 hospitals	6 hospitals
More than 20 patients	10 hospitals	10 hospitals

Table 1: **Distribution of patients between participating hospitals**

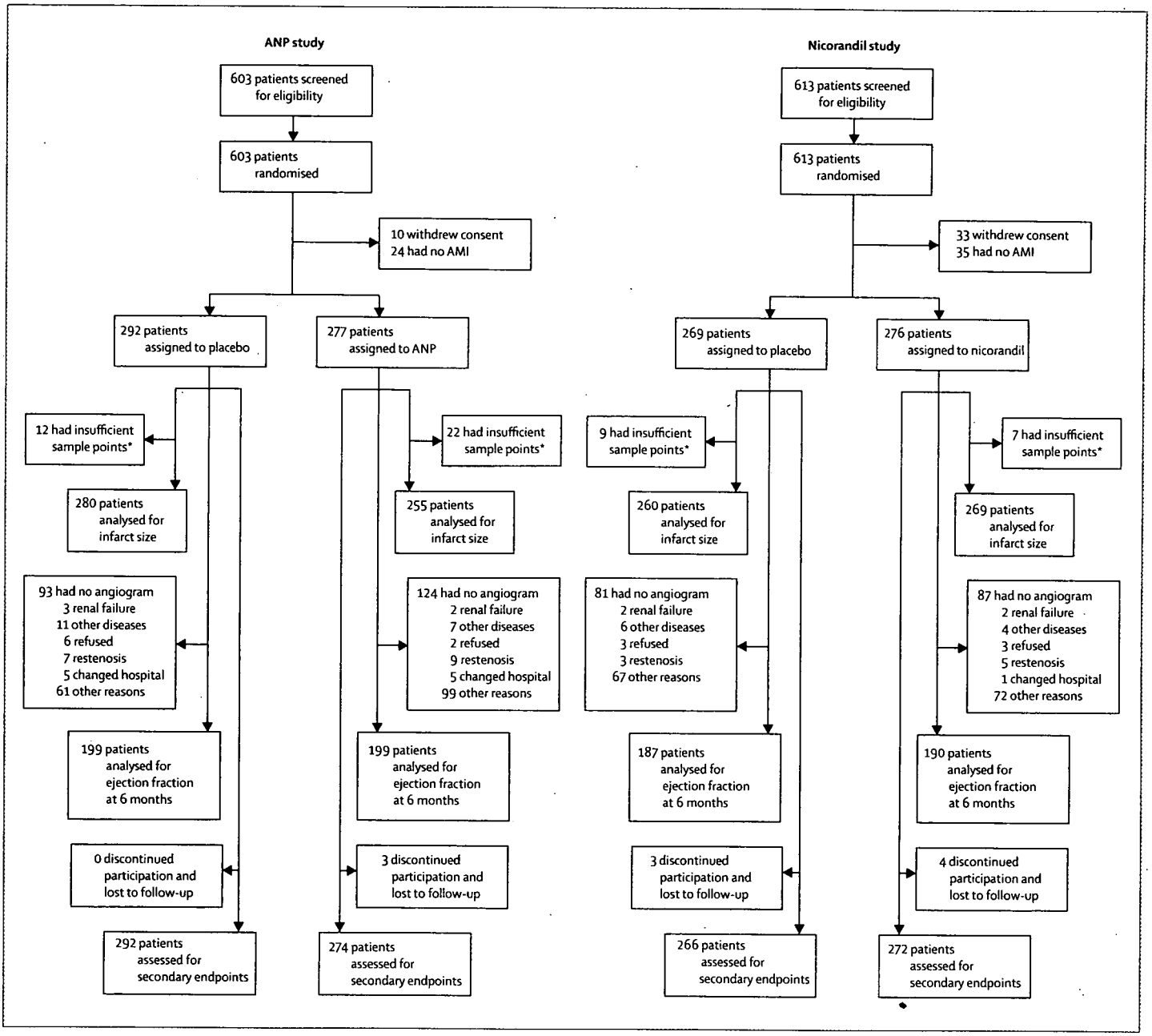

Figure 1: **Trial profiles**
ANP=atrial natriuretic peptide. AMI=acute myocardial infarction. *Fewer than six blood samples.

heart failure; or reperfusion injury before discharge from coronary care unit (such as malignant ventricular arrhythmia during reperfusion, recurrence of ST segment elevation, or worsening of chest pain). We also assessed infarct size, estimated by peak creatine kinase and troponin T;[28,29] left ventricular ejection fraction at acute phase; and end-diastolic or end-systolic volume index (assessed by angiography of the left ventricle). We looked at the effects of each drug on the primary endpoints in prespecified subgroups (sex, age, body-mass index, pre-angina, elapsed time between acute myocardial infarction and intervention, diabetes mellitus, hyperlipidaemia, smoking, and family history of acute myocardial infarction). We also did post-hoc analyses on the effect of chronic administration of nicorandil on the ejection fraction.

All data were collected by Koteisho-kyokai (Tokyo), an organisation established by the Japanese government in 2001–2003 and by NTT Data (Tokyo) in 2004–2006. Left ventricular ejection fraction and end-diastolic volume were measured by the area–length method, from angiography of the left ventricle. Two independent

interpreters, who were unaware of the treatment assigned to patients, measured left ventricular ejection fractions from the angiographs. We calculated the average value, unless the two investigators disagreed, in which case we referred to a third opinion.

Clinical findings and medications during the follow-up period were reported to a data and safety committee after registration. This committee, which consisted of three physicians and one statistician who did not participate in the trial, monitored all adverse events. Research nurses or doctors visited all participating hospitals to check that patients were registered, drugs were given, and data collected according to the protocol. Committee members did not provide any results to the steering committee, because discontinuation of the study was not recommended.

Statistical analysis

We calculated that a sample size of 300 patients would be needed in each group to detect a 20% reduction in the most important primary endpoint (total creatine kinase) with a statistical power of 80% at significance level of 0·05 (with a two-sided *t* test), accounting for dropout of some patients. We set equal sample sizes in both groups, because we expected to see almost the same reduction in infarct size with either treatment. Since creatine kinase and total creatine kinase are both log-normally distributed,[30] total creatine kinase was log-transformed before analysis. The left ventricular ejection fraction was also log-transformed before the analysis since the distribution was skewed.

Statistical analysis was done according to a prespecified analytical plan. Efficacy analysis was based on intention to treat. The primary efficacy analyses for total creatine kinase and left ventricular ejection fraction were done simply by *t* test. The estimated mean and differences on the log scale were transformed back to the original scale and were expressed as geometric means and ratios of geometric mean. If the calculated 95% CI for the ratio of the geometric mean did not cross the point of no effect (ie, 1) the difference between groups was regarded as significant. Furthermore, analysis of covariance for the two endpoints was used to estimate adjusted mean comparison, with effect of covariates and the interactions. We imputed missing data for patients by the predicted mean imputation method, with nonlinear regression. We applied multiple imputation techniques (with group means, Markov Chain Monte Carlo, Bayesian bootstrap, and last-observation-carried-forward methods) to assess the robustness and sensitivity of our conclusions.

Proportions were examined by Fisher's exact test. We examined time-to-event by the Kaplan-Meier method to estimate the survival for each group and then the differences in survival between groups by the log-rank test. The Cox proportional hazards model was used to assess baseline risk factors and an adjusted hazard ratio. The proportional hazards assumption was investigated graphically, with a test based on Schoenfeld residuals.[31,32]

All tests were two-sided, and a p value of less than 0·05 was regarded as significant. All analyses were done with SAS software (version 8.2). The trials are registered with Clinicaltrials.gov, numbers NCT00212056 and NCT00212030.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data at the end of the study, and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Table 2 shows baseline characteristics. Median follow-up was 2·7 (IQR 1·5–3·6) years in the atrial natriuretic peptide trial and 2·5 (1·5–3·7) years in the nicorandil trial. Table 3 shows

	Atrial natriuretic peptide study			Nicorandil study		
	ANP (n=277)	Control (n=292)	p	Nicorandil (n=276)	Control (n=269)	p
Age (years)	63·0 (10·4)	61·8 (10·7)	0·1652	61·1 (11·4)	63·7 (10·2)	0·0035
Sex (male)	211 (76·2%)	243 (83·2%)	0·0374	246 (89·1%)	220 (81·8%)	0·0153
Body-mass index	24·3 (3·5)	24·0 (2·9)	0·3733	24·2 (3·0)	23·4 (2·8)	0·0007
Killip classification (I, II, III, IV)	88·6%, 9·5%, 1·1%, 0·8%	90·3%, 7·5%, 1·4%, 0·7%	0·5274	91·1%, 8·2%, 0·4%, 0·4%	92·0%, 4·2%, 2·7%, 1·1%	0·7843
Pre-angina	105 (44·5%)	118 (46·1%)	0·7862	111 (44·6%)	111 (43·9%)	0·9284
Risk factors						
Hypertension	137 (56·1%)	162 (62·1%)	0·2046	127 (48·5%)	137 (53·9%)	0·2190
Diabetes mellitus	81 (33·8%)	86 (33·9%)	1·0000	104 (39·5%)	82 (32·9%)	0·1413
Hyperlipidaemia	127 (54·3%)	131 (50·6%)	0·4181	121 (46·7%)	114 (46·2%)	0·9291
Smoking	158 (63·7%)	175 (67·3%)	0·4022	178 (68·7%)	170 (66·1%)	0·5732

Data are number (%) or mean (SD), unless otherwise specified. ANP=atrial natriuretic peptide.

Table 2: **Baseline characteristics on admission**

	Atrial natriuretic peptide study		Nicorandil study	
	ANP (n=277)	Control (n=292)	Nicorandil (n=276)	Control (n=269)
Elapsed time (h)*	4·00 (3·00–6·00)	4·00 (2·50–6·00)	3·50 (2·50–5·00)	3·50 (2·50–5·00)
Infusion time (h)	1·00 (0·50–1·00)	1·00 (0·50–1·00)	0·70 (0·50–1·00)	0·75 (0·50–1·00)
IRA (LAD, LCx, RCA)	55·3%, 6·4%, 38·3%	52·3, 10·6, 37·1%	53·9, 7·4, 38·7%	44·5, 9·9, 45·6%
Stents	176 (63·5%)	193 (66·1%)	187 (67·8%)	183 (68·0%)
Rescue	64 (23·1%)	92 (31·5%)	94 (34·1%)	92 (34·2%)
Intra-aortic balloon pump	17 (6·1%)	14 (4·8%)	14 (5·1%)	15 (5·6%)
Final stenosis (<75%)	246 (93·5%)	266 (94·7%)	257 (96·6%)	255 (97·0%)
Final thrombolysis in myocardial infarction (0, 1, 2, 3)	3·9%, 1·9%, 5·0%, 89·1%	5·2%, 0·7%, 4·1%, 90·0%	3·7%, 0·7%, 5·2%, 90·3%	3·4%, 1·1%, 6·9%, 88·5%
Medications at 1 month				
ACE inhibitor	155 (57·8%)	173 (60·7%)	164 (61·0%)	163 (62·0%)
ARB	77 (28·7%)	99 (34·7%)	72 (26·8%)	69 (26·2%)
Spinorolactone	28 (10·4%)	33 (11·6%)	17 (6·3%)	22 (8·4%)
β blocker	112 (41·8%)	128 (44·9%)	110 (40·9%)	121 (46·0%)
Aspirin	225 (84·0%)	252 (88·4%)	251 (93·3%)	250 (95·1%)
Nitrates	81 (30·2%)	86 (30·2%)	50 (18·6%)	63 (24·0%)
Statins	129 (48·1%)	156 (54·7%)	126 (46·8%)	115 (43·7%)
Nicorandil	62 (23·1%)	52 (18·2%)	79 (29·4%)	34 (12·9%)
Medications at 6 months				
ACE inhibitor	103 (48·1%)	117 (44·8%)	120 (50·6%)	131 (53·9%)
ARB	69 (32·2%)	110 (42·1%)	68 (28·7%)	75 (30·9%)
Spinorolactone	26 (12·1%)	26 (10·0%)	11 (4·6%)	15 (6·2%)
β blocker	93 (43·5%)	118 (45·2%)	104 (43·9%)	113 (46·5%)
Aspirin	179 (83·6%)	233 (89·3%)	217 (91·6%)	229 (94·2%)
Nitrates	51 (23·8%)	63 (24·1%)	37 (15·6%)	49 (20·2%)
Statins	112 (52·3%)	150 (57·5%)	123 (51·9%)	118 (48·6%)
Nicorandil	46 (21·5%)	39 (14·9%)	55 (23·2%)	23 (9·5%)
Medications at 24 months				
ACE inhibitor	66 (47·5%)	63 (37·5%)	83 (52·5%)	75 (49·3%)
ARB	42 (30·2%)	72 (42·9%)	39 (24·7%)	43 (28·3%)
Spinorolactone	13 (9·4%)	21 (12·5%)	9 (5·7%)	4 (2·6%)
β blocker	57 (41·0%)	61 (36·3%)	77 (48·7%)	71 (46·7%)
Aspirin	113 (81·3%)	133 (79·2%)	143 (90·5%)	137 (90·1%)
Nitrates	29 (20·9%)	45 (26·8%)	23 (14·6%)	25 (16·4%)
Statins	66 (47·5%)	78 (46·4%)	81 (51·3%)	71 (46·7%)
Nicorandil	26 (18·7%)	26 (15·5%)	28 (17·7%)	11 (7·2%)

Data are median (IQR), number (%) or mean (SD), unless otherwise specified. ANP=atrial natriuretic peptide. IRA=infarct-related artery. LAD=left anterior descending coronary artery. LCx=left circumflex artery. RCA=right coronary artery. ARB=antiotensin receptor blocker. ACE=angiotensin-converting enzyme. *Period between acute myocardial infarction and start of intervention.

Table 3: **Treatments and prescribed drugs**

treatments and drugs throughout the study. Drugs used in the chronic stage did not differ between groups in either study, except that some patients in the nicorandil trial were given oral nicorandil during follow-up.

Table 4 and figure 2 show infarct size and left ventricular function at 2–8 weeks and 6–12 months in both studies. The ratio of total creatine kinase between the atrial natriuretic peptide and placebo groups was 0·85 (95% CI 0·75–0·97, p=0·0155); which indicates that atrial natriuretic peptide was associated with a reduction of 14·7% in infarct size. Subanalyses identified no factors that enhanced or reduced the influence of atrial natriuretic peptide on infarct size (figure 2). Nicorandil did not reduce infarct size compared with placebo, and no factors affected this finding. Treatment with atrial natriuretic peptide tended to increase the left ventricular ejection fraction (ratio 1·043, 95% CI 1·000–1·089, p=0·0525) at 2–8 weeks after the onset of acute myocardial infarction, and at 6–12 months (ratio 1·051, 95% CI 1·006–1·099, p=0·0236). By contrast, table 4 and figure 2 show that left ventricular ejection fraction did not differ in patients given nicorandil and controls at either 2–8 weeks or 6–12 months.

	J-WIND-ANP study			J-WIND-KATP study		
	Atrial natriuretic peptide	Control	p	Nicorandil	Control	p
Infarct size						
n	255	280		269	260	
Creatine kinase (area under curve) (IU/L h)	66 459·9 (60 258·2–73 300·0)	77 878·9 (71 590·2–84 720·1)	0·016	70 520·5 (64 309·8–77 331·0)	70 852·7 (65 066·7–77 153·2)	0·941
Peak creatine kinase (IU/L)	2487·5 (2217·6–2790·3)	2784·2 (2526·7–3067·9)	0·141	2557·1 (2306·1–2835·4)	2428·7 (2199·8–2681·5)	0·479
Troponin-T concentration (12–18 h) (ng/mL)	5·36 (4·76–6·03)	6·13 (5·55–6·79)	0·084	6·18 (5·51–6·93)	5·60 (4·97–6·32)	0·244
Troponin T (96 h) (ng/mL)	2·57 (2·25–2·94)	2·94 (2·64–3·27)	0·125	2·63 (2·36–2·94)	2·89 (2·61–3·19)	0·225
Left ventricle (2–8 weeks)						
n	187	207		168	170	
Median elapsed time (days)*	18·5 (IQR 15·0–27·0)	19·0 (IQR 16·0–25·0)		17·0 (IQR 14·0–23·0)	17·0 (IQR 14·0–24·0)	
Ejection fraction	43·0% (41·8–44·3)	41·3% (40·0–42·6)	0·053	42·0% (40·7–43·3)	41·6% (40·4–42·9)	0·680
End diastolic volume index (mL/m²)	98·8 (94·4–103·4)	102·3 (98·1–106·6)	0·272	111·2 (106·4–116·3)	105·9 (100·9–111·3)	0·147
End systolic volume index (mL/m²)	54·2 (51·2–57·4)	58·3 (55·5–61·4)	0·058	62·8 (59·2–66·6)	60·4 (57·0–64·1)	0·360
Left ventricle (6–12 months)						
n	155	199		190	187	
Median elapsed time (days)*	196·5 (IQR 180·5–230·5)	200·5 (IQR 183·0–226·0)		195·0 (IQR 180·0–231·0)	195·5 (IQR 183·0–232·0)	
Ejection fraction	44·7% (43·4–46·0)	42·5% (41·2–43·9)	0·024	42·5% (41·2–43·8)	43·2% (42·0–44·4)	0·460
End diastolic volume index (mL/m²)	100·6 (95·2–106·2)	100·9 (96·8–105·1)	0·930	109·8 (105·4–114·4)	105·7 (100·8–110·8)	0·230
End systolic volume index (mL/m²)	54·2 (50·6–58·0)	56·0 (53·1–58·9)	0·452	61·7 (58·4–65·2)	58·5 (55·1–62·1)	0·198

Data are mean (95% CI) or median (IQR). *Time between acute myocardial infarction and start of intervention.

Table 4: **Primary endpoints and other outcomes obtained by angiography of left ventricles**

Figure 3 shows reperfusion injuries, survival rates, and cardiovascular events. Reperfusion injuries were less common in the atrial natriuretic peptide group than in the placebo group (ratio 0·743, 95% CI 0·58–0·952, p=0·019). Although there were no differences between groups in either survival rates or the incidence of cardiovascular events, both cardiac death and readmission to hospital for heart failure were lower in patients given atrial natriuretic peptide than in controls (HR 0·267, 95% CI 0·089–0·799, p=0·0112). By contrast, cardiac death and readmission to hospital for heart failure were not significantly lower in patients given nicorandil than in controls (HR 0·799, 95% CI 0·307–1·973, p=0·5972). When nicorandil was given orally throughout the study after reperfusion treatment, the change of left ventricular ejection fraction increased substantially between the acute and chronic phase. The ejection fraction was 3·66% in the 61 patients who were given nicorandil orally, and 1·47% in the 241 patients who were not (difference 2·20, 95% CI 0·17–4·22, p=0·0338).

In the atrial natriuretic peptide trial, 29 patients given that drug had severe hypotension during the acute phase, compared with one control. In the other trial, three patients in the nicorandil group had severe hypotension, compared with no controls. No other severe adverse events were reported during the course of either study.

Discussion

We showed that adjunctive, acute-phase treatment with atrial natriuretic peptide after reperfusion therapy in patients with acute myocardial infarction reduced infarct size by 14·7%, increased the left ventricular ejection fraction during the chronic phase, and decreased the incidence of cardiac death and readmission to hospital because of heart failure. Intravenous treatment with nicorandil did not affect the primary endpoints, although patients who were given nicorandil orally had better cardiac function outcomes.

Interest in the cardioprotective effects of adenosine has increased, because of its variety of cardioprotective mechanisms. Unfortunately, in trials of adenosine, it only marginally improved infarct size and showed no clinical benefits.[7,33] We hypothesised that treatment with atrial natriuretic peptide and nicorandil in the acute phase might prove more effective than chronic-phase treatment for limitation of infarct size. The first window of ischaemic preconditioning is mediated by opening of the KATP channel,[34] which is the mechanism of action of nicorandil; and the second window is mediated by nitric oxide and activation of G kinase, which is the mechanism of action of atrial natriuretic peptide.

Before this clinical trial, we had tested whether atrial natriuretic peptide could limit infarct size in a canine model in which the left anterior coronary artery was ligated for 90 min, followed by 6 h of reperfusion. Treatment with atrial natriuretic peptide reduced infarct size by about 40% after reperfusion (unpublished data). Our results are consistent with the finding of Hayashi and coworkers[20] that infusion of atrial natriuretic peptide immediately after reperfusion in patients with their first anterior acute myocardial infarction increased left ventricular ejection fraction.

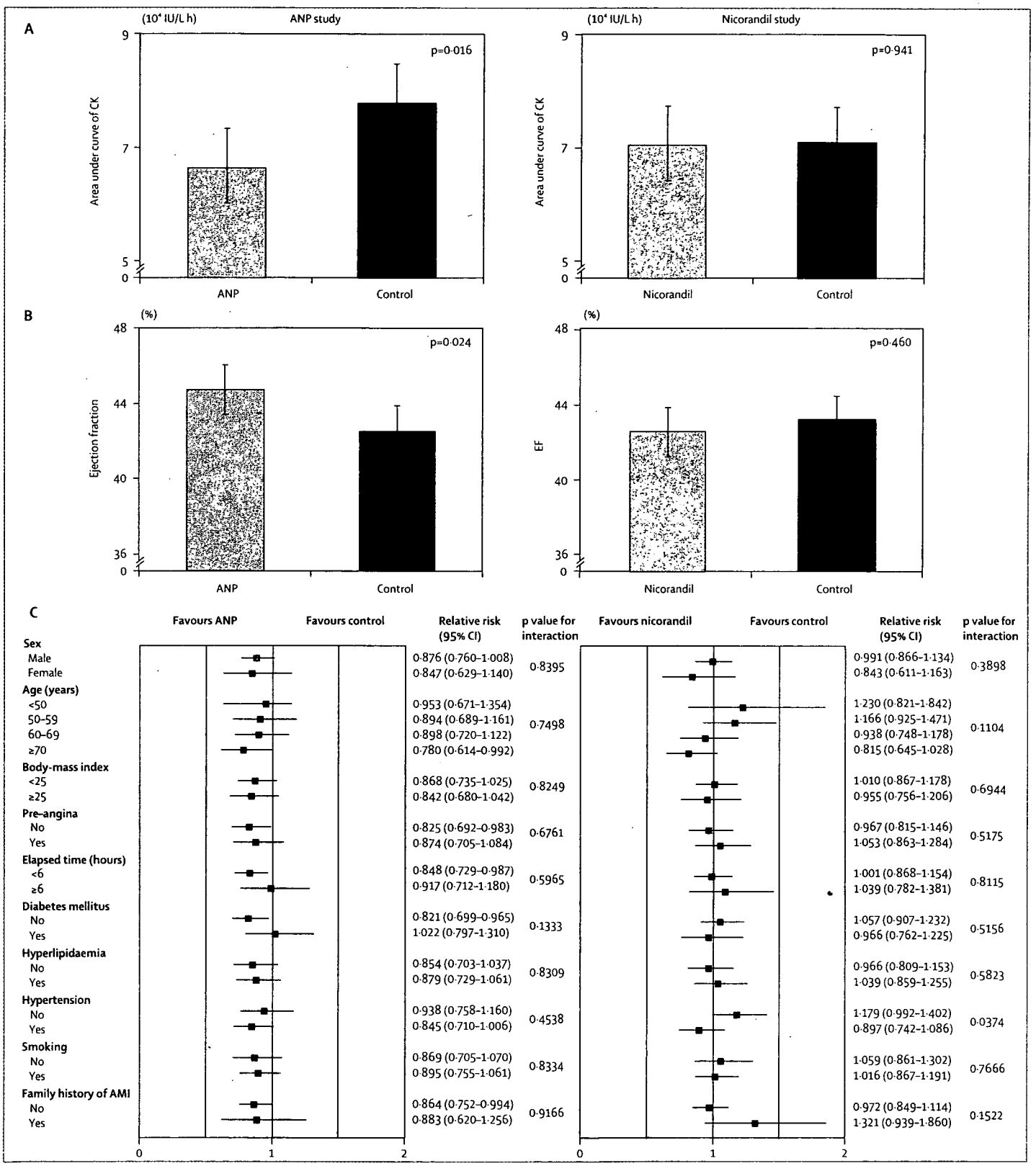

Figure 2: **Primary endpoints and subgroup analyses**
CK=creatine kinase. AMI=acute myocardial infarction. ANP=atrial natriuretic peptide. Panel A shows area under curve of creatine kinase concentration versus time. Panel B represents left ventricular ejection fraction measured at 6–12 months.

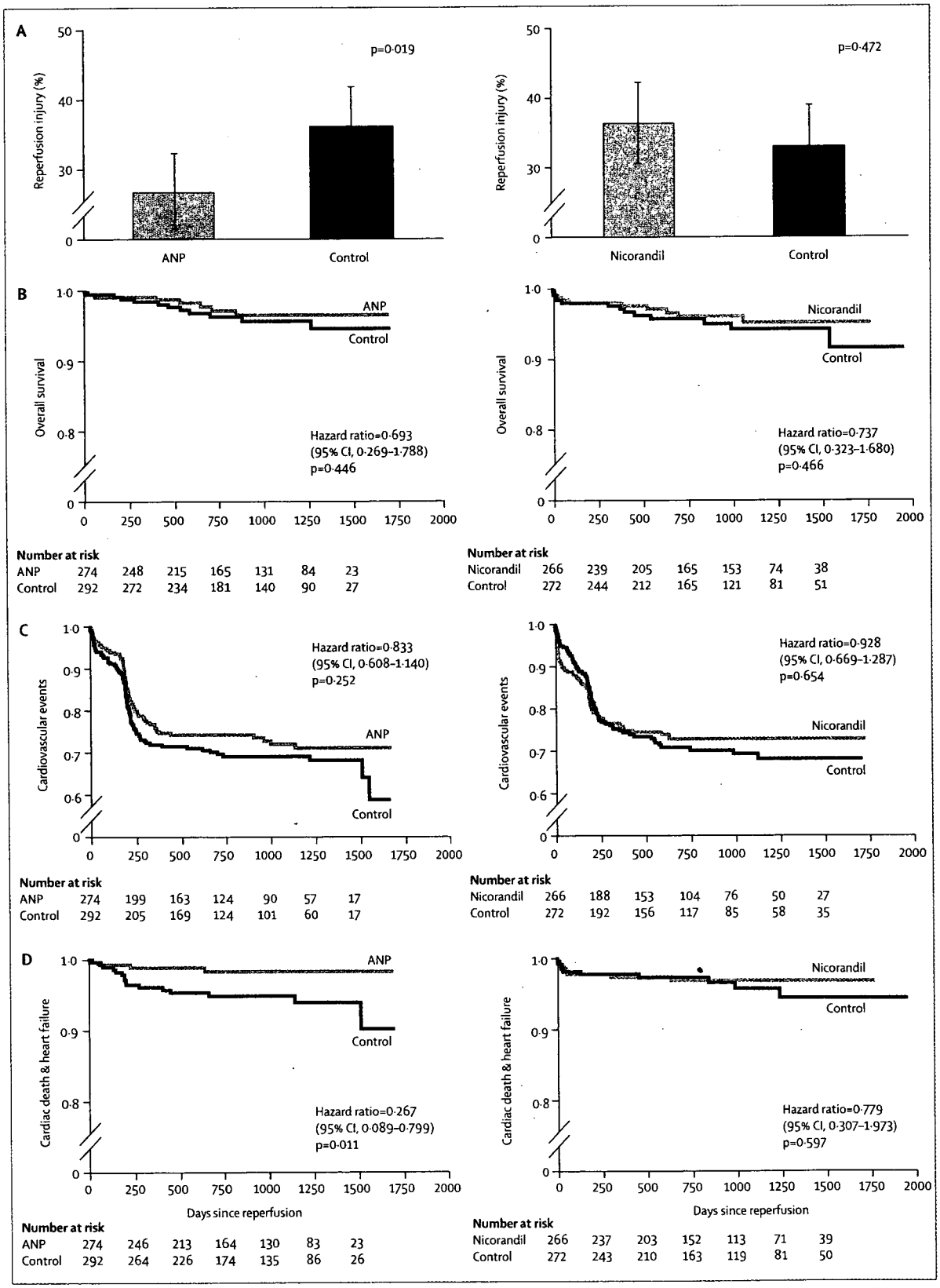

Figure 3: **Secondary endpoints and other subanalyses**
ANP=atrial natriuretic peptide.

The reduction of infarct size and the improvement of left ventricular ejection fraction might decrease mechanical stress on the non-infarcted myocardium, which might decrease hypertrophy and dilatation of the non-infarcted myocardium. Since cardiac hypertrophy and dilatation cause diastolic and systolic heart failure, a reduction of infarct size and an increase of left ventricular ejection fraction could mediate beneficial clinical outcomes. However, we need to do another large-scale clinical trial to target clinical outcomes such as cardiovascular death, because our primary aim here was to test the reduction of infarct size. Moreover, Hayashi and colleagues[20] showed that plasma concentrations of angiotensin II, aldosterone, and endothelin-1 were lower in patients given atrial natriuretic peptide than in controls. Sudden exposure to high concentrations of angiotensin II, aldosterone, and endothelin-1 for several days caused vascular or ventricular remodelling, and attenuation of these harmful effects by infusion of atrial natriuretic peptide could reduce the incidence of cardiac death and readmission to hospital for chronic heart failure.[20]

One reason that nicorandil treatment did not limit infarct size in our study could be the size of the dose. Ishii and colleagues[25] have reported that one intravenous administration of a dose of nicorandil that was three times higher than that which we used decreased the infarct size and reduced the rate of cardiovascular death or readmission to hospital for chronic heart failure in 368 patients with acute myocardial infarction.

Patients in the nicorandil study who were given nicorandil orally in the chronic phase had greater increases in left ventricular ejection fraction, irrespective of whether nicorandil was given intravenously or orally. Since microvascular obstruction ten days after myocardial infarction was associated with left ventricular remodelling and poor prognosis, coronary perfusion might be improved by opening KATP channels in coronary blood vessels during the healing stage. The IONA study[35] showed that nicorandil could reduce the incidence of unstable angina in patients with stable angina.

Our finding that treatment with atrial natriuretic peptide in the acute phase reduced the incidence of readmission to hospital for chronic heart failure could help to reduce the physical, medical, and economic burdens on people around the world. Moreover, since intravenous nicorandil in the acute phase, followed by oral administration in the chronic phase, increased the left ventricular ejection fraction, chronic treatment with nicorandil could improve ventricular function for patients with myocardial infarction in the chronic phase.

Several limitations of our study should be discussed. First, physicians knew the random assignment of patients, and treatment for acute myocardial infarction in the chronic phase was not restricted accordingly; this could have affected the difference in nicorandil treatment at the chronic phase. Second, although we planned to do angiography of the left ventricle when patients were admitted to hospital, some hospitals could not take angiographs, because of the additional medical cost. Therefore, baseline angiographs were absent for some patients. Third, the patterns of missing angiography data on left ventriculography differed between the two studies (which were done at different hospitals) and also between the atrial natriuretic peptide group and corresponding placebo group. We cannot explain this difference, but since we did not intervene in this procedure, we believe that it must be due to chance.

Contributors

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Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

These studies were supported by grants for Comprehensive Research on Ageing and Health (H13-21seiki (seikatsu) 23), in Health and Labour Sciences Research from Ministry of Health, Labour and Welfare, Japan, and by a grant from the Japanese Cardiovascular Research Foundation. We thank Satomi Ihara for her excellent assistance with data management; Hidetoshi Okazaki, Hiroyuki Yamamoto, Masakatsu Wakeno, Atsushi Nakano, Hiroyuki Takahama, Shin Ito, Hideyuki Sasaki, and Kyungduk Min for analysis of angiographs of left ventricles; Yoshie Yanagi, Hiromi Ohara, Chikayo Tsujimoto, Naoko Matsuo, Yoshihiro Asano, Masashi Fujita, Shuichiro Higo, and Mitsutoshi Asai for data monitoring; Ms Uchida at SACT international for data analysis; Dr Tsutomu Yamazaki for data management; and Dr Ed Schweitzer for review of the manuscript.

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Circ J 2007; **71:** 449–454

Characteristics and Outcomes of Patients With Heart Failure in General Practices and Hospitals

—— Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) ——

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Background The characteristics and outcomes of patients discharged from hospitals with a diagnosis of heart failure (HF) have been described by a number of previous epidemiological studies. However, very little information is available on this issue in general practice in Japan.

Methods and Results The Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) is designed to study the characteristics, treatment and outcomes prospectively in a broad sample of outpatients with HF who were managed by cardiologists in hospital (Hospital-HF) and primary care physicians in general practice (GP-HF). Out of 2,685 patients with HF, 1,280 patients were Hospital-HF and 1,405 GP-HF. Compared to the Hospital-HF patients, GP-HF patients were more likely to be elderly and female, and they had a higher prevalence of hypertensive heart disease as a cause of HF. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and β-blockers were more prescribed to Hospital-HF than GP-HF patients. At the follow-up of 1.2 year, after adjustment, the mortality was comparable between the Hospital-HF and GP-HF groups, whereas HF-related admission was higher in the Hospital-HF group than in in the GP-HF group.

Conclusions Based on the JCARE-GENERAL, the characteristics, treatment and outcomes of GP-HF patients differed from those of Hospital-HFpatients in Japan. (*Circ J* 2007; **71:** 449–454)

Key Words: General practice; Heart failure; Hospital; Outcome; Registry

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardiac manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. HF is a leading cause of morbidity and mortality in industrialized countries[1] It is also a growing public health problem, mainly because of aging populations and the increase in the prevalence of HF in the elderly[2] The clinical characteristics, treatment and outcomes of these patients have been well described by a number of hospital-based registries performed in the United States of America[3] Europe[4–6] and Japan[7–11] However, most patients with HF are managed not only by hospital cardiologists but also by primary healthcare physicians in the community (general practitioners). Accordingly, primary care physicians must play a key role in the identification and management for these patients. Nevertheless, much less is known of HF in general practice. There have been no studies reported that provide information on the characteristics, treatment and outcomes in this setting in Japan.

The Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) was developed to provide a large, national prospective registry database describing the clinical characteristics, treatment and outcomes of outpatients with HF. The main aim of the present study was to compare the characteristics and outcomes between patients managed by hospital cardiologists with those managed by primary care physicians in general practice.

Methods

The JCARE-GENERAL is a prospective multicenter registry designed to compile a large clinical database on the characteristics, treatment and outcomes of the outpatients with HF in Japan. Baseline data were collected during November 2004. Follow-up data were collected 1 year after the enrollment.

Study Patients

Eleven participating areas, Hakodate, Shiogama, Mishima, Kahoku in Ishikawa, Motosu in Gifu, Ibaraki, Kasai, Hata in Kochi, Ube, Higashi in Fukuoka, and Kurume, have been selected throughout Japan (Fig 1). In

(Received August 17, 2006; revised manuscript received January 19, 2007; accepted January 23, 2007)

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This work is supported by the grants from the Japanese the Ministry of Health, Labour and Welfare, the Japan Heart Foundation, and Japan Arteriosclerosis Prevention Fund.

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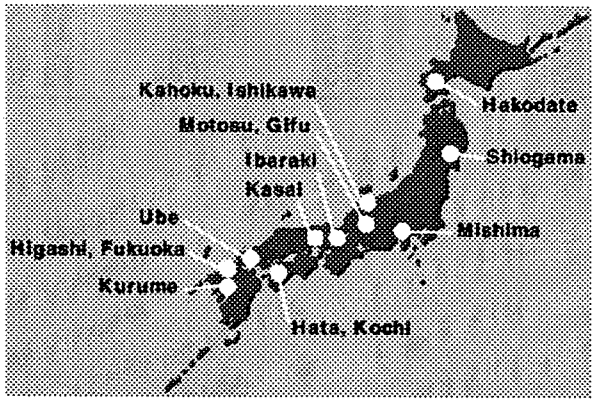

Fig 1. The Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) study areas in Japan.

each participating area, hospital cardiologists and primary healthcare physicians enrolled HF outpatients into the present study. HF patients managed by the hospital cardiologists were categorized as "Hospital-HF" and those managed by primary care physicians in general practice as "GP-HF".

HF was defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. For this registry, patients with current HF symptoms as well prior HF were enrolled. The presence of HF was confirmed by the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria according to the Framingham criteria (Table 1).[12] Patients must have been at least 15 years old at the time of enrollment. Eligibility is not contingent on the use of any particular therapeutic agent or regimen.

Data Collection and Processing

The study protocol, study procedures and data-collection forms were reviewed by the co-investigators at each study area during the central meetings and also presented to all participating physicians during training sessions before commencing the present study. The participating physicians were encouraged to register all patients meeting the entry criteria as consecutively as possible. Duplicated registry of the same patient at different institutions was avoided by checking for their prior enrollment to this registry. Compliance with these methods of registry was not strictly monitored. For each case, baseline data recorded on the form included: (1) demography including age and sex; (2) underlying causes of HF; (3) atrial fibrillation; (4) prior history of HF; and (5) medication. The status of all patients was surveyed and the following information was obtained: (1) whether they survived to the follow up; (2) their cause of death; and (3) hospital admissions due to an exacerbation of HF that required more than continuation of their usual therapy on admission. The cause of death was classified as cardiac or non-cardiac death by the participating physician in each patient based on the clinical information. Death from cardiac causes was defined as death due to cardiac events including sudden cardiac death, fatal myocardial infarction and HF death. Death from causes other than cardiac diseases such as cancer was defined as non-cardiac death.

Ischemic heart disease was considered an etiology of HF if the patient had one of the following: (1) a documented history of myocardial infarction, angina or prior coronary revascularization; (2) pathologic Q waves on the electrocardiogram; or (3) greater than 75% stenosis in one or more coronary arteries on coronary angiograms. Valvular heart disease was determined on the basis of the presence of long standing mitral or aortic valve involvement documented by physical examination and echocardiography or angiography. Hypertensive heart disease was considered present if there was a history of hypertension in the medical records or sustained hypertension and left ventricular (LV) hypertrophy confirmed by electrocardiogram or echocardiogram. Dilated cardiomyopathy was diagnosed by the presence of global LV dilatation with impaired systolic function occurring in the absence of known cardiac or systemic causes.

Table 1 Framingham Criteria for HF

Major criteria
Paroxysmal nocturnal dyspnea
Neck vein distension
Rales
Radiographic cardiomegaly (increasing heart size on chest X-ray)
Acute pulmonary edema
S3 gallop
Increased central venous pressure (>16 cm water at right atrium)
Circulation time ≥25 s
Hepatojugular reflux
Pulmonary edema, visceral congestion, or cardiomegaly at autopsy
Minor criteria
Bilateral ankle edema
Nocturnal cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Decrease in vital capacity by one-third from maximum value recorded
Tachycardia (rate ≥120/min)
Major or minor criteria
Weight loss ≥4.5 kg in 5 days in response to treatment

The diagnosis of HF was established by the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.
HF, heart failure.

Patient Confidentiality

The JCARE-GENERAL protocol was organized to ensure compliance with the Guidelines for the Epidemiological Research published by the Japanese Ministry of Health, Labour and Welfare. The original study protocol was approved by the institutional review board at Kyushu University. Informed consent was attained for each patient. The present study did not include any protocol-specified alterations of treatment or any other aspects of hospital care. Patient confidentiality was preserved because direct patient identifiers, such as name, address and identification number, were not collected.

Statistical Analysis

Data are expressed as means±SD. Differences in clinical characteristics, treatment and outcomes were evaluated using the chi-square test or Student's t-test. Survival was estimated with the Kaplan and Meier methods. Differences in survival between the groups were evaluated using the log rank test. After the adjustment for age, sex, etiology of HF, atrial fibrillation and prior history of HF, the relative risk for outcomes including all-cause death, cardiac death and HF-related admission was estimated for the Hospital-HF and GP-HF groups. They were adjusted as categorical

Table 2 Patient Characteristics

	All (n=2,685)	Hospital-HF (n=1,280)	GP-HF (n=1,405)	p value
Age, year (mean±SE)	74±12	71±13	77±10	<0.01
≥75 years, %	56	46	64	<0.01
Male, %	46	55	38	<0.01
Underlying causes of HF, %				
Ischemic	30	27	32	<0.05
Hypertensive	35	22	47	<0.05
Valvular	26	27	25	NS
Cardiomyopathic	15	22	9	<0.05
Others	12	12	12	NS
Unknown	5	4	5	NS
Atrial fibrillation, %	40	42	37	<0.01
Prior history of HF, %	83	90	77	<0.01

GP, general practice. Other abbreviation see in Table 1.

Table 3 Medication Use

	All (n=2,685)	Hospital-HF (n=1,280)	GP-HF (n=1,405)	p value
ACEIs, %	31.5	40.4	23.5	<0.01
ARBs, %	30.9	32.7	29.4	NS
ACEIs or ARBs, %	59.2	68.7	50.6	<0.01
ACEIs and ARBs, %	3.3	4.4	2.3	<0.01
β-blockers, %	27.4	38.3	17.5	<0.01
Diuretics, %	62.0	66.1	58.2	<0.01
Digitalis, %	43.0	45.4	40.8	<0.05
Calcium antagonists, %	37.1	33.4	40.5	<0.01

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers. Other abbreviations see in Tables 1,2.

Table 4 Death and HF-Related Admission Rate

	No. of patients		All cause death (%)		Cardiac death (%)		HF-related admission (%)	
	Hospital-HF	GP-HF	Hospital-HF	GP-HF	Hospital-HF	GP-HF	Hospital-HF	GP-HF
Crude rate	1,251	1,377	6.7	5.9	2.9	1.7	11.3	6.8
Age-adjusted rate (95%CI)			7.6 (2.7–12.5)	5.3 (1.9–8.7)	3.0 (0.2–6.1)	1.5 (0.3–3.3)	12.1 (6.0–18.3)	6.8 (2.3–11.3)
Age groups								
–39 years	36	4	11.1	0	5.6	0	8.3	0
40–49 years	52	16	1.9	0	1.9	0	13.5	6.3
50–59 years	132	72	3.0	0	3.0	0	8.3	5.6
60–69 years	237	200	3.4	1.5	1.7	0.5	10.1	4.0
70–79 years	439	503	6.6	3.8	2.7	1.4	11.8	7.2
80–89 years	314	472	10.5	8.3	3.8	2.8	13.1	6.4
90– years	38	108	13.2	18.5	2.6	1.9	7.9	13.9
Sex groups								
Male								
Crude rate	685	508	8.7	7.3	2.9	1.8	12.0	6.9
Age-adjusted rate (95%CI)			10.2 (4.9–15.6)	6.4 (2.7–10.0)	3.1 (0.2–5.9)	1.5 (0.5–3.5)	13.0 (7.4–18.6)	6.8 (1.3–12.3)
Female								
Crude rate	563	858	4.4	5.1	2.8	1.6	10.5	6.9
Age-adjusted rate (95%CI)			4.9 (0.8–8.9)	4.9 (2.3–7.5)	2.9 (0.2–6.1)	1.6 (0.5–2.8)	11.4 (5.2–17.6)	6.9 (3.3–10.5)

The mean follow-up periods for HP-HF and GP-HF were 431±93 days and 424±91 days, respectively.
CI, confidence interval. Other abbreviations see in Tables 1,2.

variables, except for age, which was a numerical variable. Two tailed tests of significance are reported. $p<0.05$ was considered to be statistically significant.

Results

Patient Characteristics

The present study included 2,685 outpatients with HF from 11 areas in Japan; 1,280 patients from 55 hospitals as Hospital-HF and 1,405 patients from 180 general practitioners as GP-HF. The mean number of patients at each hospital and GP was 23±27 and 8±9, respectively. The mean age was 74±12 years (range 15 to 101), and 56% of patients were >75 years of age (Table 2). The mean age and the proportion of aged patients were greater in GP-HF patients compared to Hospital-HF patients (Table 2). Overall, 46% were men and 54% women. The GP-HF patients were more often women (45% vs 62%, $p<0.01$).

Ischemic heart disease was the predominant cause of HF in both groups, but this was more prevalent in the GP-HF group. Hypertensive heart disease was more common in the GP-HF group than in the Hospital-HF group and it was the leading cause of HF in this group of patients. In contrast, cardiomyopathy was less common in GP-HP patients.

The prevalence of atrial fibrillation was greater and the prior history of HF was more frequent in Hospital-HF patients than in the GP-HF group (Table 2).

Medication Use

Angiotensin-converting enzyme (ACE) inhibitors were administered to 32% of the patients, angiotensin receptor blockers (ARBs) to 31%, β-blockers to 27%, diuretics to 62% and digitalis to 43% (Table 3). ACE inhibitors and ARBs were more prescribed to Hospital-HF than GP-HF patients (Table 3). Beta-blockers were prescribed to approximately 38% of Hospital-HF patients whereas they were prescribed to only 18% of GP-HF patients. Prescription rates of diuretics and digitalis were also higher in Hospital-HF patients. In contrast, calcium antagonists were prescribed more often to GP-HF patients.

Mortality and HF-Related Admission

Among 2,685 patients, 57 patients were lost during the follow up (2.1%). The mean follow-up periods for patients with HP-HF and GP-HF were 431±93 and 424±91 days, respectively, which were not significantly different.

During the follow-up, 165 patients (6.3%) died; 59 (36%) from cardiac causes, 53 (32%) from non-cardiac causes and 53 (32%) from unknown causes. The rates of all-cause death as well as cardiac death tended to be greater in Hospital-HF

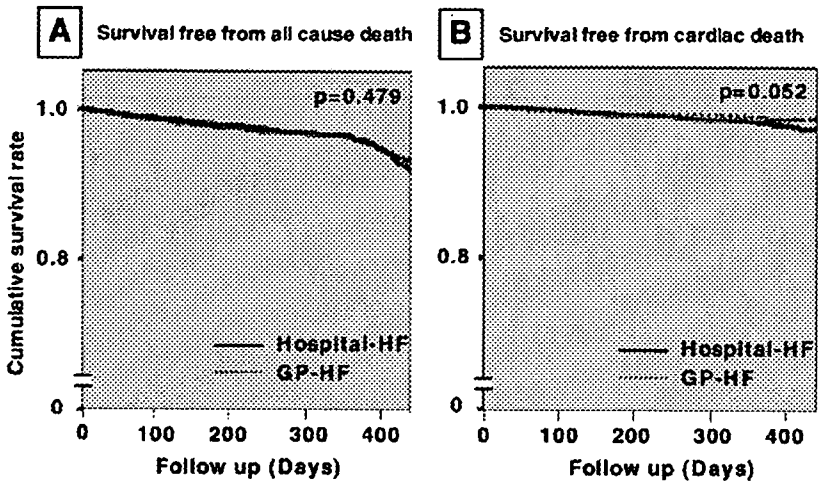

Fig 2. Cumulative survival rates. Survival estimates free from all-cause death (A) and cardiac death (B) during the follow up were derived from the Kaplan and Meier methods. HF, heart failure; GP, general practice.

Table 5 Adjusted Relative Risk for Outcomes by Hospital-HF and GP-HF

	Relative risk (95%CI)	*p value*
All cause death		
Hospital-HF	*1*	
GP-HF	*0.83 (0.59–1.18)*	*0.30*
Cardiac death		
Hospital-HF	*1*	
GP-HF	*0.69 (0.39–1.22)*	*0.20*
HF-related admission		
Hospital-HF	*1*	
GP-HF	*0.62 (0.47–0.82)*	*<0.01*

Adjusted for age, sex, etiology of HF, atrial fibrillation, and prior history of HF.
Abbreviations see in Tables 1,2,4.

patients than GP-HF (Table 4, Fig 2). For the age and sex categories studied, these rates were higher in Hospital-HF patients than in GP-HF, except for all-cause death in female patients (Table 4). However, after adjusting for age or variables including age, sex, causes of HF, atrial fibrillation and prior history of HF, the rates of all-cause death and cardiac death did not differ between Hospital-HF and GP-HF patients (Tables 4, 5).

During the same study period, 235 patients (9%) had a hospital admission due to an exacerbation of HF. The HF-related hospital admission rate was significantly higher in Hospital-HF than in GP-HF patients ($p<0.01$; Table 4), which did not alter even after adjustment (Table 5).

Discussion

The characteristics and outcomes of outpatients with HF in general practice have been poorly described, despite the importance of this disease to public health. The JCARE-GENERAL is the first diverse, large-scale, prospective multicenter database of this population in Japan. An important finding is that HF outpatients in the general practice were more likely to be elderly and women with hypertension as a predominant cause of HF. Evidence-based medications for HF, including ACE inhibitors, ARBs and β-blockers, were less prescribed to GP-HF patients compared to Hospital-HF patients. In contrast, calcium antagonists were prescribed more often to GP-HF patients. At the follow-up of 1.2 years after adjustment, the mortality was comparable between Hospital-HF and GP-HF patients, whereas HF-related admission was higher in Hospital-HF than in GP-HF patients, which might be caused by them having more definite and severe HF.

We have previously reported the characteristics and outcomes of patients hospitalized to the cardiology departments in Fukuoka, Japan[9–11] These studies highlighted several important features of "real world" patients with HF, which were not found in large-scale clinical trials. One key feature was the old age of HF patients. The mean age of the patients was 69 years; 70% were ≥65 years of age. Women especially were mostly over 70 years of age. This is consistent with previous community-based studies![3,14] Another important feature was a relatively good survival prognosis; the 1-year mortality rate being 8.3%. A prognosis of patients with decreased ejection fraction (<40%) was still good; the 1-year mortality rate being 9.1%. At the first glance, this finding appears to be contradicted by the generally held notion that advanced age and more comorbidity may be related to poor survival. In contrast to the relatively low mortality, rates of readmission due to worsening HF were as high as 40% within 1 year after discharge. This value was comparable to those in prior studies (a 3- to 6-month readmission rate 30 to 50%)![5,16] The most commonly identified precipitating cause for hospital readmission was lack of compliance with medical and dietary treatment (48%)![10]

Even though our previous studies have provided a valuable insight into the clinical characteristics, outcomes and the potential effective treatment strategies for HF patients, the generality of these results is questioned because our previous studies were conducted in hospitalized patients with HF[9–11] Outpatients with HF are managed mostly in the community by primary care physicians. Nevertheless, few studies provide objective information about these patients. Therefore, it is of critical importance to analyze the realistic data for HF outpatients in general practice, and to form a database on a national basis for future investigations. For this purpose, JCARE-GENERAL was designed to focus on the demographic and clinical characteristics, treatment strategies and outcomes in "real-world" outpatients managed by primary care physicians in general practice.

The present study demonstrated that, compared to Hospital-HF patients, GP-HF patients were more often elderly and female, and had a higher prevalence of hypertensive heart disease as a cause of HF. In concordance with the

present study, previous studies have shown that the majority of HF patients are elderly and women in the community[17–20] In contrast, more severe cases of HF are referred to hospital cardiologists, and these patients are most comparable to the HF patients included in the randomized clinical trials with respect to a high proportion of younger and male patients. This might explain, at least in part, our findings that Hospital-HF patients had higher rates of mortality and HF-related hospital admission than GP-HF patients.

Another important feature of the present study is the description of the contemporary pharmacological management of HF in general practice in Japan. Even though previous randomized controlled trials have shown that drugs such as ACE inhibitors can improve the survival of HF patients, GP-HF patients were significantly less likely to be prescribed the evidenced-based medications[21,22] However, these medications are indicated when LV systolic function is reduced and not when it is preserved. GP-HF patients are elderly and more likely to be female and hypertensive, which is more often associated with preserved LV systolic function and may explain, at least in part, the difference in the medication use between Hospital-HF and GP-HF patients[11]

Limitations

Several crucial limitations inherent in the present study should be considered when these data are interpreted. First, although the present study intended to determine the differences between HF patients in general practice and those treated by the hospital cardiologists, the selection or referral bias might be a potential limitation of the present study. This form of bias occurs when younger patients, particularly those at lower risk, are treated by the hospital cardiologists. Elderly patients are then disproportionately represented in general practice. Therefore, the present study compared the outcomes after adjustment for the differences between patients in hospital and general practice. However, more importantly, it is not known whether HF patients treated by general practices have a different outcome from those managed in hospitals. Second, the JCARE-GENERAL data are based on the decisions made by the participating primary care physicians and hospital cardiologists according to the Framingham diagnostic criteria, which may be incomplete or imprecise. The lack of a precise, universal definition of HF makes this type of registry difficult and open to many criticisms. However, it is not the objective of this survey to restrict enrollment to the narrowly defined population of HF usually included in clinical trials but rather to include a broad range of patients reflecting the current reality of clinical practice rather than trials. Moreover, the information regarding the study protocol was regularly provided at national as well as local meetings in each area. Third, even though data validation included manual verification and correction of all numeric fields in the present study, the validation of the registered data regarding the diagnosis by comparison with the source data were not performed. Further, even though the participating physicians were encouraged to register all patients meeting entry criteria as consecutively as possible, it was not verified whether all patients were indeed registered. Fourth, the present study did not determine the prevalence of patients who met 2 major Framingham criteria for HF or 1 major and at least 2 minor criteria. Fifth, the information on cardiac structure and function especially by using echocardiography were not available in the present study, which might make it difficult to diagnose structural heart disease as a cause of HF and its disease severity, and further differentiate between patients with reduced and preserved systolic function. Nevertheless, the main focus of the present study as well as most other epidemiological studies is to obtain information on the realistic picture of HF based on the symptoms, rather than LV systolic dysfunction. Sixth, the majority of HF patients in the present study had prior history of HF although it was more prevalent in Hospital-HF than in GP-HF patients (Table 2). The data regarding the length between the initial diagnosis of HF and the enrollment to this registry were not available in the study patients and might differ between Hospital-HF and GP-HF patients, which could be a potential variable affecting their outcomes. Seventh, the present study defined cardiac death as death due to cardiac events including sudden cardiac death, fatal myocardial infarction and HF death. The cause of death was diagnosed in each patient by the participating physician based on the clinical information and not verified by the death certificate.

Conclusions

The JCARE-GENERAL has provided the first, valuable information on the characteristics, management and outcomes in a broad sample of "real world" outpatients with HF in general practice in Japan. They were different from those managed by cardiologists in hospital. The mortality was comparable between Hospital-HF and GP-HF patients, whereas HF-related admission was higher in Hospital-HF patients. By helping to characterize this disease state better, it will ultimately have a significant impact on public health at the national level in Japan.

Acknowledgments

The JCARE- GENERAL is supported by the Japanese Society of Heart Failure. It is supported by grants from the Health Sciences Research Grants from the Japanese Ministry of Health, Labour and Welfare, the Japan Heart Foundation, and Japan Arteriosclerosis Prevention Fund.

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