Determining the Optimum Dose for the Intravenous Administration of Nicardipine in the Treatment of Acute Heart Failure

— A Multicenter Study —

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Nicardipine is a potent arteriolar vasodilator with a negligible negative inotropic effect. Although intravenous administration of this drug has been reported to be effective in the treatment of heart failure, the optimal dose by this route is not clear. This study was designed to determine the optimum dose for the intravenous infusion of nicardipine in the treatment of heart failure. In Trial 1, nicardipine was administered intravenously at a dose of 0.5 $\mu\text{g/kg}$ per min to 14 patients with acute heart failure. The dose was increased to 1.0 $\mu\text{g/kg}$ per min in 13 cases with marked improvement at 2 h. In Trial 2, nicardipine was administered in a double-blind manner to 53 patients at 3 different rates of infusion for 2 h: 1.0 (Group 1, $n=19$), 2.0 (Group 2, $n=15$), and 3.0 (Group 3, $n=19$) $\mu\text{g/kg}$ per min. Neither heart rate nor mean right atrial pressure changed in any of the 3 groups. Favorable hemodynamic effects were evident in all groups beginning 30 min after the start of infusion, with an increase in cardiac index (control vs 2 h after infusion, L/min per m^2) (Group 1: 2.2 ± 0.4 vs 3.1 ± 0.8 , Group 2: 2.2 ± 0.4 vs 2.9 ± 0.5 , Group 3: 2.3 ± 0.3 vs 3.1 ± 0.7 , all $p < 0.01$ compared to the control) and a decrease in diastolic pulmonary artery pressure (Group 1: 26 ± 10 vs 19 ± 7 , Group 2: 27 ± 10 vs 20 ± 8 , Group 3: 26 ± 7 vs 18 ± 5 mmHg, all $p < 0.01$). The decrease in systolic pressure was greatest in Group 3 (Group 1: 141 ± 31 vs 119 ± 18 , Group 2: 149 ± 25 vs 118 ± 17 , Group 3: 147 ± 27 vs 107 ± 14 mmHg, all $p < 0.01$ compared to control, and $p < 0.05$ between Groups 1 and 3). The intravenous drip infusion of nicardipine is effective in the treatment of heart failure by inducing an increase in cardiac output and a decrease in pulmonary artery wedge pressure. The optimal dose in this study was 1.0 $\mu\text{g/kg}$ per min.

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Key Words: Heart failure; Vasodilator therapy; Calcium channel blockade; Intravenous nicardipine

Treatment of acute heart failure is a potentially life-saving procedure the aim of which is to reduce pulmonary congestion to restore normal breathing and to maintain adequate cardiac output to ensure appropriate perfusion of the vital organs. Various intravenous agents have been used, including catecholamines to increase cardiac output via an increase in

the inotropic state^{1,2} phosphodiesterase inhibitors to reduce afterload as well as to increase the inotropic state^{3–5} loop diuretics to decrease pulmonary congestion via rapid diuresis^{6,7} and various nitrate compounds to decrease pulmonary congestion via vasodilatation of capacitance vessels^{8–10}

Nicardipine, a dihydropyridine derivative calcium

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Table 1 Exclusion Criteria

<i>Patients with the following diseases or conditions were excluded:</i>	
1. within 1 week after the onset of acute myocardial infarction	
2. obstructive diseases of the ventricle	
3. predominantly right heart failure	
4. infective endocarditis	
5. hypotension and cardiogenic shock	
6. cerebrovascular accidents with active bleeding or increased intracranial pressure	
7. thyroid dysfunction	
8. malignant arrhythmias	
9. severe liver or kidney dysfunction	
10. severe infection elsewhere in the body	
12. known to be allergic to nicardipine	
13. pregnant or possibility of being pregnant	

Table 2 Study Population in Trial 1

Gender (Male/Female)	11/3
Age (years)	68.2 ± 10.4
Underlying Heart Disease	
ischemic heart disease	6
valvular heart disease	4
dilated cardiomyopathy	3
hypertensive heart disease	1
NYHA Functional Class (III/IV)	4/10

channel blocker, is widely used for the treatment of hypertension. This agent is a potent arteriolar vasodilator with a negligible negative inotropic effect.¹¹ Although nicardipine has been used intravenously for the treatment of heart failure,¹²⁻¹⁴ the results to date have not been impressive. In contrast to these previous studies, however, recent preliminary data in a small study population suggested a marked improvement of symptoms and hemodynamic parameters by the administration of minimal doses of this drug.¹⁵ Therefore, we postulated that the reason for the poor results obtained with this agent to date might be related to an excessive decrease in afterload, and that favorable results might be obtained with doses smaller than those usually employed.

This multicenter study was designed to 1) investigate the efficacy of the intravenous infusion of nicardipine in the treatment of heart failure, and 2) establish the most effective dose for such treatment.

Methods

Study Populations

Patients who had been admitted to the hospital with the a diagnosis of acute heart failure and who were under hemodynamic monitoring with a Swan-Ganz catheter in the pulmonary artery were eligible for

enrollment. Patients were observed for at least 30 min. Treatment with nicardipine was started when stability was obtained in 2 consecutive hemodynamic measurements 15 min apart. Entry criteria were as follows: 1. cardiac index less than 2.5 L/min per m²; 2. pulmonary diastolic or wedge pressure greater than 15 mmHg; 3. age greater than 20 and younger than 80; and 4. systolic blood pressure higher than 100 mmHg. Patients with the underlying diseases or conditions listed in Table 1 were excluded. The investigations were started at least 6 h after the oral administration of inotropic agents, nitrates, α or β blockers, angiotensin-converting enzyme inhibitors, calcium antagonists, or diuretics. Oxygen inhalation was continued without changing the dose in patients who required it.

Trials 1 and 2 were both approved by the ethics committees of the participating hospitals. Written informed consent was obtained from each patient or his/her family before starting the study.

Study Protocols

Trial 1

Patient backgrounds are shown in Table 2. A 10-ml ampule containing 10 mg of nicardipine HCl was dissolved in 40 ml of normal saline, and intravenous infusion was started at a rate of 0.5 μ g/kg per min. Hemodynamic measurements were repeated every 30 min. The infusion rate was increased to 1.0 μ g/kg per min when the clinical or hemodynamic response was judged to be inadequate by the investigator. The total observation period with adequate dosing was limited to 2 h.

Trial 2

Patient backgrounds are shown in Table 3. Each infusion set consisted of 3 ampules which contained either 10 mg of nicardipine HCl or an indistinguishable placebo and an ampule of dissolving solution for the

Table 3 Study Population in Trial 2

Group infusion speed	1 1.0 $\mu\text{g/kg per min}$	2 2.0 $\mu\text{g/kg per min}$	3 3.0 $\mu\text{g/kg per min}$
No. (Male/Female)	20 (17/3)	16 (8/8)	21 (14/7)
Age (years)	62.0 $\pm$ 14.9	64.5 $\pm$ 9.4	64.0 $\pm$ 11.9
Underlying Heart Disease			
ischemic heart disease	7	8	11
valvular heart disease	3	3	4
dilated cardiomyopathy	7	3	3
hypertensive heart disease	3	2	3

Table 4 Hemodynamic Changes in Trial 1

	Before infusion	At the end of 0.5 $\mu\text{g/kg per min}$	At the end of 1.0 $\mu\text{g/kg per min}$
HR (beats/min)	89 $\pm$ 12	87 $\pm$ 12	86 $\pm$ 12
BP (S/D, mmHg)	153 $\pm$ 29/85 $\pm$ 15	146 $\pm$ 34/77 $\pm$ 13	129 $\pm$ 20/69 $\pm$ 13
DP	13692 $\pm$ 3406	12675 $\pm$ 3310	11024 $\pm$ 2028
PAP (S/D, mmHg)	58 $\pm$ 21/25 $\pm$ 8	52 $\pm$ 21/22 $\pm$ 9	46 $\pm$ 17/18 $\pm$ 6
RAP (mmHg)	8 $\pm$ 7	6 $\pm$ 5	5 $\pm$ 4
CI (l/min per m ²)	2.2 $\pm$ 0.5	2.6 $\pm$ 0.7	2.9 $\pm$ 0.6
SWI (g·m/beat per m ²)	28 $\pm$ 7	32 $\pm$ 10	34 $\pm$ 12
SVR (dyne·sec·cm ⁻⁵) (n=11)	2509 $\pm$ 813	2053 $\pm$ 734	1559 $\pm$ 357
PAR (dyne·sec·cm ⁻⁵) (n=11)	255 $\pm$ 151	213 $\pm$ 144	162 $\pm$ 78

n=13

Mean $\pm$ SD. Abbreviations: HR, heart rate; BP, blood pressure; S/D, systolic/diastolic; DP, double product; PAP, pulmonary artery pressure; RAP, right atrial pressure; CI, cardiac index; SWI, stroke work index; SVR, systemic vascular resistance; PAR, pulmonary arteriolar resistance.

infusion of 1.0, 2.0 or 3.0 $\mu\text{g/kg per min}$ per patient. Subjects were randomly assigned to the groups by the controllers (RH and KO), and 6 infusion sets were distributed to each participating institution. Each patient received either 1.0 (Group 1), 2.0 (Group 2) or 3.0 (Group 3) $\mu\text{g/kg per min}$ of nicardipine by intravenous infusion for 2 h. The case cards were reviewed by the primary investigators; patients who did not satisfy the inclusion criteria were eliminated from the analysis before the keys were opened.

Measurements

Hemodynamic variables were measured in triplicate every 30 min. Arterial and pulmonary arterial blood samples for gas analysis were obtained before, at 30 min after the start of dosing, and at the end of the observation. Venous blood was examined at baseline and at 24 h after infusion for determination of complete blood counts and blood chemistry.

Using the pressures and cardiac output (CO), left ventricular (LV) stroke work index (SWI), systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) were obtained as follows: SWI (g·m/beat per m²) = SVI $\times$ (MAP - RAP) $\times$ 0.0136,

SVR (dyne·sec·cm⁻⁵) = 79.92 $\times$ (MAP - RAP)/CO and PAR (dyne·sec·cm⁻⁵) = 79.92 $\times$ (MPAP - DPAP)/CO, where MAP is mean arterial pressure, RAP is right atrial pressure, DPAP is diastolic pulmonary artery pressure and MPAP is mean pulmonary artery pressure. Although these parameters are ideally calculated using pulmonary wedge pressure, pulmonary diastolic pressure was used here since most of the patients had cardiac dilatation, which made it difficult to measure a constant wedge pressure.

Oxygen delivery (O₂D), and oxygen consumption ($\dot{V}\text{O}_2$) were calculated from arterial and pulmonary arterial gas: O₂D (ml/min per m²) = CI $\times$ (1.34 $\times$ Hb $\times$ AO₂sat + 0.031 $\times$ PaO₂), and $\dot{V}\text{O}_2$ (ml/min per m²) = CI $\times$ 1.34 $\times$ Hb (AO₂sat - mvO₂sat), where CI is cardiac index, Hb is the blood hemoglobin concentration, AO₂sat is arterial oxygen saturation, PaO₂ is arterial partial oxygen pressure and mvO₂sat is mixed venous oxygen saturation.

Statistical Analysis

The data are expressed as the mean $\pm$ SD. Since a cumulative dose effect at 0.5 $\mu\text{g/kg per min}$ could not be avoided, it was impossible to compare the effects of

Fig 1. Changes in the cardiac index and diastolic pulmonary artery pressure with infusion of nicardipine.

Infusion of nicardipine induced an increase in cardiac index (CI) and a decrease in diastolic pulmonary artery pressure (DPAP). These beneficial effects were greater with the infusion at 1.0 µg/kg per min, and all 7 patients in Forrester's Subset IV moved to better classifications.

Table 5 Undesirable Effects Observed in Trial 2

Group 1:	Case 1 sinus tachycardia
	Case 2 hypoxemia
Group 2:	Case 1 hypotension
	Case 2 hypotension and hypoxemia
	Case 3 hypoxemia
	Case 4 nausea, back pain and dyspnea
Group 3:	Case 1 chill, cyanosis and hypotension
	Case 2 hypoxemia
	Case 3 hypotension and ventricular tachycardia
	Case 4 nausea
	Case 5 hypotension
	Case 6 ventricular premature beats

doses of 0.5 and 1.0 µg/kg per min, and a statistical analysis was not performed in Trial 1. In Trial 2, the paired Student's *t* test was used to compare intragroup data before and after treatment. The Kruskal-Wallis method was used to compare the data of the 3 groups; when significant differences were observed, Scheffe's multiple comparison was used to compare data between 2 groups.

Results

Trial 1

Among the 14 patients treated with intravenous nicardipine, an adequate response was obtained with a dose of 0.5 µg/kg per min in only 1: pulmonary arterial diastolic and right atrial pressures fell from 29 and 10 to 18 and 5 mmHg, respectively, and the cardiac index increased from 2.36 to 2.95 L/min per m².

Therefore, the dose was increased to 1.0 µg/kg per

min in the remaining 13 patients; at 30 min after the start of infusion in 11 and at 1 h in 2. Hemodynamic changes in these 13 patients are summarized in Table 4. The decrease in systemic vascular resistance, and hence in systemic pressure, induced by the drug was associated with a decrease in pulmonary artery diastolic pressure and an increase in cardiac output (Fig 1). At this dose, all 7 patients classified as Forrester's subset IV¹⁶ improved to a better classification (to subset III in 1 patient, II in 2 and I in 4).

The partial pressure of arterial oxygen (before infusion: 102±33 mmHg; after infusion: 74±19 mmHg) and oxygen saturation (97±2% to 94%±3%) decreased without any change in the partial pressure of arterial carbon dioxide (34±8 mmHg to 35±8 mmHg). However, oxygen delivery increased (387±102 to 483±125 ml/min per m²) and oxygen consumption decreased (169±27 to 151±27 ml/min per m²). No serious adverse effects were seen during infusion.

Trial 2

A total of 68 patients were enrolled in this double-blind study. However, 11 patients were excluded from the analysis before the keys were opened; some did not satisfy the inclusion criteria while others had an underlying heart disease as listed in the exclusion criteria (Table 1). Among the remaining 57 cases, treatment was terminated prematurely because of an inadequate response or adverse effects in 4 cases. All of the adverse effects that occurred among the 68 patients during the investigation are listed in Table 5.

Hemodynamic data were analyzed in the 19 patients in Group 1, 15 in Group 2 and 19 in Group 3 who completed 2 h of infusion (Table 6). Beneficial effects

Table 6 Hemodynamic Changes in Trial 2

	Group	No.	Before	30 min	60 min	120 min
HR (beat/min)	1	19	95±19	97±20	96±20	95±19
	2	15	93±17	91±13	90±13	88±11
	3	19	91±20	90±20	88±20	88±21
differences			ns	ns	ns	ns
SBP (mmHg)	1	19	141±31	127±25**	120±17**	119±18**
	2	15	149±25	128±29*	121±20**	118±17**
	3	19	147±27	118±14**	109±14**	107±14**
differences			ns	1 vs 3*	1 vs 3*	1 vs 3*
DBP (mmHg)	1	19	79±24	68±16**	66±15**	65±15**
	2	15	87±17	72±18*	67±15**	66±15**
	3	19	83±15	65±11**	59±10**	58±13**
differences			ns	ns	ns	ns
DP	1	19	13478±4312	12313±3355	11383±2592**	11326±2775*
	2	15	13725±2950	11724±3612	10937±2701*	10437±2230**
	3	19	13415±3732	10537±2496**	9616±2668**	9436±2718**
differences			ns	ns	ns	ns
SPAP (mmHg)	1	19	54±17	47±15**	44±13**	43±13**
	2	15	57±13	49±12*	45±13**	46±12**
	3	19	52±14	45±9*	43±9**	41±10**
differences			ns	ns	ns	ns
DPAP (mmHg)	1	19	26±10	21±8**	19±7**	19±7**
	2	15	27±10	23±10**	20±8**	20±8**
	3	19	26±7	20±6**	18±6**	18±5**
differences			ns	ns	ns	ns
RAP (mmHg)	1	19	10±6	9±6	9±6	8±6
	2	14	12±6	11±5	10±5	10±6
	3	19	11±4	10±4*	9±5*	9±4
differences			ns	ns	ns	ns
CI (l/min per m ²)	1	19	2.2±0.4	3.1±0.9**	3.0±0.8**	3.1±0.8**
	2	15	2.2±0.4	2.7±0.6**	3.0±0.6**	2.9±0.5**
	3	19	2.3±0.3	3.2±0.8**	3.1±0.8**	3.1±0.7**
differences			ns	ns	ns	ns
SWI (g·m/beat per m ²)	1	19	24±11	30±16*	30±15	31±14
	2	14	28±14	28±12	30±11	29±9
	3	19	28±9	32±9	29±7	29±8
differences			ns	ns	ns	ns
SVR (dyne·sec·cm ⁻⁵)	1	19	2043±589	1311±349**	1275±345**	1221±316**
	2	14	2204±501	1553±576**	1319±456**	1297±381**
	3	19	2138±654	1224±462**	1138±402**	1110±382**
differences			ns	ns	ns	ns
PAR (dyne·sec·cm ⁻⁵)	1	17	172±129	122±92	132±88	144±70
	2	13	207±126	140±65	128±65*	144±60
	3	12	126±109	104±38	103±26	96±64
differences			ns	ns	ns	ns

Mean±SD, *: $p<0.05$, **: $p<0.01$ compared to control values. Differences indicate statistical significance among 3 groups. See Table 4 for other abbreviations.

on congestive heart failure, as evidenced by a decrease in LV filling pressure with an increase in cardiac output, were seen in all 3 groups beginning at 30 min

of infusion. Cardiac work (stroke work index) did not decrease with the a decrease in filling pressure. Heart rate did not increase in any of the 3 groups, while

Table 7 Blood Gas Changes in Trial 2

	Group	No.	Before	30 min	120 min
<i>PaO₂</i> (mmHg)	1	16	86.7±20.4	67.2±18.7**	73.6±17.9**
	2	14	88.1±39.8	72.3±31.3**	66.2±20.2**
	3	16	85.9±27.3	73.4±21.6*	72.8±22.7*
differences			ns	ns	ns
<i>aO₂sat</i> (%)	1	16	96.5±1.9	92.2±5.9*	94.4±3.2*
	2	12	95.6±3.0	92.6±3.7**	92.2±3.8**
	3	14	95.2±3.1	93.5±3.1**	93.7±3.6
differences			ns	ns	ns
<i>O₂ delivery</i> (ml/min per m ²)	1	15	364.5±87.3	471.3±144.2**	504.4±162.5**
	2	12	347.9±87.3	441.0±130.9**	482.0±137.5**
	3	13	365.6±78.8	509.0±143.4**	485.3±121.3**
differences			ns	ns	ns
<i>PaCO₂</i> (mmHg)	1	16	33.0±5.4	34.2±6.7	33.0±6.1
	2	14	33.2±6.5	34.3±5.2	34.8±5.9
	3	16	35.5±5.3	35.9±4.6	35.2±5.0
differences			ns	ns	ns
<i>mvO₂sat</i> (%)	1	8	61.2±8.7	68.5±11.3*	70.5±7.8**
	2	7	59.5±11.6	62.6±13.8	63.2±11.7
	3	6	63.7±11.3	69.9±8.2	70.5±9.9*
differences			ns	ns	ns
<i>VO₂</i> (ml/min per m ²)	1	7	136.0±37.4	143.6±78.4	138.8±65.6
	2	6	123.6±9.6	126.9±37.5	132.9±35.1
	3	5	106.9±30.7	113.6±33.9	108.9±36.0
differences			ns	ns	ns

Mean ± SD, *: $p < 0.05$, **: $p < 0.01$ compared to control values. Differences indicate statistical significance among 3 groups. *PaO₂*, partial arterial oxygen pressure; *aO₂sat*, arterial oxygen saturation rate; *O₂ delivery*, blood oxygen delivery; *PaCO₂*, partial arterial carbon dioxide pressure; *mvO₂sat*, mixed venous oxygen saturation; *VO₂*, oxygen consumption

myocardial oxygen consumption decreased significantly as evidenced by a decrease in the double product. Systemic vascular resistance and systolic pressure decreased significantly, but no change was seen in pulmonary arteriolar resistance or right atrial pressure. The decrease in systolic pressure was greater in Group 3 than in Group 1; however, no other differences were seen among these 3 doses.

Partial arterial oxygen pressure and arterial oxygen saturation decreased to the same extent with the 3 doses. Although oxygen delivery increased significantly with infusion, oxygen consumption did not change (Table 7).

Discussion

Nicardipine, a dihydropyridine derivative, has a potent arteriolar vasodilatory effect and negligible negative inotropic and veno-dilating effects.¹¹ This drug has been administered intravenously in patients with acute myocardial infarction and heart failure.

Silke and his coworkers¹² showed that nicardipine induces a dose-dependent decrease in systemic vascular resistance and arterial pressure, and an increase in heart rate and cardiac output without any significant change in LV filling pressure. Furthermore, Greenbaum et al¹³ and Burlew et al¹⁴ reported that nicardipine induces a significant decrease in filling pressure. The doses used in these previous investigations ranged from 1.25 to 10 mg injected over 5 to 20 min. Since nicardipine induces a marked decrease in systemic pressure, a nonsignificant decrease in LV filling pressure, and tachycardia, this agent is not well-regarded for the treatment of heart failure.^{17,18} In a preliminary study, we evaluated the dose response to nicardipine at 10, 20 and 40 µg/kg given over 5 min in patients with heart failure; except for a greater decrease in systemic vascular resistance and systolic blood pressure at the higher doses, the response was almost identical among these 3 doses.¹⁵ Therefore, the present investigation was performed on the assumption that the optimal dose of this agent for the treatment of heart failure

might be much smaller than has been used to date.

In Trial 1, a 0.5 $\mu\text{g/kg}$ per min infusion of nicardipine produced an approximately 18% decrease in systemic vascular resistance associated with an 18% increase in cardiac output and a 13% decrease in LV filling pressure. These respective changes each improved to 30% when the dose was increased to 1.0 $\mu\text{g/kg}$ per min, and dyspnea improved. The increases in cardiac output and decreases in LV filling pressure obtained at 1.0, 2.0 and 3.0 $\mu\text{g/kg}$ per min in Trial 2 were similar to each other and also similar to the changes at 1.0 $\mu\text{g/kg}$ per min in Trial 1. The only difference among these 3 doses was the greater decrease in systolic blood pressure with 3.0 $\mu\text{g/kg}$ per min.

The main goals of treatment in acute heart failure are to reduce LV filling pressure to relieve dyspnea, and to improve the peripheral metabolic state through increased cardiac output. Nicardipine infusion achieved these important goals without increasing myocardial oxygen consumption, as manifested by a significant (15% to 30%) decrease in the double product. Although nicardipine has been reported to cause reflex tachycardia without a significant decrease in filling pressure,¹² these adverse effects in heart failure seem to be dose-dependent. An excessive decrease in systemic vascular resistance might cause reflex tachycardia and augmentation of venous return via an increase in cardiac output, since as nicardipine has essentially no effect on the venous system. Although filling pressure decreased by about 30%, we did not observe tachycardia in this investigation. The difference between our data and those reported previously appears to be related to the dosage used, which indicates that smaller doses are preferable in the treatment of heart failure.

The major adverse effect noted in the present infusion regimen was hypoxemia, which caused the interruption of treatment in some patients (Table 5). Although the cause of hypoxemia with nicardipine infusion is not clear, this phenomenon is not specific to nicardipine and has been seen with other vasodilators used to treat acute heart failure.¹⁹⁻²¹ This phenomenon may be the result of pulmonary vasodilation and poorly ventilated alveoli, which would explain the aggravation of the imbalances in ventilation and perfusion in acute heart failure. A second problem observed with this nicardipine regimen was hypotension. This phenomenon may be more frequent in patients with relatively low systolic pressure, since nicardipine is a potent arteriolar vasodilator and the effect seems to be dose-dependent.

Conclusion

Intravenous nicardipine infusion therapy is effective for the treatment of acute heart failure, especially in patients with elevated LV filling pressure, low cardiac output, and elevated systemic blood pressure. The optimal dosage in the patients studied here was 1.0 $\mu\text{g/kg}$ per min: half of this dose had inadequate effects, while, 2 or 3 times this dose had similar effects.

Appendix

Participating Institutions

Asahikawa City Hospital, Akita University School of Medicine, Iwate Medical University School of Medicine, Yamagata University School of Medicine, Utsunomiya Saiseikai Hospital, Ashikaga Red Cross Hospital, National Defense Medical College, Yokohama City University School of Medicine, Shizuoka General Hospital, Hamamatsu Rosai Hospital, Okazaki Municipal Hospital, Toyota Memorial Hospital, Nagoya University School of Medicine, Nagoya Daini Red Cross Hospital, Nagoya Ekisaikai Hospital, Nagahama Red Cross Hospital, Shiga Medical Center For Adult Disease, Shiga University of Medical Science, Otsu Red Cross Hospital, Faculty of Medicine Kyoto University, Rakuwakai Otowa Hospital, Takeda Hospital, Daini Okamoto Hospital, Nara Medical University, Nara Prefectural Hospital, Osaka Medical College, National Cardiovascular Center, Kitano Hospital, Sakurabashi Watanabe Hospital, Osaka Red Cross Hospital, Kawachi General Hospital, Osaka Police Hospital, Osaka Prefectural Hospital, Kinki University School of Medicine, Wakayama Red Cross Hospital, Hyogo Prefectural Amagasaki Hospital, Hyogo College of Medicine, Kobe University School of Medicine, Kurashiki Central Hospital, Tokuyama Central Hospital, Yamaguchi University School of Medicine, Kokura Memorial Hospital, Nagasaki University School of Medicine

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