Primary Percutaneous Coronary Intervention vs Conservative Treatment for Acute ST Elevation Myocardial Infarction

— Short- and Long-Term Follow-up According to Disease Severity —

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Background Because there is insufficient evidence to support primary percutaneous coronary intervention (PPCI) as the treatment of acute myocardial infarction (AMI), this study elucidated the efficacy of PPCI according to disease severity.

Methods and Results Between January 1999 and June 2001, 3,021 AMI patients were registered at Tokyo Women's Medical University and 17 affiliated institutions. Of these, 1,994 patients with ST-elevation AMI were admitted within 12 h of onset. PPCI was performed in 1,143 and 294 were treated conservatively. The 1,437 patients were grouped according to Thrombolysis In Myocardial Infarction-risk score: PPCI was performed in 59.5% of the low-risk group, 61.8% of the moderate-risk group, and 56.2% of the high-risk group. Cardiac death was the primary outcome. In the low-risk group, no significant differences were observed between PPCI and conservative therapy for 30-day and long-term cardiac mortality rates. In the moderate-risk group, the 30-day cardiac mortality rate for PPCI was significantly lower; however, no significant intergroup differences were observed for long-term cardiac mortality. In the high-risk group, 30-day and long-term cardiac mortality for PPCI were significantly more favourable than for conservative therapy ($p<0.001$ and $p=0.0032$, respectively).

Conclusions Although PPCI strongly correlated with low short- and long-term cardiac mortality rates in high-risk AMI patients, no similar correlation was found in low-risk patients. (Circ J 2008; 72: 1391–1396)

Key Words: Acute myocardial infarction; Percutaneous coronary intervention; Prognosis; Reperfusion therapy; TIMI-risk score

In recent years, primary percutaneous coronary intervention (PPCI) has gradually emerged as the preferred treatment strategy for ST-elevation myocardial infarction (STEMI).^{1,2} In particular, the usefulness of PPCI for acute myocardial infarction (AMI) resulting in cardiogenic shock has been recognised.³ In the treatment of STEMI, PPCI is associated with favourable vital prognosis,⁴ and current therapeutic guidelines for STEMI recommend PPCI whenever feasible.^{5,6} Numerous randomized studies and meta-analyses have demonstrated the superiority of PPCI over thrombolytic therapy for AMI. However, in recent randomized trials, investigators have demonstrated a lack of cost-effectiveness for PPCI in some cases, as compared with thrombolytic therapy.^{7,8} To the best of our knowledge, no randomized comparative studies have assessed the use-

fulness of PPCI and conservative therapy in the treatment of AMI. Whether percutaneous coronary intervention (PCI) is essential in all AMI patients thus remains unclear.

To elucidate the characteristics of AMI in the Japanese population, we conducted a prospective cohort study to investigate therapeutic modalities and prognosis of AMI at the Department of Cardiology of Tokyo Women's Medical University (The Heart Institute of Japan, Cardiology) and its 17 affiliated institutions,⁹ and report our findings here.

Methods

The protocol was approved by the Ethics Committee of Tokyo Women's Medical University.

Study Population

The study population was drawn from a registered prospective Japanese multicenter observational cohort, the Heart Institute of Japan Acute Myocardial Infarction (HIJAMI) registry.^{9,10} Briefly, 3,021 consecutive patients with AMI admitted to 17 Japanese hospitals were registered from January 1999 to June 2001. Among these, eligible patients were those over 20 years old with chest pain or ECG changes typical of AMI accompanied by an increase in cardiac enzymes to at least twice the upper limit of the normal

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Fig 1. Flow of patients in the Heart Institute of Japan Acute Myocardial Infarction (HIJAMI) Registry. MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

Table 1 Patient Characteristics in Relation to TIMI-Risk Scores

TIMI-risk score	≤3 (n=455)	4≤ ≤5 (n=517)	6≤ (n=465)
Age (years)	56±9	71±10	75±9
Women (%)	52 (11%)	172 (33%)	196 (42%)
Killip class (%)			
I	451 (99%)	496 (96%)	232 (50%)
II	4 (1%)	13 (3%)	80 (17%)
III	0 (0%)	7 (1%)	48 (10%)
IV	0 (0%)	1 (0%)	105 (23%)
Anterior MI	186 (41%)	222 (43%)	309 (66%)
Q-wave MI	342 (75%)	398 (77%)	364 (78%)
Clinical history			
Prior AP	169 (37%)	194 (38%)	183 (39%)
Hypertension	209 (46%)	273 (53%)	298 (64%)
Hyperlipidemia	213 (47%)	176 (34%)	140 (30%)
Diabetes mellitus	161 (35%)	174 (34%)	175 (38%)
Prior MI	53 (12%)	62 (12%)	86 (18%)
Prior PCI	37 (8%)	44 (9%)	35 (8%)
Prior CABG	3 (1%)	6 (1%)	5 (1%)
LVEF (%)	54±11	54±13	50±13
No. of diseased vessels			
≤1	282 (62%)	297 (57%)	215 (46%)
≥2	144 (32%)	144 (28%)	163 (35%)
Peak CK (IU/ml)*	2,681 [1,405–4,853]	2,388 [1,195–4,379]	2,699 [1,258–4,894]
LDL-C (mg/dl)	128±38	118±35	118±37
CRP (mg/dl)*	0.2 [0.1–0.4]	0.3 [0.1–0.6]	0.3 [0.1–1.1]
Medications at discharge**			
ACEI or ARBs	305 (69%)	310 (65%)	253 (67%)
β-blockers	137 (31%)	162 (34%)	121 (32%)
Calcium-channel blockers	116 (26%)	129 (27%)	114 (30%)
Nitrates	239 (54%)	284 (59%)	238 (63%)
Aspirin	406 (92%)	414 (86%)	334 (89%)

Data are means±SD. *Values are medians; **among 30 days survivors.

TIMI, Thrombolysis In Myocardial Infarction; MI, myocardial infarction; AP, angina pectoris; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; CK, creatine kinase; LDL-C, low-density lipoprotein-cholesterol; CRP, C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker.

value, and who were admitted within 48 h of onset. For each patient, a medical history was taken. Mean age was 69 years (range, 23–98 years) with a male preponderance (70.7%; 2,211 patients). As the HIJAMI study was meant for observational purposes only, treatment strategies such as pharma-

cotherapy and early reperfusion treatment were determined at the discretion of physicians at each hospital.

We classified all patients registered in the HIJAMI study based on Thrombolysis In Myocardial Infarction (TIMI)-risk scores^{12,13} in order to compare vital prognosis, and we

Table 2 Breakdown by Therapeutic Modality

TIMI-risk score	≤ 3		$4 \leq 5$		$6 \leq$	
	Conservative (n=72)	PPCI (n=383)	Conservative (n=119)	PPCI (n=398)	Conservative (n=103)	PPCI (n=362)
Age (years)	59.7±10.0	56.1±8.5	77.1±9.8	69.6±9.8	78.7±9.4	74.9±8.9
Time of onset to admission (h)*	2.6 [1.7–5.3]	2.0 [1.2–3.5]	2.8 [1.8–4.3]	2.8 [1.6–4.7]	2.6 [1.2–5.4]	3.3 [2.0–5.2]
Killip class (%)						
I	71 (98.6%)	380 (99.2%)	112 (94.1%)	384 (96.5%)	23 (22.3%)	209 (57.7%)
II	1 (1.4%)	3 (0.8%)	4 (3.4%)	9 (2.3%)	20 (19.4%)	60 (16.6%)
III	–	–	2 (1.7%)	5 (1.3%)	27 (26.2%)	21 (5.8%)
IV	–	–	1 (0.8%)	–	33 (32.0%)	72 (19.9%)
Clinical history						
Hypertension	35 (48.6%)	174 (45.4%)	63 (52.9%)	210 (52.8%)	75 (72.8%)	223 (61.6%)
Hyperlipidemia	24 (33.3%)	189 (49.3%)	30 (25.2%)	146 (36.7%)	28 (27.2%)	112 (30.9%)
Diabetes mellitus	18 (25.0%)	143 (37.3%)	42 (35.3%)	132 (33.2%)	45 (43.7%)	130 (35.9%)
Prior MI	9 (12.5%)	44 (11.5%)	20 (16.8%)	42 (10.6%)	32 (31.1%)	54 (14.9%)
No. of diseased vessels						
≤ 1	31 (43.1%)	251 (65.5%)	32 (26.9%)	265 (66.6%)	11 (10.7%)	205 (56.7%)
≥ 2	12 (16.6%)	132 (34.5%)	11 (9.2%)	133 (33.4%)	6 (5.8%)	157 (43.3%)
Unknown	29 (40.3%)	–	76 (63.9%)	–	86 (83.5%)	–
Serum creatinine (mg/dl)	0.9±0.3	0.9±0.5	1.1±1.2	1.0±0.8	1.4±1.2	1.1±1.7
POBA	–	115 (30.0%)	–	129 (32.4%)	–	111 (30.7%)
BMS	–	268 (70.0%)	–	269 (67.6%)	–	251 (69.3%)
Medications at discharge						
ACEI or ARBs	41 (58.6%)	264 (70.8%)	46 (46.0%)	264 (69.5%)	36 (56.3%)	217 (69.3%)
β -blockers	17 (24.3%)	120 (32.2%)	29 (29.0%)	133 (35.0%)	18 (28.1%)	103 (32.9%)
Calcium-channel blockers	33 (47.1%)	83 (22.3%)	38 (38.0%)	91 (23.9%)	35 (54.7%)	79 (25.2%)
Nitrates	50 (71.4%)	189 (50.7%)	81 (81.0%)	203 (53.4%)	57 (89.1%)	181 (57.8%)
Aspirin	50 (71.4%)	356 (95.4%)	64 (64.0%)	350 (92.1%)	49 (76.6%)	285 (91.1%)

PPCI, primary PCI; POBA, primary old balloon angioplasty; BMS, bare metal stent. Other abbreviations see in Table 1.

Table 3 Therapeutic Modality and Disease Severity

TIMI-risk score	PCI alone, n (%)	Lytic alone, n (%)	Both, n (%)	Conservative, n (%)
≤ 3 (n=644)	383 (59.5)	59 (9.2)	130 (20.2)	72 (11.2)
$4 \leq$ TIMI-risk score ≤ 5 (n=643)	398 (61.8)	36 (5.6)	90 (14.0)	119 (18.5)
$6 \leq$ (n=529)	362 (56.2)	12 (1.9)	52 (8.1)	103 (16.0)
Total (n=1,816)	1,143 (62.9)	107 (5.9)	272 (15.0)	294 (16.2)

Abbreviations see in Table 1.

then assessed the usefulness of PCI for AMI. Prognosis was assessed as of November 30, 2004. Mean duration of follow-up observation was 4.2 years, with a follow-up rate of 97%.

Definition of Endpoints

The primary study outcome was cardiac death.

Statistical Analysis

Analyses were performed using SAS ver. 9.1 statistical software (SAS Institute, Cary, NC, USA). Data are presented as medians with interquartile ranges or frequencies. Cumulative probabilities of event-free curves were estimated using the Kaplan-Meier method. Cox proportional hazards models were used to evaluate the effects of primary reperfusion on the prognosis of AMI patients. The proportional hazards assumption was confirmed by the log survival function. The influences of profile, interaction and colinearity in the generalized linear model were examined using regression diagnostic analysis. Two-tailed p-values of less than 0.05 were considered to indicate statistically significant differences.

Results

A total of 3,021 consecutive AMI patients were registered. Of these, 1,994 had ST-elevation myocardial infarction within 12h of onset and of them 178 who underwent coronary artery bypass grafting; the 379 in whom thrombolytic therapy was performed either alone or combined with PCI were excluded. Thus, 1,437 patients served as subjects (Fig 1). Patient baseline characteristics are summarized in Table 1 and the breakdown by therapeutic modality is summarized in Table 2.

The 1,437 patients were divided into 3 groups based on TIMI-risk score: low-risk group (TIMI-risk score ≤ 3), moderate-risk group (TIMI-risk score 4 and 5) and high-risk group (TIMI-risk score ≥ 6) (Table 3). For the entire patient population, 30-day cardiac mortality rates for PPCI and conservative therapy were 5.4% and 17.7%, respectively.

A comparison between PPCI and conservative therapy for each group is presented below. Prognoses of patients treated with PPCI, as compared with conservative therapy, are shown in Table 4.

In the low-risk group, the 30-day cardiac mortality rate was compared between 383 patients who underwent PPCI and 72 patients treated conservatively. When compared with conservative therapy, no significant correlation was

Table 4 The 30-Day and Long-Term Prognosis in Relation to Risk Scores (Cardiac Deaths)

	TIMI-risk score ≤ 3			4 $\leq$ TIMI-risk score ≤ 5			6 $\leq$ TIMI-risk score		
	n	Deaths (%)	HR (95%CI)	p value	n	Deaths (%)	HR (95%CI)	p value	p value
30-day mortality									
Conservative	72	2 (2.8%)	1.00		119	16 (13.4%)	1.00		
PPCI	383	10 (2.6%)	0.93 (0.20–4.23)	0.92	398	13 (3.3%)	0.23 (0.11–0.48)	<0.001	<0.001
Long-term mortality									
Conservative	69	1 (1.4%)	1.00		101	10 (9.9%)	1.00		
PPCI	372	6 (1.6%)	1.23 (0.15–10.2)	0.85	381	20 (5.2%)	0.47 (0.22–1.01)	0.054	0.003

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.
HRs were obtained by Cox non-proportional hazards model with emergency treatment as time-dependent variables.

Table 5 The 30-Day and Long-Term Prognoses According to Risk Scores (All Deaths)

	TIMI-risk score ≤ 3			4 $\leq$ TIMI-risk score ≤ 5			6 $\leq$ TIMI-risk score		
	n	Deaths (%)	HR (95%CI)	p value	n	Deaths (%)	HR (95%CI)	p value	p value
30-day mortality									
Conservative	72	2 (2.8%)	1.00		119	18 (15.1%)	1.00		
PPCI	383	10 (2.6%)	0.93 (0.2–4.23)	0.923	398	17 (4.3%)	0.27 (0.14–0.52)	<0.001	<0.001
Long-term mortality									
Conservative	69	3 (4.3%)	1.00		101	33 (32.7%)	1.00		
PPCI	372	16 (4.3%)	1.04 (0.3–3.58)	0.946	381	52 (13.6%)	0.37 (0.24–0.57)	<0.001	<0.001

Abbreviations see in Tables 1,2,4.
HRs were obtained by Cox non-proportional hazards model with emergency treatment as time-dependent variables.

Fig 2. Kaplan-Meier curves for long-term cardiac mortality in relation to risk scores. Dotted line, conservative therapy; solid line, primary percutaneous coronary intervention.

seen between PPCI and improvement in 30-day cardiac mortality (hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.20–4.23, $p=0.93$). No significant correlation was seen between PPCI and improvement of long-term cardiac mortality (HR 1.23, 95% CI 0.15–10.19, $p=0.85$) (Fig 2).

In the moderate-risk group, 30-day cardiac mortality rate was compared between 398 patients who underwent PPCI and 119 patients who underwent conservative therapy. When compared with conservative therapy, PPCI was significantly correlated with improved 30-day cardiac mortality (HR 0.23, 95% CI 0.11–0.45, $p<0.0001$). However, no significant correlation was seen between PPCI and improvement of long-term cardiac mortality (HR 0.47, 95% CI 0.22–1.01, $p=0.054$) (Fig 2).

In the high-risk group, 30-day cardiac mortality rate was compared between 362 patients who underwent PPCI and 103 patients who underwent conservative therapy. Compared with conservative therapy, significant correlations were seen between PPCI and short-term cardiac mortality rate (HR 0.27, 95% CI 0.18–0.44, $p<0.0001$), and between PPCI and long-term cardiac mortality rate (HR 0.40, 95% CI 0.22–0.73, $p=0.0032$) (Fig 2).

Similarly, no correlation was found between PPCI and total mortality in the low-risk AMI patients, although a significant correlation was found between these 2 factors in the moderate-risk and high-risk AMI patients (Table 5).

Discussion

In the present study, there were no significant differences in vital prognosis between conservative therapy and PPCI for low-risk ST-elevation AMI patients. On the other hand, in the moderate- and high-risk ST-elevation AMI patients, a significant correlation was seen between PPCI and the short-term cardiac mortality rate. Furthermore, in the high-risk ST-elevation AMI patients, a significant correlation was seen between PPCI and the long-term cardiac mortality rate. As previously reported in the DANAMI study, our study subjects were divided according to their TIMI-risk scores in order to determine the types of patients that respond to PCI.

In Western countries, thrombolytic therapy is the main reperfusion modality in the treatment of acute coronary syndrome (ACS). According to a recent report by the National Registry of Myocardial Infarction in the United States,¹⁴ PPCI monotherapy and thrombolytic treatment account for 7.3% and 20.8%, respectively, of overall AMI treatments. In the GRACE registry, PPCI accounted for 52.7% of treatments for ACS.¹⁷ In contrast, in Japan PPCI accounts for approximately 60% of all treatments for AMI.^{9,15,16} The following 2 factors are considered to influence the frequent use of PCI in Japan. First, most Japanese live in urban areas and have good access to medical facilities, which is also why t-PA treatment is not common in Japan (Table 3). Second, Japan has a universal health insurance system with fixed medical costs.

Grines et al compared the efficacy of primary PTCA and thrombolytic therapy in AMI patients and reported that when compared with thrombolytic therapy, primary PTCA significantly improved both short- and 6-month outcomes.¹⁸ Widimsky et al performed PCI alone or thrombolytic therapy with or without PCI in AMI patients, and then assessed ≤ 30 -day mortality, re-infarction and stroke as the primary endpoints; their incidence of the primary endpoint was lowest in the PPCI group.¹⁹ The usefulness of PCI for ST-elevation AMI has thus been established, but there is not a general consensus that PPCI is essential for all AMI patients and no randomized comparative studies have assessed the usefulness of PPCI vs conservative therapy in the treatment of AMI.

In the present study, thrombolytic therapy was performed in a very small number of patients and could not serve as a control for PPCI. In the DANAMI study,⁷ the mortality rate for thrombolytic therapy was 5.6% in the low-risk group and 36.2% in the high-risk group, which is comparable with the conservative therapy group used in the present study (Table 5). We therefore compared PPCI with conservative therapy. To demonstrate the usefulness of PPCI in patients with ST-elevation AMI, Thune et al⁷ compared PPCI with thrombolytic therapy based on disease severity and found no significant differences between the 2 treatments in the long-term mortality rate in low-risk AMI patients. However, in

high-risk AMI patients, PCI significantly improved vital prognosis. The results of that study also support our findings. We thus believe that PPCI does not significantly improve prognosis in all patients with ST-elevated AMI.

Study Limitations

The present prospective cohort study was an observational study, not a randomized controlled trial, that randomly divided subjects into PCI and non-PCI groups. Some intergroup bias may thus have been present.

Conclusions

PPCI was actively performed in AMI patients. In high-risk AMI patients, it was strongly correlated with better outcomes than conservative treatment. Conversely, in low-risk AMI patients, no correlation was identified between PPCI and vital prognosis. Beneficial effects of PPCI on both early and late outcomes were not observed in low-risk AMI patients when compared with conservative treatment. PPCI is thus not beneficial in all patients with STEMI. Aggressive approaches using PPCI should be performed for deteriorating AMI patients to improve their prognosis.

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