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The Impact of Initial Treatment Delay Using Primary Angioplasty on Mortality among Patients with Acute Myocardial Infarction: from the Korea Acute Myocardial Infarction Registry

The impact of treatment delays to reperfusion on patient mortality after primary percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI) is controversial. We analyzed 5,069 patients included in the Korea Acute Myocardial Infarction Registry (KAMIR) between November 2005 and January 2007. We selected 1,416 patients who presented within 12 hr of symptom onset and who were treated with primary PCI. The overall mortality at one month was 4.4%. The medians of door-to-balloon time, symptom onset-to-balloon time, and symptom onset-to-door time were 90 (interquartile range, 65-136), 274 (185-442), and 163 min (90-285), respectively. One-month mortality was not increased significantly with any increasing delay in door-to-balloon time (4.3% for ≤90 min, 4.4% for >90 min; p=0.94), symptom onset-to-balloon time (3.9% for ≤240 min, 4.8% for >240 min; p=0.41), and symptom onset-to-door time (3.3% for ≤120 min, 5.0% for >120 min; p=0.13). These time variables had no impact on one-month mortality in any subgroup. Thus, this first nationwide registry data in Korea showed a good result of primary PCI, and the patient prognosis may not depend on the initial treatment delay using the current protocols.

Key Words : *Myocardial Infarction; Mortality; Angioplasty*

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INTRODUCTION

A shorter time to reperfusion is beneficial in treating patients with fibrinolytic therapy for acute ST-segment elevation myocardial infarction (STEMI) (1-4). In contrast, there is some controversy regarding the relationship between mortality and time to reperfusion with primary percutaneous coronary intervention (PCI), although the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that the door-to-balloon time (or medical contact-to-balloon) for PCI should be kept under 90 min (5). Some studies have shown that delays in symptom onset-to-balloon time (6-9) or door-to-balloon time adversely affects the prognosis in patients with STEMI (10, 11). However, in other studies, there was no significant difference in clinical outcomes according to the time to reperfusion (4, 12). In addition, because the initial treatment delay is an important quality indicator of the treatment for such patients, it is worthwhile to investigate how many cases are performed according to the guidelines. Therefore, the aim of this study was to evaluate the current status of delay in the time to reperfusion during primary PCI and its impact on patient mortality one month later using data from the Korea Acute Myocardial Infarction Registry (KAMIR), the first nationwide multicenter registry of acute MI in Korea. We also tried to define the subgroups that were mostly influenced by treatment delay.

MATERIALS AND METHODS

Study design and subjects

A cohort of patients with STEMI who underwent primary PCI was selected from the KAMIR, which is a nationwide study for acute myocardial infarction in Korea. Between November 2005 and January 2007, 5,069 patients at 41 hospitals were registered.

Patients were eligible for enrollment if they had STEMI, presented within 12 hr after symptom onset, and were treated with primary PCI, and if they had completed a 30-day clinical follow-up at the analysis time point. The following patients were excluded sequentially: patients without ST elevation or left bundle branch block on the first electrocardiogram (n=2,076), those with cardiogenic shock (n=137), those with unknown time of symptom onset or missing data

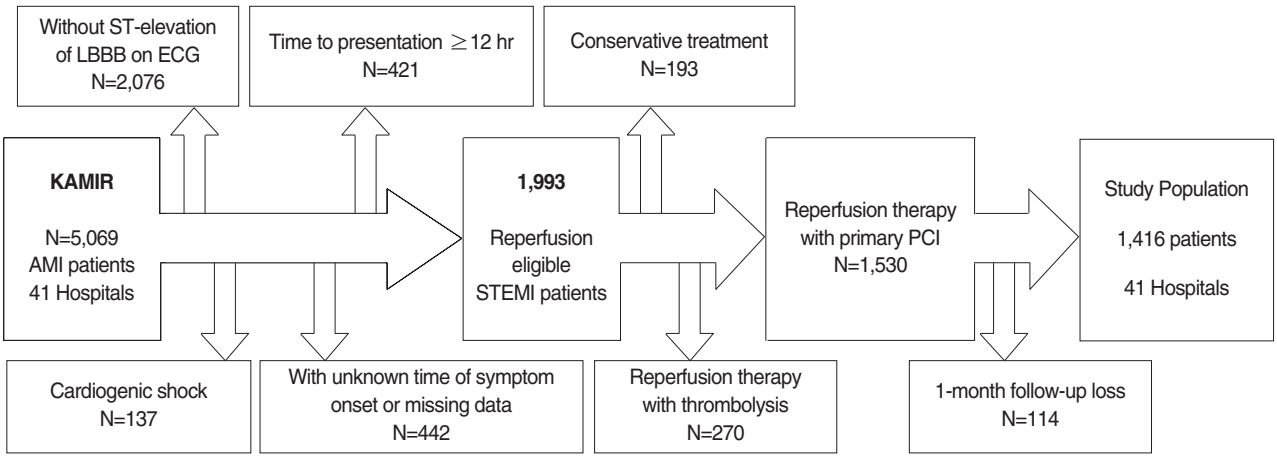

Fig. 1. Selection criteria.

(n=442), and those with symptom onset-to-door time ≥12 hr (n=421). Among the 5,069 patients, 1,993 patients had reperfusion eligible for STEMI and 1,800 (90.3%) received reperfusion therapy. Reperfusion therapy with primary PCI was performed in 1,530 patients (85.0% of 1,800) and with thrombolysis in 270 (15.0% of 1,800). Patients who did not undergo the one-month follow-up were excluded (n=114). We finally included 1,416 patients with STEMI who were treated with primary PCI and who completed the one-month follow-up (Fig. 1).

Demographic and clinical characteristics recorded were gender, age, and medical history. The latter included any history of smoking, dyslipidemia, hypertension, diabetes mellitus, chronic renal insufficiency, stroke, ischemic heart disease, family history of coronary artery disease, previous PCI, previous coronary artery bypass graft surgery, or any past regular medication. The presentation characteristics included symptoms at admission, systolic and diastolic blood pressure, heart rate and rhythm, Killip classification, the results of the diagnostic electrocardiography (ECG), and ischemic location on ECG.

Definitions and outcomes measures

Time variables were defined as follows: door-to-balloon time was the time from arrival in the emergency department until initial balloon inflation; symptom onset-to-balloon time was the time from the onset of symptoms until the first balloon inflation; and symptom onset-to-door time was the time from the onset of symptoms until arrival in the emergency department. Patients were divided into two groups according to door-to-balloon time (≤90 min and >90 min), symptom onset-to-balloon time (≤240 min and >240 min), and symptom onset-to-door time (≤120 min and >120 min), respectively.

The main outcomes were mortality at one month and major cardiovascular adverse events (MACEs). MACEs included death, reinfarction, and target vessel revascularization.

Statistical analysis

SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, U.S.A.) was used for all analyses. Continuous data are expressed as the mean±SD or as the median and interquartile range (25th and 75th percentiles); categorical data were expressed as percentages. Statistical comparisons of baseline, angiographic, and outcome variables were performed for categorical variables using the Chi-squared test or Fisher's exact test (if the expected value of the variable was <5 in at least one group). Student's t test was applied to continuous variables. $p<0.05$ was considered statistically significant. Multiple logistic regression analysis was performed to assess the relation between predictor variables and one-month mortality.

RESULTS

Baseline characteristics

Medians of times to treatment were as follows: door-to-balloon time, 90 min (interquartile range, 65-136 min); symptom onset-to-balloon time, 274 min (185-442); and symptom onset-to-door time, 163 min (90-285). Of all patients, 36% presented to the hospital within 120 min of symptom onset. Door-to-balloon time was 90 min or less in 51% of patients and 42% of patients were reperfused within 240 min of symptom onset. A post-PCI thrombolysis in myocardial infarction (TIMI) grade 3 flow was achieved in 92.8% of the patients.

Demographic, clinical, and angiographic characteristics according to door-to-balloon time, symptom onset-to-balloon time, and symptom onset-to-door time are presented in Table 1. Patients with door-to-balloon times >90 min had hypertension and Killip class ≥3 more frequently than did

Table 1. Baseline patient characteristics by time variables

	Door-to-balloon time			Symptom onset-to-balloon time			Symptom onset-to-door time		
	≤90 (n=715)	>90 (n=701)	*p*	≤240 (n=597)	>240 (n=819)	*p*	≤120 (n=515)	>120 (n=901)	*p*
Clinical variables									
Age (yr)	60.8±12.9	61.8±12.9	0.14	59.0±12.9	62.9±12.8	<0.01	58.2±13.0	63.0±12.6	<0.01
Age >70 yr (%)	29.2	31.7	0.32	23.5	35.5	<0.01	21.2	35.7	<0.01
Women (%)	23.8	26.3	0.28	19.1	29.3	<0.01	18.5	28.7	<0.01
Diabetes mellitus (%)	21.6	25.9	0.06	20.7	25.9	0.03	22.3	24.5	0.34
Hypertension (%)	41.9	49.3	<0.01	40.8	49.0	<0.01	42.7	47.2	0.10
Prior MI (%)	2.4	3.1	0.38	2.5	2.9	0.64	3.7	2.2	0.10
Prior PCI (%)	3.6	3.1	0.61	3.9	3.1	0.41	4.3	2.9	0.17
Anterior infarction (%)	53.7	52.9	0.77	51.7	54.4	0.31	49.7	55.3	0.04
Killip class ≥3 (%)	5.5	11.0	<0.01	6.5	9.5	0.04	8.5	8.1	0.79
Serum Cr ≥1.5 mg/dL (%)	6.0	8.3	0.10	6.1	8.0	0.17	7.3	7.1	0.93
Angiographic/procedural variables									
Pre-PCI TIMI 0-1 flow (%)	73.8	68.8	0.05	72.9	70.2	0.28	72.3	70.8	0.56
Post-PCI TIMI 3 flow (%)	93.3	92.2	0.43	94.0	91.9	0.13	93.5	92.4	0.46
Multivessel diseases (%)	47.3	52.6	0.05	46.3	52.5	0.02	48.6	50.6	0.47
Ejection fraction (%)	51.5±11.6	50.8±11.7	0.26	52.3±11.4	50.3±11.8	<0.01	52.4±11.1	50.4±11.9	<0.01

MI, myocardial infarction; PCI, percutaneous coronary intervention; Cr, creatinine; TIMI, thrombolysis in myocardial infarction.

Table 2. One-month outcomes by time variables

	Door-to-balloon time (min)			Symptom onset-to-balloon time (min)			Symptom onset-to-door time (min)		
	≤90 (n=715)	>90 (n=701)	*p*	≤240 (n=597)	>240 (n=819)	*p*	≤120 (n=515)	>120 (n=901)	*p*
Mortality (%)	4.3	4.4	0.94	3.9	4.8	0.41	3.3	5.0	0.13
MACEs (%)	5.5	5.8	0.75	4.5	6.5	0.12	4.5	6.3	0.15
Follow-up LVEF (%)	54.3±10.9	54.0±11.7	0.80	54.7±10.1	53.6±12.2	0.38	55.4±10.1	53.4±11.8	0.13

MACEs, major adverse cardiovascular events; LVEF, left ventricular ejection fraction.

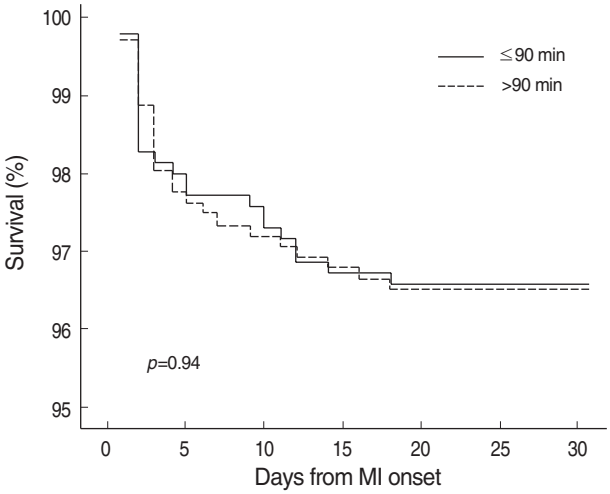

Fig. 2. Kaplan-meier estimates of cumulative survival stratified by door-to-balloon time.

patients with door-to-balloon times ≤90 min. The prevalences of older patients, women, having diabetes mellitus, hypertension, Killip class ≥3, multivessel disease, and lower left ventricular ejection fraction were higher in patients with longer symptom onset-to-balloon times than in those with shorter symptom onset-to-balloon times. Patients with longer symptom onset-to-door times tended to be older, to be women, and to have anterior infarction more frequently and lower left ventricular ejection fraction than did patients with shorter symptom onset-to-door times.

Of the patients enrolled in the study, 262 patients (18.5%) were treated with glycoprotein IIb/IIIa inhibitors. Triple antiplatelet agents with aspirin, clopidogrel, and cilostazol were prescribed in 598 patients (42.1%). One-hundred and twenty-two patients (8.6%) with antiplatelet use before the index MI were not statistically different in mortality (5.7% vs. 4.3%, p=0.44) and MACE (7.4% vs. 5.5%, p=0.39) compared with those without antiplatelet use. Sixty-three patients (4.5%) were treated with statin before the index MI.

Clinical outcomes by time variables

Sixty-two patients (4.4%) had died by one month after the procedure. Table 2 shows the association between treatment delay and clinical outcomes. Mortality at this point did not increase significantly with increasing delay in door-

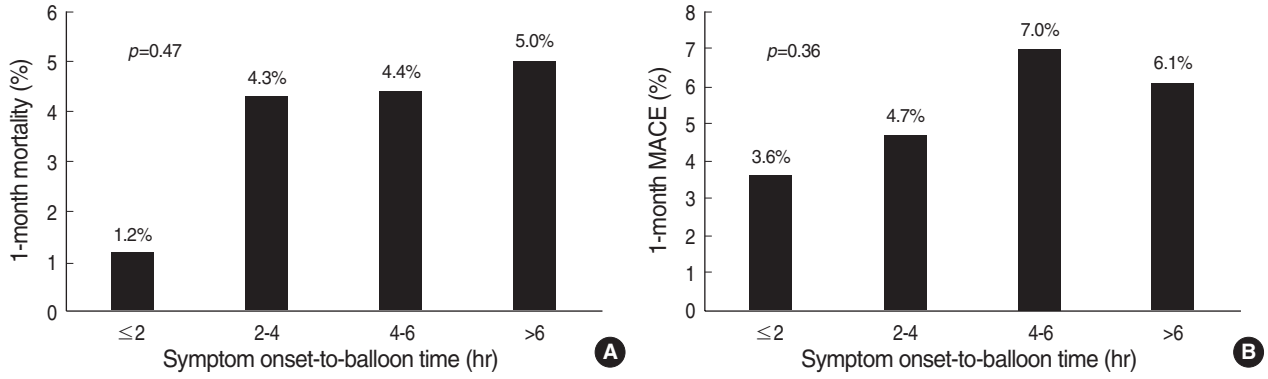

Fig. 3. The one-month mortality (A) and MACEs (B) stratified by door-to-balloon time.

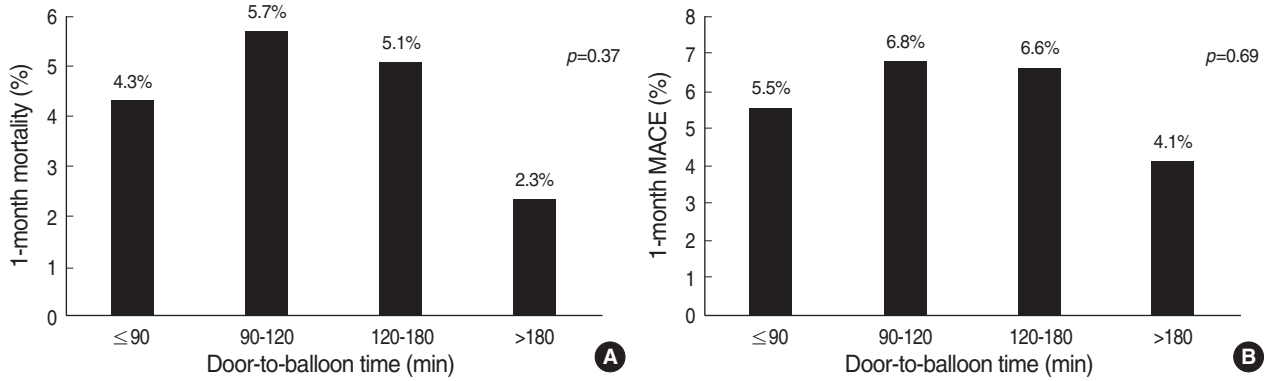

Fig. 4. The one-month mortality (A) and MACEs (B) stratified by symptom onset-to-balloon time.

Table 3. Univariate predictors of one-month mortality and MACEs

	Mortality (n=62)	*p*	MACEs (n=80)	*p*
Clinical variables				
Age >70 yr	37/431 (8.6%)	<0.01	41/431 (9.5%)	<0.01
Women	27/354 (7.6%)	<0.01	28/354 (7.9%)	0.03
Diabetes mellitus	16/331 (4.8%)	0.58	21/331 (6.3%)	0.49
Hypertension	30/637 (4.7%)	0.48	39/637 (6.1%)	0.42
Prior myocardial infarction	3/39 (7.7%)	0.31	6/39 (15.4%)	<0.01
Prior PCI	2/48 (4.2%)	0.94	4/48 (8.3%)	0.41
Anterior infarction	35/750 (4.7%)	0.61	46/750 (6.1%)	0.44
Killip classification ≥3	20/115 (17.4%)	<0.01	21/115 (18.3%)	<0.01
Serum creatinine ≥1.5 mg/dL	14/101 (13.9%)	<0.01	17/101 (16.8%)	<0.01
Ejection fraction ≤40%	25/232 (10.8%)	<0.01	29/232 (12.5%)	<0.01
Angiographic/procedural variables				
Pre-PCI TIMI 0-1 flow	48/994 (4.8%)	0.08	58/994 (5.8%)	0.43
Post-PCI TIMI 0-2 flow	15/100 (15.0%)	<0.01	16/100 (16.0%)	<0.01
Multivessel diseases	46/702 (6.6%)	<0.01	63/702 (9.0%)	<0.01

MACEs, major adverse cardiovascular events; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

to-balloon time (4.3% for ≤90 min vs. 4.4% for >90 min; p=0.94), symptom onset-to-balloon time (3.9% for ≤240 min vs. 4.8% for >240 min; p=0.41), and symptom onset-to-door time (3.3% for ≤120 min vs. 5.0% for >120 min; p=0.13) (Fig. 2). The rate of MACEs at one month was not significantly different according to door-to-balloon time, symptom onset-to-balloon time, or symptom onset-to-door time. When patients were divided into 4 groups according to door-to-balloon time (≤90, 90-120, 120-180, ≥180 min) or symptom onset-to-balloon time (≤2, 2-4, 4-6, ≥6 hr), incremental delays in reperfusion appeared to have little effect on the one-month mortality and MACE rate (Fig. 3, 4). The left ventricular ejection fraction at the one-month follow-up was also similar between the early reperfused and late reper-

Table 4. Multivariate predictors of one-month mortality and MACEs

	Odds ratio of mortality (95% confidence interval)	*p*	Odds ratio of MACEs (95% confidence interval)	*p*
Age >70 yr	2.43 (1.12-5.23)	0.02	1.29 (0.68-2.43)	0.44
Women	1.34 (0.61-2.99)	0.47	0.85 (0.42-1.74)	0.66
Serum creatinine ≥1.5	3.53 (1.45-8.57)	<0.01	2.76 (1.27-5.98)	0.01
Killip classification ≥3	3.65 (1.62-8.22)	<0.01	2.56 (1.21-5.40)	0.01
LVEF ≤40%	8.02 (3.64-17.64)	<0.01	4.77 (2.59-8.82)	<0.01
Multivessel disease	2.16 (0.97-4.81)	0.06	3.64 (1.80-7.38)	<0.01
Post-PCI TIMI flow 0-2	3.27 (1.26-8.48)	0.02	2.27 (0.97-5.24)	0.06

MACEs, major adverse cardiovascular events; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Table 5. One-month mortality by time variables in patients subsets

	Door-to-balloon time			Symptom onset-to-balloon time			Symptom onset-to-door time		
	≤90 min (%)	>90 min (%)	*p*	≤240 min (%)	>240 min (%)	*p*	≤120 min (%)	>120 min (%)	*p*
Age >70 yr (n=431)	24/209 (11.5)	13/222 (5.9)	0.06	12/140 (8.6)	25/291 (8.6)	0.99	11/109 (10.1)	26/322 (8.1)	0.52
Age ≤70 yr (n=985)	7/506 (1.4)	18/479 (3.8)	0.06	11/457 (2.4)	14/528 (2.7)	0.81	6/406 (1.5)	19/579 (3.3)	0.08
Serum Cr ≥1.5 mg/dL (n=101)	9/43 (20.9)	5/58 (8.6)	0.08	5/36 (13.9)	9/65 (13.8)	0.99	2/37 (5.4)	12/64 (18.8)	0.06
Serum Cr <1.5 mg/dL (n=1,306)	21/668 (3.1)	26/638 (4.1)	0.37	18/557 (3.2)	29/749 (3.9)	0.54	15/473 (3.2)	32/833 (3.8)	0.53
Killip class 3-4 (n=115)	5/39 (12.8)	15/76 (19.7)	0.35	6/38 (15.8)	14/77 (18.2)	0.75	6/43 (14.0)	14/72 (19.4)	0.45
Killip class 1-2 (n=1,281)	26/666 (3.9)	16/615 (2.6)	0.19	17/549 (3.1)	25/732 (3.4)	0.75	11/463 (2.4)	31/818 (3.8)	0.17
LVEF ≤40% (n=232)	12/106 (11.3)	13/126 (10.3)	0.81	9/72 (12.5)	16/160 (10.0)	0.57	7/65 (10.8)	18/167 (10.8)	0.99
LVEF >40% (n=1,045)	6/543 (1.1)	4/502 (0.8)	0.61	0/454 (0)	10/591 (1.7)	0.06	0/392 (0)	10/653 (1.5)	0.06
Post-PCI TIMI <3 (n=100)	5/47 (10.6)	10/53 (18.9)	0.25	6/35 (17.1)	9/65 (13.8)	0.66	5/33 (15.2)	10/67 (14.9)	0.98
Post-PCI TIMI 3 (n=1,286)	26/657 (4.0)	18/629 (2.9)	0.28	15/549 (2.7)	29/737 (3.9)	0.24	10/472 (2.1)	34/814 (4.2)	0.06
High risk* (n=682)	29/318 (9.1)	23/364 (6.3)	0.17	19/228 (8.3)	33/454 (7.3)	0.62	14/199 (7.0)	38/483 (7.9)	0.71
Low risk (n=734)	2/397 (0.5)	8/337 (2.4)	0.06	4/369 (1.1)	6/365 (1.6)	0.51	3/316 (0.9)	7/418 (1.7)	0.401

*High risk: Age >70 yr; serum creatinine ≥1.5 mg/dL; Killip class ≥3; LVEF ≤40% or post-PCI TIMI <grade 3.
Cr, creatinine; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

fused patients regarding door-to-balloon time, symptom onset-to-balloon time, and symptom onset-to-door time.

Predictors of one-month clinical outcomes

Applying univariate analysis, various clinical and angiographic or procedural variables were significantly associated with one-month mortality and MACEs (Table 3). In multivariate analysis, old age (>70 yr), Killip class ≥3, serum creatinine ≥1.5 mg/dL, post-PCI TIMI flow grades of 0-2, and left ventricular dysfunction (ejection fraction ≤40%) were significantly associated with mortality. From the multivariate analysis, Killip class ≥3, serum creatinine ≥1.5 mg/dL, left ventricular dysfunction (ejection fraction ≤40%), and multivessel disease were independent predictors for MACEs (Table 4).

Clinical outcomes by time variables in subgroups

We performed subgroup analysis to identify those patients with outcomes most influenced by treatment delay. Based upon multivariate analysis for one-month mortality, we divided patients by age, serum creatinine, Killip classification, left ventricular ejection fraction, and post-PCI TIMI flow grade. Treatment delay was not significantly associated with increased short-term mortality in any subgroup. Moreover, among patients at high risk (age >70 yr, serum creatinine ≥1.5 mg/dL, Killip classification ≥3, left ventricular ejection fraction ≤40%, post-PCI TIMI flow grades 0-2), the increase in door-to-balloon time, symptom onset-to-balloon time, or symptom onset-to-door time did not correlate with one-month mortality; nor were there any such associations among low-risk patients (Table 5).

DISCUSSION

Primary PCI was the preferred reperfusion strategy in this registry, and more than half of the patients underwent primary PCI within the time window recommended in the guidelines. The one-month mortality was 4.4% and was not increased significantly with increasing delay in door-to-balloon time, symptom onset-to-balloon time, or symptom onset-to-door time. These time variables had no impact on

one-month mortality in any subgroup.

Among 5,069 patients registered in the KAMIR between November 2005 and January 2007, 1,993 patients had STEMI and was eligible for reperfusion. Reperfusion therapy was performed over 90% of these patients, and only a minority received conservative treatment. The rate of receiving reperfusion therapy among these eligible patients with STEMI in the KAMIR seems to be higher than in previous data. From data of the National Registry of Myocardial Infarction (NRMI) in the U.S.A., one-half of the patients with STEMI who were eligible for reperfusion received reperfusion therapy (13). Notably, primary PCI was the overwhelmingly preferred reperfusion strategy in this registry. Among those patients receiving reperfusion therapy, primary PCI was performed in 85%. This rate of primary PCI is much higher than results from other countries, which showed that primary PCI was performed in one-fourth to one-third (13, 14). In the KAMIR, the incidence of post-PCI TIMI grade 3 flow was also very high at 92.8%. This is higher than that reported in studies from the U.S.A. (15, 16). Moreover, the median door-to-balloon time was 90 min, which means that one-half of patients undergoing primary PCI received reperfusion in the recommended time in this registry. Recently published studies in U.S.A. showed that fewer than one-half of patients with STEMI received reperfusion in the recommended door-to-balloon time, and the mean door-to-balloon time was 108.0 min (95% CI, 106.5-109.4 min) (17). The growing interest in primary PCI and easy accessibility to the large-volume hospitals capable of performing primary PCI, most of which participated in the KAMIR, may account for the higher performance of primary PCI in this registry than in those reports.

In our study, the overall one-month mortality was 4.4%. This rate is similar to that reported in the NRMI in the U.S.A. (11). Our study found that old age, high Killip class, left ventricular dysfunction, elevated serum creatinine, and post-PCI TIMI flow grades of 0-2 were independent predictors of one-month mortality after primary PCI. These risk factors also predicted the mortality consistently with several other studies (18-20).

Despite the notion the efficacy of fibrinolytic therapy is largely dependent on time to reperfusion (1-4, 21, 22), several studies suggest that time to reperfusion may be less important in PCI (10, 11). Myocardial salvage has been found to be related to time from symptom onset to fibrinolytic therapy but was not related to time from symptom onset to ballooning (12, 23). In some studies, delays in door-to-balloon time have an impact on late survival rates only in high-risk patients and in patients presenting early after the onset of symptoms (19). In our study, door-to-balloon time and symptom onset-to-balloon time also appeared to have little effect on one-month mortality and MACEs. Moreover, we could not identify any subgroups that were influenced by treatment delay.

There are several possible reasons for the poor relationship between early mortality and time variables of treatment delay in primary PCI, unlikely in fibrinolytic therapy. First, with thrombolytic therapy, the successful reperfusion rate decreases dramatically with delay to reperfusion (24, 25), whereas the procedural success rate of primary PCI remains high regardless of this (6, 12). Second, higher TIMI grade 3 flow was achieved even in the high-risk patients, regardless of time to reperfusion in patients with primary PCI (6, 12). Third, death from myocardial rupture increases progressively with increasing time to treatment with thrombolytic therapy (26) but is uncommon following primary PCI (27). Fourth, the assessment of the time of symptom onset is often difficult because of patient's reporting error. Patients frequently are unsure of the exact time of symptom onset and usually give an estimate. Finally, the patients with high risk factors are more prone to die before they arrive at hospital and are therefore selected out from this registry. It is likely that the exclusion of these patients decreased the effect of symptom onset-to-door time on mortality.

Because time to reperfusion did not have a major impact on clinical outcomes in our study, in patients presenting to local hospitals without interventional facilities, a transfer to interventional centers for primary PCI may be considered despite additional treatment delays. Several randomized trials suggest that this implication may be true (28-30). However, we would like to emphasize that these data do not defend treatment delay without a justifiable cause. We consider that all efforts should be made to shorten time to reperfusion following the ACC/AHA guidelines, which were based on six randomized controlled trials according to the Zwolle group meta-analysis (5).

Our study had several limitations. First, although the KAMIR is the nationwide multicenter trial in Korea, the number of patients, especially in this study cohort, was relatively small. Therefore, the statistical power to detect differences in mortality between time variable groups was limited. Second, we included only 1,416 patients from 5,069. Moreover, 114 patients (7.5%) of 1,530 who had been treated with primary PCI did not undergo the one-month follow-up. This may influence the one-month mortality and MACE rate. Third, as mentioned previously, only large hospitals that were capable of performing primary PCI participated in the KAMIR. Consequently, these subsets may not be representative of the entire cohort and this could have introduced selection bias. Finally, techniques of primary PCI vary with hospitals, which might have influenced the outcomes of primary PCI, and in turn, the results of our study.

In conclusion, this first nationwide registry of acute myocardial infarction in Korea showed a good result of primary PCI. The one-month mortality was not associated with initial time variables to reperfusion, suggesting that patient prognosis may not depend on the initial treatment delay with the current practice of primary PCI. However, further stud-

ies are warranted to validate our observations.

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