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Prognostic Value of Pre-Procedural Thrombolysis in Myocardial Infarction Flow in ST-Segment Elevation Myocardial Infarction Patients with Primary Percutaneous Coronary Intervention

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Abstract

Background: We investigated the prognostic value of pre-procedural Thrombolysis in Myocardial Infarction (TIMI) flow for major adverse cardiac events (MACE) and cardiovascular death (CVD) using Korean registry data in ST-elevation myocardial infarction patients underwent primary percutaneous coronary intervention.

Methods: Between October of 2005 and May of 2013, a total of 16,843 patients were registered. Of these, 8,428 patients (mean age 62.8 years) were enrolled. Depending on pre-procedural TIMI flow, we divided into 2 groups by TIMI flow 0-2 vs. 3.

Results: During follow-up (median 350 days), 938 (11.1%) of MACE and 488 (5.8%) CVD occurred. Preprocedural TIMI 3 flow group showed high event rates in \leq 30 day MACE (3.5% vs. 5.9% p = 0.001), \leq 30 day CVD (2.4% vs. 4.8%, p = 0.001), 1-year MACE (9.4% vs. 11.4% p = 0.047) and 1-year CVD (3.8% vs. 6.1% p = 0.002). In the multivariate Cox regression analysis, pre-procedural TIMI 0-2 flow was not an independent predictor of \leq 30 day MACE, \leq 30 CVD, 1-year MACE, and 1-year CVD.

Conclusion: The pre-procedural TIMI 0-2 flow is not independent predictor of \leq 30 day MACE and \leq 30 day CVD, 1-year MACE, and 1-year CVD.

Keywords

Myocardial infarction, Thrombolysis in myocardial infarction (TIMI) Flow, Percutaneous coronary intervention (PCI), Outcome

Introduction

In patients with acute myocardial infarction (MI), it would be mandatory to rapidly perform reperfusion therapy for coronary artery involved in MI. This is an essential procedure to reduce the occurrence of myocardial injury and to lower the mortality, which is also effective in protecting cardiac muscles, preserving the left ventricular function and improving a clinical prognosis [1]. Recent studies have shown that primary coronary intervention (PCI) is effective in reducing the mortality, recurrent myocardial infarction and complications of stroke as compared with the thrombolytic therapy. The former

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has been performed more frequently than the latter [2].

According to the conventional Thrombolysis in Myocardial Infarction (TIMI) flow grading system, the degree of pre- or post-procedural perfusion on coronary angiography is classified as grade 0-3. To date, multiple studies have been conducted to examine the relationship between TIMI flow grading system and clinical outcomes. These showed that pre- or post-procedural TIMI flow are key prognostic factors in patients with ST-segment elevation MI (STEMI). Moreover, it has also been shown that TIMI flow grade 3 is evidence demonstrating successful treatment outcomes of reperfusion therapy [3-8].

Given the above background, we conducted this study to examine the prognostic value of pre-procedural TIMI flow for \leq 30 days mortality, 1-year mortality and major adverse cardiac events (MACEs) using the Korea Acute Myocardial Infarction Registry (KAMIR) and the Korean Registry of Myocardial Infarction (KorMI) data in patients with STEMI.

Subjects and Methods

Study population

The KAMIR and the KorMI, are Korean prospective, open, observational, multicenter on-line registry designed to reflect the "real-world" practice for Asian patients presenting with acute MI. Both these registries were supported by the Korean Working Group of Acute Myocardial Infarction. The aims and protocols of the registries have been published elsewhere [9,10]. The data from the KAMIR and KorMI were merged to maximize statistical power. The KAMIR and the KorMI are investigating the risk factors of mortality in AMI and establishing the universal management for the prevention of AMI with support of Korean Circulation Society since Nov 2005. The 41 participating hospitals are capable of primary percutaneous coronary intervention (PCI). This study included age, sex, body mass index, initial symptom, vital sign, Killip class, symptom, onset time, ambulance arrival time, first medical contact time, transfer time from first hospital to the primary PCI centers, door to needle time, door to balloon time, each risk factors, past regular medication, co-morbidities, electrocardiographic locations of MI, initial treatment strategy, drugs, angiographic findings, in-hospital complication, medical therapy in hospital and 1, 6, 12 month follow-up major adverse cardiac event (cardiac death, reinfarction, re-PCI, coronary artery bypass graft) and so on. Data are collected by the attending physician and trained clinical research coordinators though a web-based case report form in the clinical data management system [11]. In these study, the data from patients diagnosed with STEMI were extracted from the database (Figure 1).

A total of 16,843 patients were registered with the KAMIR and KorMI Between October of 2005 and May of 2013.

Inclusion criteria for the current study are as follows:

- 1. The patients with STEMI.
- 2. The patients who underwent coronary angiography and primary PCI within 12 hours of the onset of symptoms.

Patient with STEMI (< 12 hr) who didn't receiving primary PCI were excluded. Patients with missing outcome data or no TIMI flow data were also excluded. Finally, Patients divided two groups according to the pre-procedural TIMI flow: Pre-procedural TIMI flow 0-2 group (n = 7,309) and pre-procedural TIMI flow 3 group (n = 1,119).

The current study was approved by the Institutional Review Board (IRB) of our medical institution. Informed consent was waived due to the retrospective nature of the current study. The present study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

Patient assessment

Depending on pre-procedural TIMI flow, we divided our clinical series of patients into the two groups: The TIMI 0-2 group and the TIMI 3 group. Then, we compared 1-month MACE, 1-year MACE and 1-month cardiovascular death (CVD) 1-year CVD between the two groups. MACE was defined as the death of any cause, the recurrence of MI, target lesion revascularization (TLR), target vessel re-vascularization (TVR), CABG (coronary artery bypass grafting).

Classification of coronary angiography findings

Coronary angiography findings were graded based on the ACC/AHA (American College of Cardiology/American Heart Association) classification system [12]. This is also associated with the complexity of the lesions. Blood

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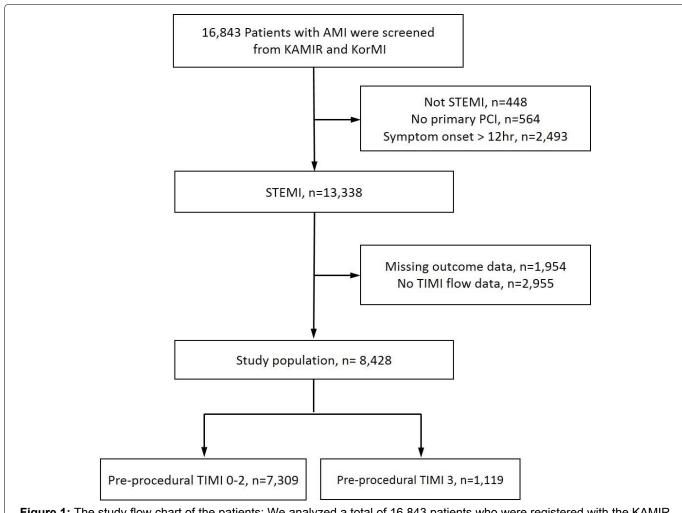


Figure 1: The study flow chart of the patients: We analyzed a total of 16,843 patients who were registered with the KAMIR and KorMI. Patient with STEMI (< 12 hr) who didn't receive primary PCI were excluded. Patients with missing outcome data or no TIMI flow data were also excluded. Finally, Patients divided two groups according to the pre-procedural TIMI flow: Pre-procedural TIMI flow 0-2 group (n = 7,309) and pre-procedural TIMI flow 3 group (n = 1,119).

AMI: Acute Myocardial Infarction; KAMIR: Korea Acute Myocardial Infarction Registry; KorMI: Korean Registry of Myocardial Infarction; STEMI: ST Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; TIMI: Thrombolysis in Myocardial Infarction.

flow on coronary angiography was evaluated based on the TIMI flow [13]. TIMI flow 0,1,2,3 are defined as follows:

- 1. TIMI flow grade 0: No contrast flow.
- 2. TIMI flow grade 1: Small amount of flow but incomplete opacification of distal vessel.
- 3. TIMI flow grade 2: Slowed distal filling but full opacification of distal vessel.
- 4. TIMI flow grade 3: Prompt anterograde flow and rapid clearing.

Statistical analysis

Continuous variables were expressed as mean \pm SD (SD: standard deviation) or the median and interquartile range, and they were compared using the independent t test or Mann-Whitney U test between the two groups. Categorical variables were compared with Pearson's Chi-square or

Fisher's exact tests between the two groups. Cox regression analysis was performed to identify independent predictors of 1-year MACE and CVD and \leq 30 days MACE and \leq 30 days CVD. Event-free survival curves for MACE were plotted according to the Kaplan-Meier method, and statistical differences were tested using the log-rank test. All tests were two-sided, and a p-value of < 0.05 was considered statistically significant. Statistical analysis was done using the SPSS version 18.0 (SPSS, Inc., Chicago, IL).

Results

Baseline and clinical characteristics

A total of 8,428 patients were enrolled in the current study. The mean age of the patients was 62.8 ± 13.5 years old. The proportion of the female patients was 25.3%. Clinical characteristics depending on the pre-procedural TIMI flow of coronary artery were summarized in (Table 1).

| | Overall patients | Pre TIMI 0-2 | Pre TIMI 3 | p-value |
|--------------------------------------|-------------------------|-----------------|-----------------|---------|
| | (n = 8428) | (n = 7309) | (n = 1119) | |
| Clinical characteristics | | | | |
| Age (year) | 62.8 ± 13.5 | 62.8 ± 13.6 | 62.5 ± 13.1 | 0.45 |
| Female gender (%) | 2129 (25.3) | 1857 (25.4) | 272 (24.3) | 0.46 |
| Diabetes (%) | 1573 (18.6) | 1346 (18.4) | 227 (20.3) | 0.138 |
| Hypertension (%) | 3791 (44.9) | 3287 (44.9) | 504 (45.0) | 0.974 |
| Dyslipidemia (%) | 846 (10.0) | 726 (9.9) | 120 (10.7) | 0.423 |
| Current Smoking (%) | 3993 (47.4) | 3426 (46.8) | 567 (50.6) | 0.019 |
| Family history of IHD (%) | 607 (7.2) | 540 (7.4) | 67 (6.0) | 0.094 |
| Previous IHD | | | | 0.417 |
| Previous MI (%) | 213 (2.5) | 184 (2.5) | 29 (2.6) | |
| Previous PCI (%) | 382 (4.5) | 342 (4.8) | 40 (3.6) | |
| Previous CABG (%) | 21 (0.2) | 18 (0.2) | 3 (2.7) | |
| Previous Angina (%) | 273 (3.2) | 233 (3.2) | 40 (3.6) | |
| Laboratory and hemodynamic data at | admission | | | |
| Creatinine (mg/dL) | 1.11 ± 1.24 | 1.11 ± 1.28 | 1.10 ± 0.97 | 0.841 |
| Troponin I (ng/mL) | 35.6 [6.8-79.4] | 40.0 [8.6-83.9] | 16.6 [3.3-50.0] | < 0.001 |
| CK-MB (ng/mL) | 130 [36-279] | 142 [42-294] | 66 [17-173] | < 0.001 |
| LDL-C | 117.2 ± 40.1 | 117.7 ± 40.6 | 114.5 ± 37.1 | 0.018 |
| NT-proBNP (pg/mL) | 261 [62-1306] | 266 [62-1338] | 228 [59-1122] | 0.262 |
| Killip class III-IV (%) | 991 (11.8) | 883 (12.1) | 108 (9.7) | 0.019 |
| LVEF (%) | 51.7 ± 21.2 | 51.3 ± 21.1 | 54.5 ± 21.5 | < 0.001 |
| Door to balloon time (min) | 76 [57-111] | 75 [57-109.5] | 81 [60-125] | < 0.001 |
| Medical characteristics at admission | | | | |
| Antiplatelet agents (%) | 8392 (99.6) | 7273 (99.6) | 1119 (100) | 0.028 |
| Aspirin (%) | 8392 (99.6) | 7273 (99.6) | 1119 (100) | 0.022 |
| Clopidogrel (%) | 8273 (98.2) | 7172 (98.1) | 1101 (98.4) | 0.556 |
| Glycoprotein IIb/IIIa inhibitor (%) | 1624 (19.3) | 1467 (20.1) | 157 (14.0) | < 0.001 |
| Beta-blocker (%) | 6537 (77.6) | 5636 (77.1) | 901 (80.5) | 0.011 |
| ARB/ACEi (%) | 6849 (81.3) | 5897 (80.7) | 952 (85.1) | < 0.001 |
| Statin (%) | 6713 (79.6) | 5805 (79.4) | 908 (81.1) | 0.188 |

TIMI: Thrombolysis in Myocardial Infarction; IHD: Ischemic Heart Disease; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; SBP: Systolic Blood Pressure; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; ARB: Angiotensin Receptor Blocker; ACEi: Angiotensin Converting Enzyme Inhibitor.

Clinical characteristics were not significantly different between pre-procedural TIMI 0-2 group and pre-procedural TIMI 3 group. In the laboratory and hemodynamic data, pre-procedural TIMI 0-2 group was shown elevated CK-MB level, higher Killip class, and more decreased left ventricular ejection fraction (LVEF) compared with pre-procedural TIMI 3 group. In the medication data, uses of antiplatelet agent, beta-blocker, angiotensin receptor blocker (ARB) and angiotensin converting enzyme inhibitor (ACEi) at admission were also tended to be lower in pre-procedural TIMI flow 0-2 group when compared with pre-procedural TIMI 3 group.

Coronary angiographic findings

Of the 8,428 patients, 7,309 (86.7%) patients showed pre-procedural TIMI flow 0-2 and 658 (7.8%) patients showed post-procedural TIMI flow 0-2. From an aspect of the pre-procedural TIMI flow, culprit lesion and multi-vessel disease were not different in both groups, but type B2/C lesions were more often in the pre-procedural TIMI 0-2 group (Table 2).

Correlations between clinical outcomes and the pre-procedural TIMI flow

We compared clinical outcomes depending on the pre-procedural TIMI flow. Median clinical follow-up was 350 days (interquartile range [IQR], 113-385). During clinical follow-up, a total of 938 (11.1%) MACE occurred, including 488 (5.8%) CVD. There were higher event rates in \leq 30 day MACE, \leq 30 day CVD, 1-year MACE, 1-year all-cause death, 1-year CVD in pre-procedural TIMI 0-2 group compared with pre-procedural TIMI 3 group. Following comparisons based on the pre-procedural TIMI flow in the patients who excluded \leq 30 day MACE and \leq 30 day CVD, however, the incidence of MACE and CVD were not different between the pre-procedural TIMI 0-2 group and the pre-procedural TIMI 3 group (Table 3).

| | Overall patients | Pre TIMI 0-2 | Pre TIMI 3 | p-value |
|--|------------------|--------------|-----------------|---------|
| | (n = 8428) | (n = 7309) | (n = 1119) | |
| Culprit lesion (%) | | | | < 0.001 |
| Left anterior descending | 4364 (51.8) | 3721 (50.9) | 643 (57.4) | |
| Left circumflex | 3157 (37.5) | 2790 (38.2) | 367 (32.8) | |
| Right | 813 (9.6) | 729 (9.9) | 84 (7.5) | |
| Left main | 94 (1.1) | 69 (0.9) | 25 (2.2) | |
| Multi-vessel disease (%) | | | | 0.084 |
| 1 vessel | 4198 (49.8) | 3646 (49.8) | 552 (49.3) | |
| 2 vessels | 2459 (29.2) | 2134 (29.2) | 325 (29.0) | |
| 3 vessels | 1625 (19.3) | 1414 (19.3) | 211 (18.9) | |
| Left main | 146 (1.7) | 115 (1.6) | 31 (2.8) | |
| Lesion classification (%) | | | | |
| type B2/C | 6388 (75.8) | 5603 (76.7) | 785 (70.2) | < 0.001 |
| Mean stent diameter of culprit vessel (mm) | 3.22 ± 0.45 | 3.21 ± 0.45 | 3.24 ± 0.44 | 0.146 |
| Total number of stents | 1.4 ± 0.7 | 1.4 ± 0.7 | 1.4 ± 0.8 | 0.123 |

TIMI: Thrombolysis in Myocardial Infarction.

Table 3: Comparison of various clinical outcomes according to the pre-procedural TIMI flow.

| Overall patient | Total | Pre TIMI 0-2 | Pre TIMI 3 | p-value |
|--|-----------------------------|-------------------------|-----------------------|---------|
| | (n = 8428) | (n = 7309) | (n = 1119) | |
| ≤ 30 day MACE | 468 (5.6) | 429 (5.9) | 39 (3.5) | 0.001 |
| ≤ 30 day CVD | 381 (4.5) | 353 (4.8) | 28 (2.4) | 0.001 |
| 1-year MACE | 938 (11.1) | 833 (11.4) | 105 (9.4) | 0.047 |
| 1-year all-cause death | 689 (8.2) | 619 (8.5) | 70 (6.3) | 0.014 |
| 1-year CVD | 488 (5.8) | 446 (6.1) | 42 (3.8) | 0.002 |
| MI | 76 (0.9) | 64 (0.9) | 12 (1.1) | 0.61 |
| RePCI (TVR/TLR) | 231 (2.7) | 197 (2.7) | 34 (3.0) | 0.555 |
| CABG | 22 (0.3) | 19 (0.3) | 3 (0.3) | 0.999 |
| Patients who excluded ≤ 30 day events | Overall patients (n = 7960) | Pre TIMI 0-2 (n = 6880) | Pre TIMI 3 (n = 1080) | p-value |
| MACE (> 30 day) | 470 (5.9) | 404 (5.9) | 66 (6.1) | 0.781 |
| CVD (> 30 day) | 107 (1.3) | 93 (1.4) | 14 (1.3) | 0.999 |

TIMI: Thrombolysis in Myocardial Infarction; MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; TVR: Target Vessel Revascularization; TLR: Target Lesion Revascularization; RePCI: Recurrent Percutaneous Coronary Intervention. MACE is defined as the composite of the death of any cause, recurrence of MI, TLR, TVR, and CABG.

 Table 4: Unadjusted and adjusted hazard ratio for pre-procedural TIMI 0-2 flow vs. pre-procedural TIMI 3 flow.

| Pre TIMI 0-2 | Unadjusted hazard ratio (95% CI) | p-value | Adjusted hazard ratio (95% CI) | p-value |
|------------------------|----------------------------------|---------|--------------------------------|---------|
| ≤ 30 day MACE | 1.587 [1.132-2.225] | 0.007 | 1.281 [0.894-1.836] | 0.177 |
| ≤ 30 day CVD | 1.681 [1.142-2.476] | 0.009 | 1.233 [0.816-1.862] | 0.32 |
| 1-year MACE | 1.198 [0.975-1.473] | 0.086 | 1.111 [0.893-1.382] | 0.334 |
| > 30 day MACE | 0.977 [0.752-1.270] | 0.864 | 0.948 [0.720-1.249] | 0.705 |
| 1-year all-cause death | 1.300 [1.011-1.672] | 0.041 | 1.125 [0.861-1.470] | 0.387 |
| 1-year CVD | 1.496 [1.084-2.063] | 0.014 | 1.265 [0.903-1.773] | 0.172 |
| > 30 day CVD | 0.984 [0.570-1.696] | 0.953 | 1.029 [0.589-1.798] | 0.921 |
| MI | 0.922 [0.486-1.748] | 0.803 | 1.129 [0.529-2.410] | 0.753 |
| RePCI (TVR/TLR) | 0.911 [0.633-1.311] | 0.616 | 0.923 [0.632-1.346] | 0.923 |

TIMI: Thrombolysis in Myocardial Infarction; MACE: Major Adverse Cardiac Events; CVD: Cardiovascular Death; TVR: Target Vessel Revascularization; TLR: Target Lesion Revascularization; RePCI: Recurrent Percutaneous Coronary Intervention.

MACE is defined as the composite of the death of any cause, recurrence of MI, TLR, TVR, and CABG. Adjustment : Age, sex , history of hypertension, diabetes, dyslipidemia, and smoking, killip I-II vs. III-IV, multi-vessel disease, lesion type A/B1 vs. B2/C, target vessels, Door to balloon time, CK-MB, Creatinine, use of aspirin, clopidogrel, beta-blocker, RAS blocker, statin at admission.

The Kaplan-Meier survival curve for \leq 30 day CVD showed significant increase of CVD events in pre-proce-

dural TIMI flow 0-2 group compared to pre-procedural TIMI flow 3. However, the CVD after 30 days was not

different according to pre-procedural TIMI flow grade (0-2 vs. 3) (Figure 2).

We analyzed that the pre-procedural TIMI 0-2 flow could predict clinical outcomes in STEMI patients underwent primary PCI using Cox regression analysis. In univariate Cox regression analysis, pre-procedural TIMI flow 0-2 flow was predictor for \leq 30 day MACE, \leq 30 day CVD, 1-year all-cause death and 1-year CVD, but it was not independent predictor in multivariate analysis (Table 4).

We also evaluated the clinical outcomes by dividing the pre-procedural TIMI flow 0-1 vs. 2 vs. 3 in supplement tables. However, the results also did not show improved clinical outcomes in pre-procedural TIMI 3 group compared with TIMI 0-1 group (Supplement Table 1, Supplement Table 2, Supplement Table 3 and Supplement Table 4).

Discussion

Our results showed that the pre-procedural TIMI 0-2 flow was not important predictors of \leq 30 day MACE, \leq 30 day CVD, 1-year MACE, 1-year CVD in STEMI patients who underwent primary PCI.

According to previous studies, prompt reperfusion of coronary artery involved in the MI was effective in reducing the occurrence of MI as well as the mortality in patients with STEMI. It has also been reported that both pre- and post-procedural TIMI flow are a key prognostic indicator [14-16].

Stone, et al. [3] showed that the pre-procedural TIMI

flow 3 was an independent determinant of good prognosis in STEMI patients. Brodie, et al. [7] conducted a study to examine the relationship between pre-procedural TIMI flow and clinical outcomes in patients with acute MI, thus reporting that the degree of pre-procedural reperfusion is a key prognostic indicator. According to this study, the 1-month mortality was significantly lower in the pre-procedural TIMI 2 or 3 flow group as compared with the TIMI 0 or 1 flow group. Giuseppe, et al. [6] also reported that there was a significant correlation between pre-procedural TIMI flow and the mortality in patients with acute MI. These authors classified patients into a high-risk group of patients (TIMI risk score \geq 4) and a low-risk group of patients depending on the age, Killip class, reperfused MI, the time to the procedure and pre-existing cardiovascular risk factors, thus reporting that TIMI 3 flow in a high-risk group of patients is an independent prognostic factor associated with the 1-year mortality.

Even though poor pre-procedural TIMI flow showed significant correlation to the mortality in these studies, our data showed that pre-procedural TIMI flow 0-2 was not significantly correlated with adverse clinical outcomes in all comer registry. These differences might be presumed due to several causes such as improvements in adjunctive pharmacological therapies, and advances in intervention techniques during and after PCI. Stone, et al. [3] reported that the pre-procedural TIMI flow 3 was highly associated with good prognosis in STEMI patients, but rates of glycoprotein IIb/IIIa inhibitors use

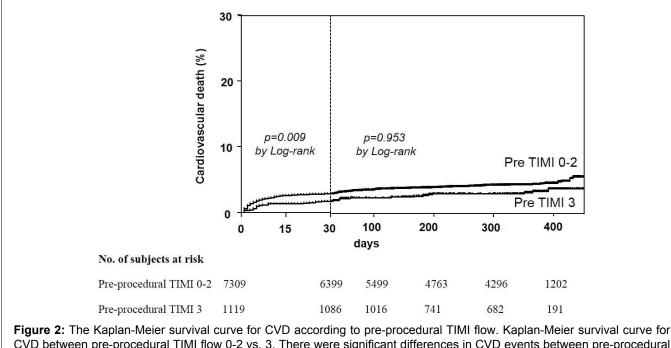


Figure 2: The Kaplan-Meier survival curve for CVD according to pre-procedural TIMI flow. Kaplan-Meier survival curve for CVD between pre-procedural TIMI flow 0-2 vs. 3. There were significant differences in CVD events between pre-procedural TIMI flow grades (0-2 vs. 3) during \leq 30 days. However, the CVD after 30 days was not different between pre-procedural TIMI flow grades (0-2 vs. 3).

were about 2.8% and 3.9% in both TIMI 0-2 and TIMI 3 groups, respectively. And the roughly estimated door to balloon time was more than 100 minutes in mean value. Unlike this study, we use the glycoprotein IIb/IIIa inhibitors about 19.3% in all patients (20.1% in pre-procedural TIMI 0-2 group and 14.0% in pre-procedural TIMI 3 group); median door to balloon time was 76 min. In Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI) trial, an intracoronary bolus of the glycoprotein IIb/IIIa inhibitor abciximab was effective in reduction in 30-day infarct size [16]. Hachinohe, et al. [17] also reported that use of glycoprotein IIb/IIIa inhibitor with thrombus aspiration has a synergistic effect on clinical outcomes. These results implies that reduced embolization by use of glycoprotein IIb/IIIa inhibitor could result in improved myocardial perfusion and better clinical outcomes.

As shown in the previous paragraph, Giuseppe, et al. [6] reported pre-procedural TIMI flow grade 3 is an independent predictor of one-year survival, but they only used statins, ACE inhibitors, ticlopidine or clopidogrel to about 47%, 52%, 28% of enrolled patients. On the other hand, we prescribed statins, ARB/ACEi, and clopidogrel to 79.6%, 81.3%, and 98.2% of enrolled patients, respectively. Even though it is not possible to compare these differences directly, but it is clear that more statin, ARB/ACEi, and clopidogrel were used in the patients registered in our study. Ndrepepa, et al. [18], analyzed the association of clinical outcome depending on the final TIMI flow and pre-procedural TIMI flow in patients with acute coronary syndrome, baseline TIMI flow grade is not an independent predictor of 30-day mortality and 1-year mortality. This study was similar to our data, but performed in patients with acute coronary syndrome including non-ST-segment elevation acute myocardial infarction, unstable angina and divided pre-procedural TIMI flow 0 to 1 vs. 2 vs. 3.

Limitations

The current study was conducted in the patients with MI registered with the KAMIR and KorMI. But we excluded a considerable number of patients whose TIMI flow data were unavailable. TIMI flow, an indicator of the reperfusion on coronary angiography, is a subjective one based on gross examination. Information of thrombus burden was not reported in our registry. There were significant differences in baseline clinical characteristics between the two groups.

Conclusions

In conclusion, although pre-procedural TIMI flow 0-2 increased in the incidence of \leq 30 day MACE, \leq 30 day CVD, 1-year MACE and 1-year CVD in patients

with STEMI underwent primary PCI, there were no significances in multivariate analysis. Effort to get post-procedural TIMI flow grade 3 regardless of the pre-procedural TIMI flow should be needed.

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Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Data Availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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| | Pre TIMI 0-1 | Pre TIMI 2 | Pre TIMI 3 | p-value |
|--------------------------------------|-----------------|-----------------|-----------------|---------|
| | (n = 6235) | (n = 1074) | (n = 1119) | |
| Clinical characteristics | | | | |
| Age (year) | 62.7 ± 13.6 | 63.8 ± 13.9 | 62.5 ± 13.1 | 0.224 |
| Female gender (%) | 1585 (25.5) | 272 (25.3) | 272 (24.3) | 0.755 |
| Diabetes (%) | 1130 (18.1) | 216 (20.1) | 227 (20.3) | 0.138 |
| Hypertension (%) | 2801 (44.9) | 486 (45.3) | 504 (45.0) | 0.979 |
| Dyslipidemia (%) | 636 (10.2) | 90 (8.3) | 120 (10.7) | 0.133 |
| Current Smoking (%) | 2933 (47.0) | 493 (45.9) | 567 (50.6) | 0.048 |
| Family History of IHD (%) | 469 (7.5) | 71 (6.6) | 67 (6.0) | 0.136 |
| Previous IHD | | | | 0.695 |
| Previous MI (%) | 159 (2.5) | 25 (2.3) | 29 (2.6) | |
| Previous PCI (%) | 294 (4.7) | 48 (4.5) | 40 (3.6) | |
| Previous CABG (%) | 14 (0.2) | 4 (0.4) | 3 (2.7) | |
| Previous Angina (%) | 200 (3.2) | 33 (3.1) | 40 (3.6) | |
| Laboratory and hemodynamic data at | admission | | | |
| Creatinine (mg/dL) | 1.09 ± 1.09 | 1.18 ± 2.04 | 1.11 ± 0.97 | 0.009 |
| Troponin I (ng/mL) | 42.9 [9.5-86.9] | 25.5 [6.2-60.6] | 16.6 [3.3-50.0] | < 0.001 |
| CK-MB (ng/mL) | 153 [47-300] | 94 [25-213] | 66 [17-173] | < 0.001 |
| LDL-C | 117.3 ± 39.1 | 119.5 ± 48.2 | 114.5 ± 37.1 | 0.513 |
| NT-proBNP (pg/mL) | 261 [62-1308] | 324 [71-1649] | 228 [59-1122] | 0.073 |
| Killip class III-IV (%) | 760 (12.2) | 133 (12.4) | 108 (9.6) | 0.05 |
| LVEF (%) | 50.9 ± 20.4 | 53.1 ± 24.6 | 54.5 ± 21.5 | 0.12 |
| Door to balloon time (min) | 75 [56-108] | 79.5 [59-116] | 81 [60-125] | < 0.001 |
| Medical characteristics at admission | | | | |
| Antiplatelet agents (%) | 6209 (99.6) | 1069 (99.5) | 1119 (100) | 0.09 |
| Aspirin (%) | 6206 (99.5) | 1067 (99.3) | 1119 (100) | 0.043 |
| Clopidogrel (%) | 6117 (98.1) | 1055 (98.2) | 1101 (98.4) | 0.796 |
| Glycoprotein IIb/IIIa inhibitor (%) | 1306 (20.9) | 161 (15.0) | 157 (14.0) | < 0.001 |
| Beta-blocker (%) | 4785 (76.7) | 851 (79.2) | 901 (80.5) | 0.008 |
| ARB/ACEi (%) | 5031 (80.6) | 866 (80.6) | 952 (85.1) | 0.002 |
| Statin (%) | 4961 (79.6) | 844 (78.6) | 908 (81.1) | 0.09 |

TIMI: Thrombolysis in Myocardial Infarction; IHD: Ischemic Heart Disease; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; SBP: Systolic Blood Pressure; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; ARB: Angiotensin Receptor Blocker; ACEi: Angiotensin Converting Enzyme Inhibitor.

Supplement Table 2: Coronary angiographic characteristics according to the TIMI flow.

| | Pre TIMI 0-1 | Pre TIMI 2 (n = 1074) | Pre TIMI 3 (n = 1119) | p -value |
|---------------------------|--------------|--------------------------|--------------------------|----------|
| | (n = 6235) | | | |
| Culprit lesion (%) | | | | < 0.001 |
| Left anterior descending | 3081 (49.4) | 640 (59.5) | 643 (57.4) | |
| Left circumflex | 619 (9.9) | 110 (10.2) | 367 (32.8) | |
| Right | 2484 (39.8) | 306 (28.5) | 84 (7.5) | |
| Left main | 51 (0.8) | 18 (1.7) | 25 (2.2) | |
| Multi-vessel disease (%) | | | | 0.005 |
| 1 vessel | 3145 (50.4) | 501 (46.6) | 552 (49.3) | |
| 2 vessels | 1821 (29.2) | 313 (29.1) | 325 (29.0) | |
| 3 vessels | 1181 (18.9) | 233 (21.7) | 211 (18.9) | |
| Left main | 88 (1.4) | 27 (2.5) | 31 (2.8) | |
| Lesion classification (%) | I | | | |
| type B2/C | 4828 (77.4) | 775 (72.2) | 785 (70.2) | < 0.001 |
| Total number of stents | 1.37 ± 0.71 | 1.42 ± 0.71 | 1.41 ± 0.76 | 0.025 |

TIMI: Thrombolysis in Myocardial Infarction.

| Overall patient | Pre TIMI 0-1 | Pre TIMI 2 | Pre TIMI 3 | p-value |
|---------------------------------------|--------------|--------------|------------|---------|
| | (n = 6235) | (n = 1074) | (n = 1119) | |
| ≤ 30 day MACE | 382 (6.1) | 47 (4.4) | 39 (3.5) | 0.001 |
| ≤ 30 day CVD | 316 (5.1) | 37 (3.4) | 28 (2.4) | 0.001 |
| 1-year MACE | 714 (11.5) | 119 (11.1) | 105 (9.4) | 0.126 |
| 1-year all-cause death | 537 (8.6) | 82 (7.6) | 70 (6.3) | 0.021 |
| 1-year CVD | 392 (6.3) | 54 (5.0) | 42 (3.8) | 0.001 |
| Recurrent MI | 52 (0.8) | 12 (1.1) | 12 (1.1) | 0.47 |
| RePCI (TVR/TLR) | 165 (2.6) | 32 (3.0) | 34 (3.0) | 0.622 |
| CABG | 17 (0.3) | 2 (0.2) | 3 (0.3) | 0.999 |
| Patients who excluded ≤ 30 day events | Pre TIMI 0-1 | Pre TIMI 0-2 | Pre TIMI 3 | |
| | (n = 5853) | (n = 1027) | (n = 1080) | |
| MACE (> 30 day) | 332 (5.6) | 72 (7.0) | 66 (6.1) | 0.228 |
| CVD (> 30 day) | 76 (1.3) | 17 (1.7) | 14 (1.3) | 0.637 |

Supplement Table 3: Comparison of various clinical outcomes according to the pre-procedural TIMI flow.

TIMI: Thrombolysis in Myocardial Infarction; MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; TVR: Target Vessel Revascularization; TLR: Target Lesion Revascularization; RePCI: Recurrent Percutaneous Coronary Intervention. MACE is defined as the composite of the death of any cause, recurrence of MI, TLR, TVR and CABG.

Supplement Table 4: Unadjusted and adjusted hazard ratio for pre-procedural TIMI 0-2 flow vs. pre-procedural TIMI 3 flow.

| Pre TIMI 0-2 | Unadjusted hazard ratio (95% Cl) | p-value | Adjusted hazard ratio | p-value |
|------------------------|-------------------------------------|---------|-----------------------|---------|
| ≤ 30 day MACE | 1.566 [1.124-2.181] | 0.008 | 1.312 [0.920-1.869] | 0.134 |
| ≤ 30 day CVD | 1.816 [1.223-2.697] | 0.003 | 1.430 [0.945-2.165] | 0.09 |
| 1-year MACE | 1.204 [0.978-1.483] | 0.081 | 1.149 [0.922-1.433] | 0.216 |
| > 30 day MACE | 0.977 [0.746-1.279] | 0.865 | 0.964 [0.726-1.280] | 0.799 |
| 1-year all-cause death | 1.321 [1.025-1.703] | 0.031 | 1.185 [0.906-1.551] | 0.216 |
| 1-year CVD | 1.511 [1.097-2.081] | 0.012 | 1.328 [0.947-1.862] | 0.999 |
| > 30 day CVD | 0.999 [0.564-1.768] | 0.997 | 1.089 [0.601-1.974] | 0.779 |
| Recurrent MI | 0.710 [0.461-1.694] | 0.71 | 1.039 [0.479-2.252] | 0.922 |
| RePCI (TVR/TLR) | 0.899 [0.622-1.302] | 0.574 | 0.944 [0.642-1.388] | 0.769 |

TIMI: Thrombolysis in Myocardial Infarction; MACE: Major Adverse Cardiac Events; CVD: Cardiovascular Death; TVR: Target Vessel Revascularization; TLR: Target Lesion Revascularization; RePCI: Recurrent Percutaneous Coronary Intervention. MACE is defined as the composite of the death of any cause, recurrence of MI, TLR, TVR and CABG.

Adjustment: age, sex, history of hypertension, diabetes, and smoking, killip I-II vs. III-IV, multi-vessel disease, lesion type A/B1 vs. B2/C, target vessels, Door to balloon time, CK-MB, Creatinine, use of aspirin, glycoprotein IIb/IIIa inhibitors, beta-blocker, RAS blocker, statin at admission.

