Predictive Factors of Major Adverse Cardiac Events in Acute Myocardial Infarction Patients Complicated by Cardiogenic Shock Undergoing Primary Percutaneous Coronary Intervention

Sang Yup Lim, MD; Myung Ho Jeong, MD; Eun Hui Bae, MD; Weon Kim, MD; Ju Han Kim, MD; Young Joon Hong, MD; Hyung Wook Park, MD; Dong Goo Kang, MD; Yeon Sang Lee, MD; Kye Hun Kim, MD; Sang Hyun Lee, MD; Kyung Ho Yun, MD; Seo Na Hong, MD; Jeong Gwan Cho, MD; Young Keun Ahn, MD; Jong Chun Park, MD; Byoung Hee Ahn, MD; Sang Hyung Kim, MD; Jung Chaee Kang, MD

Background The aim of this study was to assess in-hospital mortality and major adverse cardiac events (MACE) during long-term clinical follow-up of patients who developed cardiogenic shock (CS) after acute myocardial infarction (AMI) and who underwent primary percutaneous coronary intervention (PCI).

Methods and Results The data from 147 patients with CS after AMI (61.7±10.4 years, M:F =156:99) who underwent primary PCI at Chonnam National University Hospital between January 1999 and December 2002 were analyzed: clinical characteristics, coronary angiographic findings and mortality during admission, and MACE during a 1-year clinical follow-up. Of the enrolled patients, 121 patients survived (group I, M:F =94:27) and 26 died (group II, M:F =14:12) during admission. By binary logistic regression analysis, in-hospital death was associated with low Thrombolysis In Myocardial Infarction (TIMI) flow after coronary revascularization (p=0.02, odds ratio (OR) =1.3). Eighty-nine patients (60.5%) survived without MACE during the 1-year clinical follow-up and MACE was associated with a C-reactive protein (CRP) of more than 1 mg/dl (p=0.002, OR =6.3) and low TIMI flow after coronary revascularization (p<0.001, OR =7.8).

Conclusions Primary PCI achieving TIMI 3 flow reduces in-hospital death in AMI with CS. High concentration of CRP and low TIMI flow are associated with MACE during long-term clinical follow-up. (*Circ J 2005; 69: 154–158*)

Key Words: Coronary diseases; Myocardial infarction; Prognosis; Shock

Acute coronary syndrome (ACS) is still one of the most important causes of death despite the development of new therapeutic methods. Cardiogenic shock (CS) after acute myocardial infarction (AMI) is known to occur in 5–10% of ACS cases and is associated with a high mortality rate. Most cases of CS occur within the first few days of admission, thus the mortality rate could be reduced by early invasive treatment. Primary or rescue percutaneous coronary intervention (PCI) with thrombolytic therapy is known to be effective in the management of AMI.

It has been reported that an elevated concentration of C-reactive protein (CRP) is a predictor of adverse outcomes after primary or rescue PCI, and is associated with high incidence of CS and complications. Tomoda et al reported that CRP was the only prognostic factor in AMI patients in terms of predicting major adverse cardiac events (MACE), such as recurrent myocardial infarction (MI), the need for target lesion revascularization (TLR) because of restenosis, or cardiac death. However, there is little information available about the concentration of CRP in AMI with CS after primary PCI or on the correlation between CRP concentration and MACE. Thus, the aim of this study was to assess the predictive factors of in-hospital mortality to identify the MACE occurring during a long-term clinical follow-up of patients with AMI and CS after undergoing primary PCI.

Study Patients Of the 1,968 AMI patients admitted to Chonnam National University Hospital (CNUH) via the Emergency Medical Center between January 1999 and December 2002, 289 were diagnosed as having CS after AMI and 147 (66.0±11.0 years, M:F =108:39) were treated with primary PCI. Primary PCI was defined as PCI performed within 6 h of the onset of chest pain; patients who underwent PCI more than 6 h after symptom onset were excluded.

Of the 147 patients enrolled in the present study, 121...
Table 1  Baseline Clinical Characteristics of the 2 Study Groups

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Group I (n=121)</th>
<th>Group II (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>64±10.6</td>
<td>68±10.0</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>94 (77.7)</td>
<td>14 (53.8)</td>
<td>0.030</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45±10.9</td>
<td>37±10.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (23.9)</td>
<td>8 (30.7)</td>
<td>0.547</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (24.8)</td>
<td>8 (30.7)</td>
<td>0.531</td>
</tr>
<tr>
<td>Smoking</td>
<td>66 (54.3)</td>
<td>12 (46.1)</td>
<td>0.440</td>
</tr>
<tr>
<td>Previous MI history</td>
<td>2 (1.6)</td>
<td>1 (3.8)</td>
<td>0.476</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17 (14.0)</td>
<td>2 (7.6)</td>
<td>0.384</td>
</tr>
<tr>
<td>Family history</td>
<td>4 (3.2)</td>
<td>1 (3.8)</td>
<td>0.851</td>
</tr>
</tbody>
</table>

Table 2  Laboratory Findings for the 2 Study Groups

<table>
<thead>
<tr>
<th>Creatine kinase (U/L)</th>
<th>Group I (n=129)</th>
<th>Group II (n=126)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,319±111.4</td>
<td>1,889±6443.2</td>
<td>0.274</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase-MB (IU)</td>
<td>140±67.18</td>
<td>240±5270.8</td>
<td>0.043</td>
</tr>
<tr>
<td>Troponin-I (mg/dl)</td>
<td>27.6±11.8</td>
<td>63±59.7</td>
<td>0.034</td>
</tr>
<tr>
<td>Troponin-T (mg/dl)</td>
<td>4±15.4</td>
<td>8±47.3</td>
<td>0.231</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>159±55.79</td>
<td>136±82.8</td>
<td>0.348</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>168±35.9</td>
<td>136±65.2</td>
<td>0.738</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>40.8±10.8</td>
<td>42±8.7</td>
<td>0.716</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>115±44.4</td>
<td>98±26.0</td>
<td>0.266</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>3.6±3.8</td>
<td>13.8±10.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3  Coronary Angiographic Findings of the 2 Study Groups

<table>
<thead>
<tr>
<th>Infarct-related artery</th>
<th>Group I (n=121)</th>
<th>Group II (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>3 (2.7)</td>
<td>1 (3.8)</td>
<td>0.383</td>
</tr>
<tr>
<td>LAD</td>
<td>62 (51.2)</td>
<td>14 (53.8)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>16 (13.2)</td>
<td>2 (7.7)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>42 (33.2)</td>
<td>9 (34.6)</td>
<td></td>
</tr>
<tr>
<td>No. involved vessels</td>
<td>1</td>
<td>58 (47.9)</td>
<td>0.527</td>
</tr>
<tr>
<td>≥2</td>
<td>63 (52.1)</td>
<td>15 (57.6)</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>58 (47.9)</td>
<td>3 (11.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>B</td>
<td>24 (19.8)</td>
<td>10 (38.4)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>39 (32.2)</td>
<td>13 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Complex lesion (&gt;B1)</td>
<td>63 (52.0)</td>
<td>23 (88.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>TIMI flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53 (43.8)</td>
<td>20 (76.9)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 (9.9)</td>
<td>1 (3.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23 (19.0)</td>
<td>1 (3.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33 (27.3)</td>
<td>4 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Total occlusion on CAG</td>
<td>53 (43.8)</td>
<td>20 (76.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LM, left main disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction; CAG, coronary angiogram.

Clinical and Angiographic Analysis

Table 1 and 2 show the baseline clinical characteristics and laboratory findings of the 2 study groups, respectively. The number of patients in Group I was 129 and in Group II was 126. The demographic characteristics such as age, sex, and family history were not significantly different between the 2 groups. The laboratory findings showed that the levels of creatine kinase, Troponin, and C-reactive protein were significantly higher in Group I than in Group II. The coronary angiographic findings showed that the incidence of LM was significantly higher in Group I than in Group II. The incidence of Complex lesion (>B1) was also significantly higher in Group I than in Group II.

Clinical and angiographic analysis indicated that the incidence of LM and Complex lesion (>B1) were significantly higher in patients with higher creatine kinase, Troponin, and C-reactive protein levels. The incidence of LM and Complex lesion (>B1) were also significantly higher in patients with higher LM, left main disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction; CAG, coronary angiogram.

Results

Baseline Clinical Characteristics

No significant differences were observed in the risk factors of the 2 groups, other than age (64±11 vs 68±10, p=0.004), and group I had more male patients than group II (77.7% vs 53.8%, p=0.03). Mean left ventricular ejection fraction was greater than 50% in both groups. The incidence of hypotension was greater in Group I than in Group II. The incidence of hypercholesterolemia was also greater in Group I than in Group II.

Emergency PCI was performed as soon as possible in patients who were able to undergo CAG (96±56 min after arrival at the Emergency Medical Center). Successful reperfusion was defined as TIMI 3 flow in the infarct-related artery after PCI and ≤25% residual stenosis.

The incidence of MACE, such as death, cerebrovascular accident, AMI, repeated PCI, and coronary artery bypass grafting (CABG), during hospitalization and after 6 months and 1 year of clinical follow-up.

Statistical Analysis

All data are presented as mean±standard deviation. Nominal variables were analyzed using the chi-square test and various continuous variables were compared using the t-test and chi-square test. Differences were considered significant if the p-value was less than 0.05. Also, predictive factors were sought using binary logistic regression analysis after adjusting for age, sex, and the risk factors of coronary artery disease.
fraction (LVEF) was 43.6±13.8% in all patients, and was significantly higher in group I than in group II (45.7±10.9% vs 37.4±10.9%, p=0.001, Table 1).

Laboratory Findings
The concentrations of creatinine kinase (CK)-MB (140.6±121.1 mg/dl vs 240.5±270.8 mg/dl, p=0.043), troponin (Tn) (17 (14.0) 8 (30.8) 0.151, TIMI 3 flow after PCI (%) 92 (76.0) 8 (30.8) <0.001 were lower in group I than group II (Table 2).

CAG Findings
No significant differences in the CAG findings of the 2 groups was observed, other than group I had less cases of frequent complex lesions (52% vs 88%, p=0.001) and total occlusion (43.8% vs 76.9%, p=0.001, Table 3).

Coronary Revascularization
With regard to procedural characteristics, there were no significant differences in door-to-needle time or door-to-balloon time, but intra-aortic balloon pump (IABP) insertion was performed more frequently in group I (20.1% vs 8.7%, p=0.012), TIMI 3 flow after PCI was obtained more frequently in group I (76.0% vs 30.8%, p<0.001), and complications after PCI occurred less frequently in group I (76.0% vs 30.8%, p<0.001, Table 3).

The concentration of CRP negatively correlated with LVEF (r =–0.180, p=0.029), preprocedural TIMI flow (r =–0.209, p=0.011) and post-procedural PCI (r =–0.498, p<0.001) by Pearson’s correlation.

In group I, there were 5 cases of ventricular tachycardia (VT), 6 cases of no-reflow phenomenon, and 2 cases of ventricular septal defect, and 1 patient underwent emergen-

cy CABG for a recurrence of AMI. In group II, there were 6 cases of VT and 3 cases of no-reflow. According to binary logistic regression analysis, the factor most related to in-hospital mortality was TIMI flow <3 after PCI (p=0.02, odds ratio (OR)=1.3, Table 5).

Long-Term Clinical Follow-up
Among the survivors, there were 7 cases of recurrent MI and 10 cases of TLR, but no cases of cardiac death, during 6-month follow-up. After 1-year follow-up, there were 2 cases of recurrent MI, 10 cases of TLR, and 3 cases of cardiac death. The causes of death were sudden cardiac death in 2 cases and intractable VT in 1 case.

Event-Free Survival
At the end of the year of clinical follow-up, 89 patients (60.5%) had survived MACE-free. The patients who developed a MACE had a higher CRP (5.8±4.9 mg/dl vs 2.7±2.1 mg/dl, p=0.003), more frequent multi-vessel involvement (70.6% vs 41.3%, p=0.018) and less than TIMI 3 flow after PCI (55.8% vs 81.6%, p=0.006). The occurrence of MACE during the 1-year follow-up period was associated with a CRP ≥1 mg/dl (p=0.002, OR=6.3) and low TIMI flow after coronary revascularization (p<0.001, OR=7.8, Table 6).

Discussion
CS resulting from AMI is a serious complication with a high mortality rate19 and although the incidence of CS has been reduced by early treatment, it still remains high; for example, in the present study it was 14.7% overall (289/1,968 patients between 1999 and 2002) and despite having been much reduced since 1990, the in-hospital mortality rate was 17.6%.

The causes of CS after AMI are extensive infarction involving several vessels, left main stem (LMS) involvement, ventricular septal defect, extensive mitral regurgitation (MR) and cardiac rupture.3,6,16,19 In the present study, the cause of CS was extensive MI in 130 patients (88.4%), extensive MR in 11 patients (7.5%), LMS involvement in 4 patients (2.7%) and ventricular septal defect in 2 patients (1.4%).

Old age, diabetes mellitus, a previous MI, a large infarct as estimated as by cardiac enzyme assay, the presence of left anterior descending artery occlusion or multiple vessel disease, prolonged occlusion of an infarct-related artery, and decreased LVEF were also associated with CS20–22.

Elevated CRP concentration is associated with a poor

| Table 4 Therapeutic Approach and TIMI Flow After Revascularization in the 2 Study Groups |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Group I (n=121)                           | Group II (n=26) | p value         |
| Door-to-balloon time (min)                 | 99.8±121.1      | 93.6±54.8      | 0.843            |
| IABP insertion (%)                        | 30 (20.1)       | 7 (8.7)        | 0.012            |
| Stent size (mm)                           | 2.6±1.2         | 2.1±1.5        | 0.112            |
| Stent length (mm)                         | 16.4±8.9        | 13.1±10.3      | 0.159            |
| Use of ReoPro (%)                         | 23 (19.0)       | 5 (19.2)       | 0.405            |
| Thrombosis (%)                            | 17 (14.0)       | 8 (30.8)       | 0.151            |
| TIMI 3 flow after PCI (%)                 | 92 (76.0)       | 8 (30.8)       | <0.001           |
| Complication after PCI (%)                | 14 (11.5)       | 9 (34.6)       | 0.041            |

IABP, intra-aortic balloon pump; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention.

| Table 5 Binary Logistic Regression Analysis for In-Hospital Death |
|-----------------------------|-----------------|-----------------|-----------------|
| p value OR 95% CI |
| Low TIMI flow after PCI     | 0.02            | 1.3             | 0–0.49          |
| Age ≥70 years               | 0.15            | 2.90            | 0–2.42          |
| EF <40%                     | 0.14            | 1.63            | 0.53–85.84      |
| CK-MB >10-fold increase     | 0.53            | 2.07            | 0–46.25         |
| CRP >1 mg/dl                | 0.71            | 5,587.24        | 0–56,949.0      |
| Multi-vascular disease      | 0.83            | 1.51            | 0.02–104.98     |
| Total occlusion on CAG      | 0.51            | 2.945           | 0.12–71.13      |
| IABP insertion              | 0.17            | 6.113           | 0–0.46–80.53    |
| Complication after PCI (%)  | 0.55            | 1.988           | 0.20–19.34      |

TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention; EF, ejection fraction; CK, creatine kinase; CRP, C-reactive protein; CAG, coronary angiogram; IABP, intra-aortic balloon pump.

| Table 6 Binary Logistic Regression Analysis for MACE During the 1-Year Clinical Follow-up |
|---------------------------------------------|-----------------|-----------------|-----------------|
| p value OR 95% CI |
| Low TIMI flow after PCI                     | <0.001          | 7.84            | 0–0.31          |
| CRP >1 mg/dl                                | 0.002           | 6.27            | 2.04–22.10      |
| Age ≥70 years                               | 0.512           | 2.90            | 0–0.63          |
| EF <40%                                     | 0.406           | 1.52            | 0.56–4.11       |
| Multi-vascular disease                      | 0.20            | 1.92            | 0.71–5.22       |
| Total occlusion on CAG                      | 0.79            | 1.15            | 0.40–3.27       |
| IABP insertion                              | 0.298           | 1.71            | 0.62–4.71       |
| Complication after PCI (%)                  | 0.15            | 0.84            | 0–1.72          |

MACE, major adverse cardiac event; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention; CRP, C-reactive protein; EF, ejection fraction.
prognosis in ACS. We previously reported that a high CRP concentration is related to a poor prognosis in patients with AMI and poor long-term clinical outcomes after primary or rescue PCI.

In present study, the concentration of CRP was negatively correlated with LVEF, procedural TIMI flow and post-procedural PCI. No differences in risk factors such as hypertension, diabetes, and hypercholesterolemia were observed, but old age, high concentrations of CK-MB, troponin-I, and CRP were associated with death after AMI complicated by CS. Our results suggested that a large infarct and severe inflammation of a coronary artery contributed to in-hospital death after CS.

Revascularization with primary or rescue PCI is important for the survival of AMI patients, especially in patients with CS. The SHOCK trial investigators reported that early revascularization more effectively reduced mortality than from optimal medical therapy, so revascularization should be performed in all patients with CS after AMI as soon as possible. We previously reported that primary PCI reduced in-hospital mortality from 46.7% to 17.2%, and in the present study the in-hospital mortality of the enrolled patients was 17.6%, which suggests that the early revascularization strategy significantly improved short-term survival; however, the moribund group, including the critical patients, were unable to undergo intensive invasive procedures, such as IABP insertion.

Recently, the TIME trial reported that patients aged 75 years or older with angina benefit more from revascularization than from optimal medical therapy in terms of symptom relief and quality of life. Therefore, older patients should undergo an invasive assessment despite a high-risk profile, followed by revascularization if feasible.

The mortality rate for an early revascularization strategy depends on the door-to-needle time, the TIMI flow grade after revascularization, and whether 2 or more vessels or a left main stem lesion are involved. In the present study, there was no significant difference in door-to-balloon time, but the TIMI flow grade was significantly lower in the moribund patients, and they more often had complex lesions and/or total occlusion.

The use of IABP before primary PCI for AMI in all patients with CS is beneficial for patients with depressed left ventricular function. In the present study, more patients in the survivor group had IABP inserted. KIYOSAWA et al reported that IABP was effective in patients with persistent ST elevation after PCI for AMI.

Study Limitations
One limitation is the criteria used to diagnose CS. We did not perform a full diagnostic hemodynamic study, such as right-heart catheterization or measurement of cardiac output, because we wanted to recanalize the infarct-related artery as soon as possible. Another is that our study was a single-center and retrospective clinical study.

Conclusion
Establishing TIMI 3 flow by primary PCI may reduce the in-hospital mortality of patients with CS. A high concentration of CRP was identified as an additional predictive factor of long-term survival after primary PCI for AMI with CS.

Acknowledgement
This work was supported by a grant from Clinical Research Institute of Chonnam National University Hospital.

References
8. Zebrack JS, Anderson JL, Maycock CA, Horne BD, Lair TL, Mulheinest JB; The Intermountain Heart Collaborative (IHC) Study group. Usefulness of high-sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol 2002; 89: 145–149.
18. Hasdai D, Holmes DR Jr, Topol EJ, Berger PB, Criger DA, Hochman JS, et al. Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction in patients receiving reteplase or alteplase: Results from GUSTO-III (Global Use of Strategies to Open...


Circulation Journal Vol.69, February 2005