Incidence, Predictors, and Subsequent Mortality Risk of Recurrent Myocardial Infarction in Patients Following Discharge for Acute Myocardial Infarction

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Background: In the percutaneous coronary intervention (PCI) era, little evidence exists regarding the incidence, predictors and long-term mortality of recurrent myocardial infarction (Re-MI) following discharge for acute myocardial infarction (AMI).

Methods and Results: A total of 7,870 patients who survived AMI were studied with a median follow-up period of 3.9 years: 353 patients (4.5%) experienced Re-MI, with 7 of those dying within 30 days, which was classified as fatal Re-MI. The incidence of Re-MI per year was 2.65% for the first year, and 0.91–1.42% thereafter up to 5 years. Multivariate Cox regression analyses revealed that predictors of Re-MI were diabetes mellitus (hazard ratio (HR): 2.079, P<0.001), history of MI (HR: 1.767, P=0.001), and advanced age (HR: 1.021, P=0.001). These 3 predictors remained significant when angiographic and procedural parameters were incorporated into the analyses. The incidence and adjusted risk of Re-MI increased when these variables were clustered (P<0.001). The all-cause mortality rate was significantly higher in patients with Re-MI than in those without (HR: 2.206, P<0.001).

Conclusions: In post-AMI patients treated in the PCI era, the incidence of Re-MI is low compared with that reported during the past 30 years. Patients' clinical factors of diabetes mellitus, history of MI, and advanced age appear to affect the occurrence of Re-MI after hospital discharge, and Re-MI still carries a risk for subsequent mortality. (Circ J 2013; 77: 439–446)

Key Words: Acute coronary syndrome; Epidemiology; Prevention; Prognosis
Design of the Present Study

The purpose of the present study was to investigate the incidence, predictors and long-term mortality of Re-MI following discharge for AMI in real-world settings. In the present study, the subjects were patients who were discharged alive among the 8,603 consecutive patients registered in the OACIS registry between April 1, 1998, and December 31, 2008. The endpoints of this study were nonfatal or fatal Re-MI after discharge. Re-MI was defined as recurrence of AMI regardless of lesion derived from culprit site, as used in previous studies. A diagnosis of AMI was made if the patient fulfilled at least 2 of the following 3 criteria: (1) history of central chest pressure, pain, or tightness lasting 30 min, (2) typical ECG changes (ie, ST-segment elevation ≥0.1 mV in 1 standard limb lead or 2 precordial leads, ST-segment depression ≥0.1 mV in 2 leads, abnormal Q waves, or T-wave inversion in 2 leads), and (3) an increase in serum creatine kinase levels of twice the upper normal limit in each hospital. All the collaborating hospitals were encouraged to enroll consecutive patients with AMI. During the period of hospitalization, investigative cardiologists and specialist research nurses recorded patient data on demographic variables, medical histories, therapeutic procedures, and clinical events. Following discharge of the patient, further data were obtained at 3 and 12 months after AMI, and annually thereafter for up to 5 years from the hospital medical records, as well as from the patients, family members, and attending physicians by direct interview or written communication.

The study protocol was approved by the ethics committee of each participating hospital. All data acquired in the respective hospitals were transmitted to the data collection center at the Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan for processing and analysis. The corresponding author had full access and validated to all data in the study.

Table 1. Baseline Patient Characteristics Stratified by the Occurrence or Absence of Re-MI

<table>
<thead>
<tr>
<th></th>
<th>No Re-MI (n=7,517)</th>
<th>Re-MI (n=353)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.2±11.8</td>
<td>65.9±11.6</td>
<td>0.263</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7±3.5</td>
<td>23.8±3.3</td>
<td>0.489</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>32.5</td>
<td>47.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>58.4</td>
<td>63.6</td>
<td>0.052</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>44.6</td>
<td>43.8</td>
<td>0.749</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>64.0</td>
<td>67.2</td>
<td>0.212</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>12.0</td>
<td>19.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of angina pectoris (%)</td>
<td>23.1</td>
<td>26.3</td>
<td>0.186</td>
</tr>
<tr>
<td>Onset to admission (h)</td>
<td>3.5 (1.5, 12.8)</td>
<td>4.0 (1.5, 13.0)</td>
<td>0.976</td>
</tr>
<tr>
<td>Onset to admission ≤24h (%)</td>
<td>84.6</td>
<td>84.8</td>
<td>0.895</td>
</tr>
<tr>
<td>Cardiopulmonary arrest on arrival (%)</td>
<td>1.2</td>
<td>0.3</td>
<td>0.116</td>
</tr>
<tr>
<td>ST-segment elevation MI (%)</td>
<td>85.4</td>
<td>83.7</td>
<td>0.368</td>
</tr>
<tr>
<td>Killip ≥II on admission (%)</td>
<td>15.2</td>
<td>18.5</td>
<td>0.095</td>
</tr>
<tr>
<td>Reperfusion therapy (%)</td>
<td>90.2</td>
<td>90.1</td>
<td>0.933</td>
</tr>
<tr>
<td>Emergency PCI (%)</td>
<td>85.3</td>
<td>85.3</td>
<td>0.972</td>
</tr>
<tr>
<td>Peak CK ≥3,000IU/L (%)</td>
<td>33.3</td>
<td>28.3</td>
<td>0.068</td>
</tr>
<tr>
<td>EF before discharge (%)*</td>
<td>51.0±11.7</td>
<td>52.9±11.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Antiplatelet therapy (%)</td>
<td>97.3</td>
<td>97.5</td>
<td>0.858</td>
</tr>
<tr>
<td>ACEI (%)</td>
<td>50.6</td>
<td>55.2</td>
<td>0.086</td>
</tr>
<tr>
<td>ARB (%)</td>
<td>22.7</td>
<td>21.2</td>
<td>0.510</td>
</tr>
<tr>
<td>β-blockers (%)</td>
<td>44.2</td>
<td>39.1</td>
<td>0.060</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>37.6</td>
<td>35.7</td>
<td>0.470</td>
</tr>
</tbody>
</table>

*EF was measured before discharge by echocardiogram using the Teichholz method.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; EF, ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; Re-MI, recurrent MI.

Statistical Analysis

Categorical variables were compared by chi-square test with continuity correction or Fisher’s exact test. Continuous variables are presented as median (25th, 75th percentiles) or mean value±SD, and were compared by unpaired t-test or 2-tailed Wilcoxon rank sum test between patients with and without occurrence of Re-MI. The cumulative Re-MI and mortality rates were determined by Kaplan-Meier method. The rates of Re-MI and mortality were compared by log-rank test. A likelihood ratio test was performed to identify the most appropriate changing point of hazard for Re-MI. To identify predictors of the occurrence of Re-MI, Cox regression analysis was performed with 2 models: model 1 was derived from overall cohort and model 2 was derived from patients underwent emergency coronary angiography. Variables with a P value <0.20 shown in Table 1 (male sex, diabetes mellitus (DM), hypertension, history of MI, history of angina pectoris, cardiopulmonary events, and family members, and attending physicians by direct interview or written communication.

The study protocol was approved by the ethics committee of each participating hospital. All data acquired in the respective hospitals were transmitted to the data collection center at the Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan for processing and analysis. The corresponding author had full access and validated to all data in the study.
Re-MI After AMI in the PCI Era

Among the 8,603 consecutive AMI patients who were registered into the OACIS registry, a total of 733 (8.5%) patients died in hospital, so we enrolled the remaining 7,870 patients who were discharged alive. The median age of the study sample was 66.2 years, and 75.8% were men. Baseline patient characteristics stratified by the presence or absence of Re-MI are summarized in Table 1. Patients who experienced Re-MI were more likely to have DM and a history of MI. In addition, a trend towards a higher frequency of Killip ≥2 on admission was observed in patients with Re-MI. Among patients who underwent percutaneous coronary intervention (PCI) followed by emergency coronary angiography (n=6,716, 85.3%), those with Re-MI were less likely to have had thrombus aspiration.

Table 2. Angiographic and Procedural Results in AMI Patients Who Underwent Emergency Coronary Angiography and PCI

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Re-MI (n=6,415)</th>
<th>Re-MI (n=301)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial TIMI grade flow 3 (%)</td>
<td>16.0</td>
<td>15.8</td>
<td>0.924</td>
</tr>
<tr>
<td>Collateral circulation (%)</td>
<td>36.1</td>
<td>37.3</td>
<td>0.672</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>37.0</td>
<td>42.1</td>
<td>0.060</td>
</tr>
<tr>
<td>Left anterior descending artery (%)</td>
<td>41.4</td>
<td>39.9</td>
<td>0.582</td>
</tr>
<tr>
<td>Stent implantation (%)</td>
<td>71.0</td>
<td>70.1</td>
<td>0.708</td>
</tr>
<tr>
<td>BMS/DES (%)</td>
<td>97.1/2.9</td>
<td>98.8/1.2</td>
<td>0.096</td>
</tr>
<tr>
<td>Thrombectomy (%)</td>
<td>39.1</td>
<td>31.8</td>
<td>0.011</td>
</tr>
<tr>
<td>Final TIMI grade flow 3 (%)</td>
<td>87.9</td>
<td>90.4</td>
<td>0.189</td>
</tr>
</tbody>
</table>

AMI, acute MI; BMS, bare metal stent; DES, drug-eluting stent; TIMI, Thrombolysis In Myocardial Infarction. Other abbreviations as in Table 1.

Results

Patients’ Backgrounds

Among the 8,603 consecutive AMI patients who were registered into the OACIS registry, a total of 733 (8.5%) patients died in hospital, so we enrolled the remaining 7,870 patients who were discharged alive. The median age of the study sample was 66.2 years, and 75.8% were men. Baseline patient characteristics stratified by the presence or absence of Re-MI are summarized in Table 1. Patients who experienced Re-MI were more likely to have DM and a history of MI. In addition, a trend towards a higher frequency of Killip ≥2 on admission was observed in patients with Re-MI. Among patients who underwent percutaneous coronary intervention (PCI) followed by emergency coronary angiography (n=6,716, 85.3%), those with Re-MI were less likely to have had thrombus aspiration.
therapy, and tended to have a higher rate of multivessel disease (Table 2). In addition, the number of patients treated with drug-eluting stents (DES) was low and did not differ between the 2 groups.

**Incidence of Re-MI**

During a median follow-up period of 1,424 days (525–1,792; 3.9 years), Re-MI occurred in 353 patients (4.5%), with 7 of those patients classified as fatal-MI. The rate of Re-MI per year was 2.65%, 0.94%, 0.91%, 1.09%, and 1.42%, for the first, second, third, fourth, and fifth year, respectively. Figure 1 shows the Kaplan-Meier curve of the cumulative Re-MI rate in AMI patients during the 5 years following discharge. A likelihood ratio test showed that there was the greatest change in AMI patients during the 5 years following discharge. A step-wise regression analyses were further performed and confirmed that age, DM, and history of MI were predictors of Re-MI in both the whole and angiographic populations, respectively (Table 3, Models 1b and 2b). The incidence and adjusted hazard ratio (HR) of Re-MI increased significantly when these 3 variables were clustered together (Table 4, Figure 2).

As shown in Figure 3, mortality was significantly higher in patients who experienced Re-MI during the follow-up period than in those who did not (15.9% vs. 6.3%; HR 2.206, 95% CI 1.580–3.122, P<0.001). These results were unchanged when patients with a history of MI were excluded (14.8% vs. 5.5%; HR 2.496, 95% CI 1.580–3.122, P<0.001). Adjusted HR of Re-MI for subsequent mortality was 2.528 (95% CI 0.371–4.664, P=0.003) for males and 1.888 (95% CI 1.296–2.748, P=0.001) for females (P for interaction=0.819). Treatments during PCI and medication at discharge in diabetic patients with and without Re-MI are listed in Table 5.

**Discussion**

The present study firstly investigated the incidence and predictors of Re-MI, as well as subsequent mortality associated with Re-MI, in the contemporary PCI era. The results showed that...
Re-MI After AMI in the PCI Era

Table 4. Incidence and Adjusted HR of Re-MI According to the Clustering of Identified Risk Factors of Re-MI

<table>
<thead>
<tr>
<th>No. of risk factors of Re-MI</th>
<th>0 (n=2,328)</th>
<th>1 (n=3,764)</th>
<th>2 (n=1,570)</th>
<th>3 (n=208)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Re-MI, n (%)</td>
<td>79 (3.4%)</td>
<td>143 (3.8%)</td>
<td>108 (6.9%)</td>
<td>23 (11.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.0 (Reference)</td>
<td>1.325</td>
<td>2.211</td>
<td>3.299</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>–</td>
<td>0.915–1.918</td>
<td>1.463–3.344</td>
<td>1.569–6.938</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>–</td>
<td>0.137</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Age ≥66 years (median value) was used as an independent variable predicting Re-MI, instead of age as a numerical value for independent prediction of Re-MI.

*P value for trend.

Abbreviations as in Tables 1,3.

Re-MI occurred at rates of 2.65% for the first year, and 0.91–1.42% per year thereafter and that Re-MI still carries a risk for subsequent mortality in post-AMI patients in the contemporary PCI era.

Incidence of Re-MI in the Contemporary Era

The incidence of Re-MI in the present study was lower compared with those reported in previous studies conducted between 1980 and early 2000,21 especially those reported in observational studies, ranging from 6.7%22 to 8.2%,23 during a 1-year follow-up period. Although it is speculative, there are several possible explanations for the decrease in Re-MI rate. First, the number of patients who underwent emergency PCI in the present study was greater than in past studies. Because primary PCI is shown to be associated with lower rates of Re-MI and other cardiac events than thrombolytic therapy,5 the increase in emergency PCI might have decreased Re-MI in the present study; implementation of PCI itself and concomitant use of intensive antiplatelet therapy could be contributing to the decrease of Re-MI, probably by reducing incidence of both re-occlusion of the culprit vessel and development of new lesions. Second, better implementation of secondary prevention programs including cardiac rehabilitation and medications such as aspirin,4 β-blockers,8 statins,7 and angiotensin-converting enzyme inhibitors9 may have contributed to the reduced occurrence of Re-MI observed here.

It was also an interesting finding that the steepness of the Kaplan-Meier curve representing the cumulative occurrence rate of Re-MI was more gradual after 1 year (Figure 1). Although the cause of this finding is unclear, several explanations may be considered. First, subclinical vascular inflammation may persist for approximately 1 year, playing a role in the occurrence of Re-MI regardless of the culprit lesion. Second, occlusive thrombus formation occurring between 1 and 12
months after stent implantation, the so-called “late stent thrombosis” could be a reason, although we do not have sufficient information. Third, discontinuation of dual antiplatelet therapy may influence the occurrence of Re-MI. In general, neointimal hyperplasia occurs up to 6 months after bare metal stent (BMS) implantation, and then regression of the neointima is observed. Therefore, some physicians may have decided to discontinue dual antiplatelet therapy during this period, affecting to the occurrence of Re-MI. Fourth, procedure-related Re-MI may also occur during the early phase. Repeated PCI resulting from neointimal hyperplasia following BMS implantation could induce Re-MI. To date, the frequency of DES usage is low in our registry. However, the number of patients who receive DES is expected to increase in the future, which may change the timing and incidence of Re-MI because of late stent thrombosis. In addition, formation of neo-atheroma inside the stent, instead of chronic inflammation, may play an important role in the development of late-phase Re-MI in patients treated with DES. Therefore, investigations regarding the incidence of Re-MI in post-AMI patients should continue in the DES era.

Predictors of Re-MI in the Contemporary Era
Kernis et al previously investigated the incidence of early Re-MI after primary PCI in 3,646 AMI patients within 12 h of onset in a pooled analysis of PAMI trials. They identified that predictors of Re-MI occurrence within 30 days of primary PCI for AMI were Killip >1, LVEF <50%, final coronary stenosis >30%, and presence of coronary dissection and thrombus. In their report, angiographic predictors were stronger risk factors for Re-MI within 30 days than clinical factors. In contrast, we found that DM, history of MI, and advanced age, rather than angiographic factors, were independent predictors of Re-MI occurrence. Furthermore, we found that the incidence and adjusted HR of Re-MI increased significantly when these determinants were clustered together (Table 4, Figure 2). These differences between Kernis et al and our study could be explained by the difference in the time phase after onset; we examined the long-term incidence of Re-MI in post-AMI patients after discharge, whereas Kernis et al investigated the incidence at 1 month after the onset of AMI (Table 3). Therefore, considering the results together, treatment approaches that address angiographic-, and clinical-related factors may effectively reduce the risk of Re-MI in the early, and late phases of AMI recovery, respectively. However, the angiographic factors that affect the incidence of early Re-MI might have been changed these days, because the increased usage of coronary stents at the time of emergency PCI could have reduced the incidence of the angiographic factors that Kernis et al investigated.

Mortality Risk Associated With Re-MI
In the present study, the incidence of all-cause mortality was significantly higher in patients with recurrence of myocardial infarction (Re-MI) than in those without it (blue line) (15.9% vs. 6.3%, P<0.001 by log-rank test). X-axis indicates the number of patients at risk.
may induce fatal arrhythmia or heart failure, could cause the increased mortality in patients with nonfatal Re-MI. These observations that a prior history of Re-MI and future occurrence of Re-MI affect subsequent mortality are consistent with results been shown in previous reports. Benhorin et al examined the prognostic significance of nonfatal Re-MI after AMI in the 1980s, and found that Re-MI was an independent predictor of subsequent cardiac mortality and was associated with a 3-fold higher risk of death. Law et al performed a meta-analysis using the data from the studies in which follow-up was completed by 1980, and found a 2-fold increase in mortality after discharge in patients with a history of prior MI on admission; cardiovascular mortality after hospital discharge were approximately 20% in the first year and 10% per year thereafter for those with prior MI, vs. approximately 10% in the first year and 5% per year thereafter for those without. These lines of evidence suggest that, regardless of the differences in study design, year, and treatment strategy among the studies, occurrence of Re-MI remains a mortality risk in post-MI patients since decades ago. In other words, recurrence of AMI still carries a mortality risk in contemporary settings, despite recent advances in secondary prevention that have decreased mortality after AMI. It is considered that not only the factors associated with the patient’s genetic background, but also those secondary to the accumulation of other metabolic lifestyle factors, may influence Re-MI occurrence. Therefore, lifestyle modifications, such as adherence to medication, cessation of smoking, and body-weight control, could help reduce the incidence of Re-MI in post-AMI patients following discharge. Particularly, DM, a significant predictor for Re-MI in both the present and previous studies, could be the strong target for treatment to prevent the occurrence of Re-MI, because intervention can be implemented, unlike advanced age or a prior history of MI. As shown in Table 5, in diabetic patients, treatments during hospitalization including stent implantation, rates of dual antiplatelet therapy, β-blockers, statins and thiazolidinediones tended to be lower in patients with than in those without Re-MI, suggesting suboptimal treatment strategies might be attributable to an increased risk of Re-MI after discharge. The usage of thrombectomy was significantly lower in diabetic patients with in than those without Re-MI. Removal of thrombi at the culprit lesion may play an important role in reducing the risk of Re-MI.

Study Limitations

Several limitations of our study warrant mention. First, we had no data to determine if Re-MI was derived from the infarct-related artery, and if Re-MI occurred because of stent thrombosis or PCI procedures. Second, we did not have information on variables such as malposition and dissection assessed by intravascular ultrasound after PCI, which could affect thrombosis and subsequent Re-MI. Also there was no information regarding blood pressure, and residual stenosis, which could also influence the occurrence of Re-MI. Third, because (DES) were not been usually available in Japan for the treatment of AMI throughout the study period, the present results might not represent those in the “real” contemporary PCI era where DES are available for the treatment for AMI. Fourth, LVEF was assessed by echocardiography using the Teichholz method, a M-mode technique widely used in large trials with limited reliability on geometric assumption. Therefore, caution is needed when interpreting the data with those obtained from other assessments of LVEF. Fifth, because our registry was initiated in 1998, we did not use the new definition of AMI, rather the traditional WHO criteria for the diagnosis of AMI, as used in recent cohort observational studies in Japan. Finally, we cannot exclude the possibility that the actual incidence of Re-MI was underestimated, because a number of patients whose cause of death was categorized as sudden death may have died from Re-MI.

In conclusion, we determined that in post-AMI patients who were predominantly treated with PCI, the incidence of Re-MI during a median follow-up period of 1,424 days (3.9 years) following discharge was 4.5%. Notably, the incidence of Re-MI declined from 1998 to 2008, and was lower than the rates reported in studies conducted in the pre-reperfusion and thrombolytic eras. The clinical background of the patients, particularly DM, history of MI, and advanced age, were independently associated with the occurrence of Re-MI, rather than angiographic parameters, and the incidence and risk of Re-MI increased with increasing number of these risk factors. Although nearly all cases of Re-MI were not fatal, Re-MI was associated with a 2-fold higher risk of subsequent mortality. To prevent Re-MI after discharge, the management of identified risk factors should lead to improved mortality in post-AMI patients. Further investigations are needed to identify the types of intervention that would be most beneficial to reduce the occurrence of Re-MI and improve long-term survival.

Acknowledgments

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References


