Primary Percutaneous Coronary Intervention Lowers the Incidence of Ischemic Mitral Regurgitation in Patients With Acute ST-Elevated Myocardial Infarction

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Background: The impact of primary percutaneous coronary intervention (PCI) for acute ST-elevated myocardial infarction (STEMI) on the incidence of ischemic mitral regurgitation (IMR) is unclear.

Methods and Results: Between January 2000 and December 2004, 318 patients presenting with first acute STEMI were enrolled in this study. Two hundred and twelve (66.67%) patients received PCI (PCI group), and 106 age- and Killip class-matched patients received medical management (non-PCI group). The median duration of follow up was 40.46 months. Compared to the non-PCI group, the PCI group had 14.6% (9.9% vs 24.5%) fewer patients with moderate or severe IMR (P<0.001). Univariate analysis demonstrated IMR was significantly associated with advanced age, higher Killip score, and posterior myocardial infarction (MI). Moreover, IMR was strongly associated with a lower left ventricular (LV) ejection fraction, larger left atrial dimension (LAd), and a larger LV end-systolic and LV end-diastolic volumes (LVEDV) (all P<0.01). Multivariate analysis revealed the odds of IMR in the PCI group was 0.208 times those of the non-PCI group (P<0.001). Additionally, moderate or severe IMR was independently correlated with advanced age, inferior MI, Killip class ≥3, larger LAd, and larger LVEDV (all P<0.05). Furthermore, long-term survival time was longer in the PCI group without IMR than in the non-PCI group with IMR (all P<0.01).

Conclusions: PCI for first acute STEMI was associated with lower incidence of IMR. Advanced age, inferior MI, Killip class ≥3, larger LAd and LVEDV were risk factors associated with IMR development. (Circ J 2010; 74: 2386–2392)

Key Words: Acute myocardial infarction; Ischemic mitral valve regurgitation; Primary coronary intervention

Ischemic mitral regurgitation (IMR) is mitral incompetence resulting from coronary artery disease in the absence of intrinsic valve lesions. This common complication of acute myocardial infarction (AMI) occurs in 15–64% of patients after this event, and is an independent predictor of future cardiovascular mortality. The presence and degree of IMR are associated with lower long-term survival in patients after a first non-ST-segment elevation acute coronary syndrome has occurred. Mild and moderate functional mitral insufficiency lead to a worse prognosis in patients undergoing coronary artery bypass grafting (CABG).

In addition, IMR severity is positively associated with development of heart failure after AMI. Although primary percutaneous coronary intervention (PCI) for AMI is known to improve outcome and that IMR after myocardial infarction (MI) worsens outcome, the effect of primary PCI on IMR incidence has not been specifically studied. This study was designed to measure the impact of primary PCI on the incidence of IMR in first acute ST-elevated MI (STEMI) patients by comparing the incidence and severity of IMR in patients treated with and without primary PCI.
Methods

Patient Population
In our hospital, all patients with acute STEMI are considered eligible for primary PCI. Between January 2000 and December 2004, 1,173 consecutive patients admitted for an AMI were screened for the study. Inclusion criteria were patients who had acute STEMI for the first time, and those who had 2-dimensional (D) echocardiography performed at our institution within 30 days post-MI; these patients were eligible for enrolment. Exclusion criteria included: (1) previous MI (defined as MI occurring >30 days before current admission); (2) history of PCI or cardiac surgery; (3) significant valvular heart disease, including rheumatic heart disease or mitral valve prolapse, detected during echocardiography performed prior to admission; (4) dilated cardiomyopathy or congenital heart disease; and (5) no longer receiving follow-up care at our institution or lost to follow-up despite contact by mail and phone survey. Two hundred and twelve age- and Killip class-matched patients presenting with acute STEMI of <12h duration underwent primary PCI (Group 1 [PCI(+)]) and 106 patients underwent intensive medical management who had a delayed presentation to the institution or had refused PCI (Group 2 [PCI(–)]), were recruited for this study. The collection of long-term follow-up data was planned in the protocol and approved by the authorized ethics committee. Informed consent was obtained from each study subject before the study.

Procedure and Protocol of Primary PCI
For patients undergoing primary PCI, a transradial artery approach using a 6-French arterial sheath is a routine treatment for acute STEMI at Kaohsiung Chang Gung Memorial Hospital unless Allen’s test has been positive on both sides since 2001. Before 2001, transfemoral arterial approach was routinely used. The details of this procedure and protocol has been described in our previous report.  

A 6-French Kimny guiding catheter (Boston Scientific, Scimed, Inc, Maple Grove, MN, USA) was used for both the diagnosis of coronary arterial occlusion and primary PCI. Intra-aortic balloon support was performed via the right femoral artery in patients experiencing acute pulmonary edema associated with an unstable condition or hemodynamic instability.

Before June 1998, primary balloon angioplasty was performed in patients with AMI as stents were not available in our country. After stents became accessible, primary stenting was performed for all eligible patients. Patients received a loading dose of ticlopidine (before 2003) or clopidogrel (since 2003) in the emergency room, followed by treatment with a maintenance dose of either ticlopidine or clopidogrel for at least 4 weeks if stent deployment was performed. Aspirin (100 mg orally once daily) was given indefinitely to each patient. Other commonly prescribed medications also included angiotensin-converting enzyme inhibitors, statins, β-blockers, isorotinate, and diuretics.

Definitions
AMI was defined as: (1) typical chest pain lasting for more than 30 min with ST-segment elevation >1 mm in 2 consecutive precordial or inferior leads; or (2) typical chest pain lasting for more than 30 min with a new onset of complete left bundle branch block. Reperfusion time was defined as the time from symptom onset of chest pain to the first balloon inflation. Procedural success was defined as a reduction to residual stenosis of <30% by balloon angioplasty or successful stent deployment at the desired position with a residual stenosis <10%, followed by Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery (IRA).

Echocardiographic Examination
Within 30 days after incurring an AMI, each subject underwent standardized 2-D color Doppler echocardiography with a commercially available system (Sonos 5500 and 7500, Philips Medical Systems, Bothell, WA, USA) using a S3 transducer. Echocardiographic parameters were analyzed, and included left atrial dimension (LAd), left ventricular (LV) end-systolic (LVES) volume, LV end-diastolic (LVED) volume, and LV ejection fraction (LVEF).

Assessment of Mitral Regurgitation (MR)
Mitral regurgitation severity was evaluated during echocardiographic examination using colour Doppler flow mapping criteria according to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) (maximal MR jet area-to-left atrial area ratio). MR severity was quantified using a 4-point scale: 0, if the percentage of maximal MR colour jet area-to-maximal left atrial area was 0%; 1 (trace MR), if the area was ≤10%; 2 (mild MR), if 10–19%; 3 (moderate MR), if 20–39%; and 4 (severe MR), if ≥40%.

Clinical and Sociodemographic Variables
Clinical and sociodemographic variables (including age, gender, body mass index (BMI), current smoker) were gathered from subjects’ histories and physical examinations as documented in their medical records. Diabetes mellitus was considered to be present if a random blood glucose level >200 mg per deciliter was observed within 24 h of admission or if there was a previous diagnosis of diabetes mellitus. Hypertension was defined (based on criteria of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7]) as a systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg within 24 h of admission. Hyperlipidemia was considered to be present when the total cholesterol was >200 mg per deciliter or if triglycerides were >150 mg per deciliter within 24 h of admission. Killip class was assessed within 24 h of admission to our hospital. All coronary angiograms were analyzed from cardiac catheterization reports in the medical records.

Statistical Analysis
Data are expressed as the mean (± standard deviation) or median (interquartile range) for continuous variables, and number (%) for categorical variables. Patient characteristics between the 2 treatment groups (PCI and non-PCI) and associations between risk factors and IMR grades were compared using a Student’s t-test for normal continuous data, a Wilcoxon rank sum test for skewed continuous data, and a chi-squared test for categorical data. The IMR grade was classed as (−) negative or (+) positive. Negative IMR was defined as trace or mild IMR, whereas positive IMR was defined as moderate or severe IMR. Factors in the univariate analysis (Student’s t-test, Wilcoxon rank sum test and chi-squared test) were entered into a forward stepwise multiple logistic regression model. Multivariate logistic regression was used to examine the effect of PCI and of individual risk factors on IMR grade after adjusting for all possible confounding factors. The Kaplan–Meier’s product limit survival
**Table 1.** Baseline Characteristics of AMI Patients (n=318), With and Without PCI

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>PCI (n=212)</th>
<th>Non-PCI (n=106)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean±SD)*</td>
<td>63.9±12.6</td>
<td>64.4±13.7</td>
<td>0.741</td>
</tr>
<tr>
<td>Female gender†</td>
<td>46 (21.7)</td>
<td>27 (25.5)</td>
<td>0.451</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>24.76±4.62</td>
<td>23.82±3.36</td>
<td>0.066</td>
</tr>
<tr>
<td>Current smoking†</td>
<td>131 (61.8)</td>
<td>68 (64.2)</td>
<td>0.682</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>101 (47.6)</td>
<td>47 (44.3)</td>
<td>0.578</td>
</tr>
<tr>
<td>Hyperlipidaemia††</td>
<td>74 (34.9)</td>
<td>27 (25.5)</td>
<td>0.088</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>83 (39.2)</td>
<td>44 (41.5)</td>
<td>0.686</td>
</tr>
<tr>
<td>Anterior MI†</td>
<td>139 (65.6)</td>
<td>66 (62.3)</td>
<td>0.562</td>
</tr>
<tr>
<td>Inferior MI†</td>
<td>72 (34.0)</td>
<td>42 (39.6)</td>
<td>0.321</td>
</tr>
<tr>
<td>Posterior MI†</td>
<td>12 (5.7)</td>
<td>6 (5.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Lateral MI†</td>
<td>11 (5.2)</td>
<td>2 (1.9)</td>
<td>0.161</td>
</tr>
<tr>
<td>LA dimension (mm)**</td>
<td>35 (20, 53)</td>
<td>35 (20, 50)</td>
<td>0.606</td>
</tr>
<tr>
<td>LVES volume (ml)**</td>
<td>54 (13, 247)</td>
<td>58 (14, 209)</td>
<td>0.334</td>
</tr>
<tr>
<td>LVED volume (ml)**</td>
<td>124 (27, 364)</td>
<td>130 (54, 272)</td>
<td>0.712</td>
</tr>
<tr>
<td>LVEF (%)*</td>
<td>53.69±15.06</td>
<td>50.54±15.65</td>
<td>0.083</td>
</tr>
<tr>
<td>Killip class†</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>102 (48.1)</td>
<td>51 (48.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18 (8.5)</td>
<td>9 (8.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>56 (26.4)</td>
<td>28 (26.4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36 (17.0)</td>
<td>18 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Total CK-MB level (μ/ml)**</td>
<td>163.88 (20.00, 1916.39)</td>
<td>38.51 (20.00,1168.64)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Post-PCI TIMI flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>186 (88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (1)</td>
<td></td>
<td></td>
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</tbody>
</table>

AMI, acute myocardial infarction; PCI, primary percutaneous coronary intervention; MI, myocardial infarction; LA, left atrial; LVES, left ventricular end-systolic; LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; CK, creatine kinase; TIMI, Thrombolysis In Myocardial Infarction.

Continuous data are presented as mean±standard deviation or median (interquartile range) and tested by a *Student's t-test or a **Wilcoxon rank sum test; categorical data are expressed as number (frequency) and tested by a †chi-squared test.

††Significantly different between PCI and non-PCI groups, P<0.05.
analysis was used to evaluate the cumulative mortality rates of acute STEMI with and without PCI, complicated with and without IMR. Differences between groups were compared by the log-rank test. P values <0.05 were considered statistically significant, and all analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC, USA).

Results

There were 318 patients enrolled in this study with first acute STEMI who received echocardiography studies. Eight hundred and fifty-five of 1,173 patients admitted to CCU during the indexed period were excluded for the following reasons: (1) patient with non-STEMI (n=251); (2) presence of rheumatic mitral stenosis (n=3); (3) history of known rheumatic moderate MR (n=1); (4) prior MI (n=31); (5) prior history of PCI (n=47); (6) patient lost to follow up from our institution after discharge (n=51); and (7) furthermore, to limit the bias related to the effect of age and Killip class, 471 patients were excluded. Of the 318 patients included in the study, 212 (66.67%) underwent PCI and 106 (33.33%) were treated medically (Figure 1). The mean length of follow up was 41.48 months (SD: 24.29 months; median: 40.46 months; range: 0–82 months).

Demographic and Clinical Characteristics

There was no significant difference in relation to features distinguishing the PCI group from the non-PCI group, which included age, gender, body mass index, current smoking, hypertension, hyperlipidemia, diabetes mellitus and Killip class (Table 1). In addition, there was no difference between patients with PCI in terms of location of AMI (anterior MI, inferior MI, posterior MI and lateral MI) compared to those without PCI. LAd, LV function, as shown by a LVEF, LVED and LVES volumes, were neither dissimilar in patients with PCI than in those receiving medical treatment alone. Total creatine phosphokinase-MB was remarkably and significantly higher in patients with PCI compared with non-PCI patients. PCI resulted in successful coronary reperfusion (defined as a post-PCI with TIMI flow 3 in the infarct-related artery in 88% receiving this intervention).
Rheumatic Mitral Regurgitation

Risk Factors for IMR Development
Univariate analysis revealed that patients with PCI were significantly less likely to have positive IMR. A number of other factors were also related to IMR severity. Patients with positive IMR were significantly more likely than those with negative IMR to have the following characteristics: advanced age, lower BMI, non-smoker, higher Killip class (≥3), and a higher likelihood of posterior MI, and a borderline likelihood of anterior MI (all P<0.05). Other characteristics of patients with positive IMR included: a lower LVEF; and larger LAd, LVES and LVED volumes. In multivariate analysis, after controlling for all possible confounding factors, PCI remained significantly associated with a lower odds of positive IMR.

Factors associated with a significantly higher risk of positive IMR included: advanced age, Killip class ≥3, increased LAd, increased LVED volume, and isolated inferior MI (Tables 2,3; Figure 1).

Effect of MI Type on IMR Development
When MI type (isolated inferior over isolated anterior) was used as a covariate, patients with an isolated inferior MI were 2.37 times more likely to have moderate or severe IMR than those with an anterior MI. Patients with PCI had a greater significantly lower incidence of positive IMR than non-PCI patients in both isolated pure anterior and inferior MI. Thus, PCI was associated with a significantly reduced risk of positive IMR in patients with inferior or anterior MI (Tables 3,4).

Effect of PCI and IMR on Long-Term Survival Rate
The 7-year cumulative survival of acute STEMI patients with and without IMR was related to having or not having PCI. Compared to acute STEMI patients with non-PCI, those who received PCI had a higher survival rate. In subgroup analysis, a comparison based on the presence or absence of IMR, notably within the PCI group, found that those without IMR had an outstandingly higher survival rate. By contrast, the non-PCI group with IMR had the worst survival rate. Of note was the PCI group with IMR, who had a survival rate even lower than the non-PCI group without IMR. Those patients who had significant IMR with or without PCI, fall into the lower strata in terms of survival rate. Overall, compared to acute STEMI patients with non-PCI, those who received PCI without IMR, had remarkably the highest survival rate (Figure 2).
Discussion

The present study, which investigated the impact of primary PCI on reducing ischemic-related MR, provided several striking clinical implications. First, IMR was associated with a higher incidence of advanced age, female gender, advanced Killip score, higher LV remodeling and notably lower LV function as compared to those without IMR. A previous study has identified female gender as a predictor of ischemic risk in the clinical settings of acute coronary syndrome. Our study was consistent with the studies by Bursi et al, which pointed out that patients with higher grade ischemic mitral regurgitation were more likely to be older women.

Our echocardiographic examination showed that lower LVEF, increased LAD and LVED volume were associated with more severe IMR. Enlarged LVES and LVED volumes are thought to indicate ventricular remodeling, in which the posterior papillary muscle that tethers the mitral valve is displaced, preventing leaflet closure and thus resulting in IMR. Constituents to the development of heart failure after AMI included the loss of functioning myocytes, development of myocardial fibrosis, and subsequent LV remodeling. The ensuing chamber dilatation and neurohormonal activation lead to progressive LV dysfunction. The presence of IMR further inflicts the hemodynamic load during a period of active LV remodeling. Aronson et al reported that there is a graded independent association between the severity of ischemic MR and the development of heart failure after MI. Ishikawa et al reported ischemic MR to be a common cause of congestive heart failure, caused by the process of MI remodeling. The present study further strengthens the context of LV remodeling in the presence of IMR, in that it eventually associates with a lower LVEF and a higher Killip score.

Second, as compared with anterior-wall infarction, inferior-wall infarction had a higher incidence of IMR. The main mechanism of IMR is tethering of the posterior mitral leaflet, secondary to LV dilatation. There is a strong association between advanced wall motion abnormalities in the posterobasal segment and significant mitral regurgitation. Inferior and inferior-lateral LV dyssynergy appears to be more important than global systolic dysfunction in the development of significant ischemic mitral regurgitation. Our study explored the relationship between moderate or severe IMR and the type of AMI, using isolated inferior MI over isolated anterior MI as one covariate, and found that patients with inferior MI were 2.37 times more likely to have moderate or severe IMR than those with anterior MI. Additionally, we examined anterior and inferior MI separately (Table 4). PCI remains more effective in decreasing the incidence of moderate or severe IMR for both inferior and anterior MI, compared to results for patients with no PCI.

Third, the results of the current study demonstrated that PCI remarkably decreased the incidence of moderate or severe IMR in patients with a first acute STEMI compared with those not receiving PCI. Theoretically, early coronary revascularization might be useful in terms of minimizing infarct size and improving LV remodeling. Options for myocardial revascularization include thrombolysis or PCI in the early period after AMI, or CABG for suitable patients. PCI is the preferred treatment modality for patients with acute coronary syndrome. Our data shows that early or rapid coronary revascularization with PCI was strongly associated with a significant risk reduction for having moderate or severe IMR by 14.6%. This is also supported by the multi-ple logistic regression analysis of patients with PCI, having positive IMR among isolated anterior and inferior STEMI patients resulted in an odd ratio of 0.208 (95% confidence interval, 0.096–0.451; P<0.001).

Finally, this study notably looks into the long-term survival rate based on the receipt of PCI, accompanied with or without IMR. IMR has been imputed as an indicator of poor prognosis in acute and early phases after MI. Chronic IMR following MI also entails a negative impact on long-term survival. There is a community based study of ischemic MR among 30 day survivors of MI that showed moderate or severe MR to be associated with a 1.6-fold increased risk of death at a 5-year follow up. However, in the chronic post-MI phase, prognostic implications of IMR presence or absence concomitant with or without the receipt of PCI are poorly defined. As early as 1989, coronary angioplasty was found to be useful for treating IMR in 5 patients and was associated with a favourable long-term outcome. Emergent PCI has been shown to improve the outcome in IMR in follow-up studies. Our study is in accordance with their findings in that emergent coronary angioplasty is associated with a favourable long-term outcome. Moreover, this study further attested patients with first acute STEMI who received PCI but not accompanied by IMR with strikingly the greatest long-term survival rate compared to those patients without PCI accompanied by IMR. In contrast, the non-PCI group with IMR had the worst prognosis. Additionally, the survival curve depicted the presence of significant IMR irrespective of whether PCI was provided; both groups fall into the lower strata. This denotes the progression after MI was markedly affected by the presence of IMR. This is in agreement with the observation made by Grigioni et al, who showed that in the chronic phase after MI, IMR presence is associated with excess mortality, which is independent of baseline characteristics and degree of ventricular dysfunction. Mortality risk is related directly to the degree of IMR. This study further demonstrated that in the chronic post-MI phase, prognostic implications of IMR presence, irrespective PCI receipt, is associated with a poorer outcome.

Study Limitations

The strength of this study includes its large STEMI population base. It provides a comprehensive view of the contemporary treatment of Asian patients with acute STEMI in the era of PCI.

The present study had some limitations. First, although there were a large number of subjects, it was an observational and non-randomized study. There is a possibility that unidentified factors might have influenced the results. The patients without PCI might have a bias, such as comorbidity, age, gender, and BMI. However, a prospective study of AMI patients in which receipt of PCI was randomized would be not feasible for ethical reasons. We have included all the confounders in the multivariate, stepwise forward regression model, to control the baselines biases. All the same, our results showed that the likelihood of IMR could have been predicted for patients who experienced a first acute STEMI without PCI. Second, the presence of prior significant mitral regurgitation can not be totally excluded. Nonetheless, we precluded this possibility through omission of those patients with organic mitral valve disease by excluding patients with rheumatic mitral valve disease, mitral valve prolapse and/or those patients known to have a mitral valve disease history.
Conclusion
In summary, PCI for first acute STEMI was associated with a decreased incidence of IMR compared to a medically managed group. Risk factors significantly associated with an increased incidence of moderate or severe IMR included: advanced age, inferior MI, Killip class ≥3, a larger LAD, and a larger LVED volume. Furthermore, the greater long-term survival rates were seen in patients reperfused with emergency PCI who were without IMR, whereas patients managed conservatively who had IMR had the lower survival rates.

Disclosure
Conflict of interest: none declared.

References
10. Sutton A, Singh D. Early invasive strategy may reduce the risk of death and myocardial infarction after five years compared to conservative strategy. Evidence-based Cardiovasc Med 2006; 10: 44 – 46.