Chronic kidney disease (CKD) has been associated with a poor clinical outcome after percutaneous coronary intervention (PCI) in patients with coronary artery disease. Previous studies have shown that PCI in patients with CKD is associated with poor clinical outcomes, such as lower procedure success rates, higher rates of in-hospital major adverse cardiac events (MACE), and worse clinical outcomes. These outcomes may be attributed to CKD-related hemostatic alteration, involving platelet function, coagulation and fibrinolytic systems, resulting in both an increased bleeding tendency and an increased thrombotic risk. Cilostazol, a selective, reversible phosphodiesterase type 3 inhibitor, exerts unique anti-thrombotic and vasodilatory effects, based on its novel mechanism of action. In patients undergoing PCI, triple antiplatelet therapy using aspirin, clopidogrel, and cilostazol has been associated with a reduced risk of stent thrombosis and MACE compared with standard dual antiplatelet therapy in several clinical studies.

The aims of this study were to evaluate the effects of triple antiplatelet therapy on the short- and long-term MACE sur-

**Background:** The question as to whether triple antiplatelet therapy is superior to dual antiplatelet therapy for patients with acute myocardial infarction (AMI) and renal dysfunction, who undergo percutaneous coronary intervention (PCI), is unresolved.

**Methods and Results:** As part of the Korea Acute Myocardial Infarction Registry (KAMIR), 2,288 AMI patients with renal dysfunction (glomerular filtration rate <60 ml/min·1.73m²) received either dual (aspirin plus clopidogrel; n=1,587) or triple (aspirin plus clopidogrel and cilostazol; n=701) antiplatelet therapy. Major adverse cardiac events (MACE) at 1 month and 1 year were compared between these 2 groups. On comparison with the dual therapy group, the triple therapy group had a similar incidence of major bleeding events but a significantly lower incidence of in-hospital mortality. The MACE rate at 1 month was significantly higher for the dual therapy group than for the triple therapy group (16.3% vs. 11.1%, P<0.05), and this difference was mainly attributed to death rather than repeat PCI (12.9% vs. 9.1%, P<0.05). The MACE rate at 1 year and the MACE-free survival time, however, did not differ between the groups.

**Conclusions:** In AMI patients with renal dysfunction, triple antiplatelet therapy has a favorable in-hospital and short-term MACE impact, but it does not have an impact on the 1-year MACE-free survival. (Circ J 2012; 76: 2405–2411)

**Key Words:** Acute myocardial infarction; Cilostazol; Glomerular filtration rate; Major adverse cardiac event; Thrombosis
vival of renal dysfunction patients with acute myocardial infarction (AMI) who underwent PCI.

**Methods**

**Korea Acute Myocardial Infarction Registry (KAMIR)**

The KAMIR is a prospective multicenter online registry designed to describe characteristics and clinical outcomes of patients with acute MI and reflects current management of patients with AMI in Korea. The registry included 32 community and university hospitals with capability of primary PCI. Data were collected at each site by a trained study coordinator based on standardized protocol retrospectively. The study protocol was approved by the ethics committee at each participating institution and all patients were informed about their participation in this registry.

**Study Design and Subjects**

The registry included 13,901 consecutive patients who were admitted to the hospital between November 2005 and July 2008, whose discharge diagnosis was AMI based on cardiac enzymes and electrocardiography. Patients who lost to follow-up within 1 year of AMI as well as those with missing data were excluded. Overall, 12,636 patients (91% of the cohort) had all data available for the calculation of estimated glomerular filtration rate (eGFR) and constituted the final study sample. We analyzed 2,288 AMI patients with renal dysfunction (eGFR <60 ml/min·1.73m²) who received either dual (aspirin plus clopidogrel; n=1,587) or triple (aspirin plus clopidogrel plus cilostazol; n=701) antiplatelet therapy based on clinician discretion.

**Definitions**

AMI, including both ST-segment elevation myocardial infarction (STEMI) and non-STEMI was defined by clinical signs or symptoms: patients were diagnosed with STEMI when they had new or presumed new ST-segment elevation of ≥1 mm seen in any location or new left bundle-branch block on the index or subsequent electrocardiogram with at least 1 positive cardiac biochemical marker of necrosis (including creatine kinase-MB and troponin I and T). Left ventricular ejection fraction (LVEF) was checked on 2-D echocardiography. Primary endpoints were death and complication, including cardiacogenic shock, recurrent ischemia and myocardial infarction (MI), cerebrovascular accident, major bleeding, or multiorgan failure during hospitalization. Secondary endpoints were MACE that included cardiogenic death, MI or stroke, and need for emergency or elective repeat revascularization, coronary artery bypass graft (CABG) during follow-up.

**Assessment of Renal Function**

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to eGFR in ml·min⁻¹·1.73m². The serum creatinine concentration was determined by the Jaffe method, which was calibrated to isotope dilution mass spectrometry.

**Data Collection**

Baseline variables were age, sex, body mass index, and coronary risk factors, which included hypertension (defined as history of hypertension, admission blood pressure >140 mmHg systolic or >90 mmHg diastolic), current smoking, previous history of ischemic heart disease (IHD), hyperlipidemia (defined as history of hyperlipidemia, total cholesterol >240 mg/dl, or low-density lipoprotein cholesterol >100 mg/dl), diabetes mellitus (DM; defined as history of DM or random blood glucose level >200 mg/dl) and Killips class.

Use of certain medications was recorded on admission (aspirin, angiotensin-converting enzyme inhibitor [ACEI], diuretics, statin, β-blocker or vasopressors). Surgical interventions (CABG, thrombolysis, or PCI) and coronary care unit stay were recorded.

**Clinical Follow-up**

The records of cardiovascular risk factors and past history (age, sex, hypertension, dyslipidemia, smoking, DM, family history of coronary heart disease, prior IHD) were dependent mainly on the patient’s self-report, but the final records were left to the physician’s discretion after he or she comprehensively considered the patient’s self-report and the in-hospital examination results. Successful PCI was defined as a patent vessel at the treatment site with Thrombolysis In Myocardial Infarction (TIMI) flow ≥ grade 2, and an angiographic residual stenosis of <30% without the occurrence of any cardiac events. All deaths were considered cardiac deaths if non-cardiac death could be excluded. Recurrent MI was defined as recurrent symptoms with new ST-segment elevation or re-elevation of cardiac markers to at least twice the upper limit of normal. Target lesion revascularization (TLR) was defined as ischemia-induced PCI of the target lesion resulting from restenosis or reocclusion within the stent or in the adjacent 5 mm of the distal or proximal segment. Total MACE was defined as the composite of all-cause death, non-fatal MI, and repeated PCI or CABG. Bleeding complications were classified as major, minor, or insignificant, according to the criteria of the TIMI Study Group. Major bleeding event was defined as intracranial bleeding; or a bleed was defined as hemoglobin decrease ≥4 g/dl or required transfusion of ≥3 U blood. Minor bleeding was defined as hemoglobin decrease <4 g/dl or required transfusion of <3 U blood. Patients were required to visit the outpatient clinic of the cardiology department at the end of the first month, every 6 months after PCI, and when angina-like symptoms occurred. The incidences of major bleeding events and various MACEs, in hospital and at 1 year, were evaluated between the dual and triple groups.

**Statistical Analysis**

For continuous variables, differences between groups were evaluated using unpaired t-test or Mann-Whitney rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analyzed using the chi-square (or Fisher exact) test between groups as appropriate. To adjust for potential confounders, a propensity score analysis was done using the logistic regression model, testing the propensity to receive triple rather than dual antiplatelet therapy. We tested all available variables that could be of potential relevance: age, sex, Killip class on admission, cardiovascular risk factors (hypertension, dyslipidemia, smoking, DM, family history of coronary heart disease), prior MI, stent type, number of diseased vessels, and cardiovascular medications (glycoprotein IIb/IIIa receptor blockers, heparins, ACEI, angiotensin II receptor blockers, β-blockers, calcium channel blockers, and statins). The logistic model by which the propensity score was estimated had good predictive value (C statistic=0.959). Multivariate Cox regression analysis was then performed using the propensity score, antiplatelet therapies (triple vs. dual), and the aforementioned variables to determine the impact of the different antiplatelet therapies on short-term and long-term clinical outcomes. All continuous variables are described as mean ± SD. All analyses were 2-tailed, with clinical significance defined as P<0.05.
Statistical analysis was done using SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA).

Results

In all, 2,288 patients were included in the present study (1,587 patients were included in the dual therapy group and 701 patients were included in the triple therapy group; STEMI=65.4% and non-STEMI=34.6%). Table 1 lists the patient baseline characteristics, and Table 2 presents the summary of the biochemical parameters and LVEF. As shown in Table 1, both the triple and dual therapy groups had similar baseline characteristics, except with regard to previous IHD. In addition, both groups had nearly similar biochemical parameters and heart functions (Table 2). On angiography, the patients in the triple therapy group were more likely to have type C lesions and post-procedure grade 3 TIMI flow. Moreover, patients in the triple therapy group were more likely to have received paclitaxel-eluting stents but less likely to have received sirolimus-eluting stents than those in the dual therapy group. The triple therapy group also had a higher total number of stents per patient and received longer stents than the patients in the dual therapy group (Table 3).

The in-hospital medications are also listed in Table 4. Patients in the triple therapy group were more likely to receive glycoprotein IIb/IIIa receptor blockers, unfractionated heparin, β-blockers, statins, and diuretics than those in the dual therapy group.
With regard to in-hospital clinical outcome, the triple therapy group had a significantly lower incidence of in-hospital death than the dual therapy group. In addition, short-term and long-term cardiac death and MACE rates were higher in the dual therapy group (Table 5).

Multivariate Cox regression showed that the MACE-free survival rate did not differ between the 2 groups after adjustments using the propensity score (Table 6; Figure).

**Discussion**

The present results suggest that triple-antiplatelet therapy does not reduce the number of adverse cardiovascular events after PCI in AMI patients with renal dysfunction. Because platelet activity is not mediated by a single mechanism, there are various antiplatelet drugs. Although newer P2Y12 inhibitors have
recently been highlighted as more specific, potent and consistent P2Y<sub>12</sub> antagonists, dual antiplatelet therapy, including aspirin and clopidogrel, is the most common antiplatelet therapy after PCI. There is remarkably poorer response to antiplatelet therapy, however, and a worse clinical outcome associated with conditions such as renal dysfunction. Renal dysfunction patients have complex hemostatic properties with an increased thrombotic risk and bleeding tendency because of the disturbed functioning of the platelets and coagulation and fibrinolytic systems. Moreover, renal dysfunction patients have poorer platelet response, and CKD-related haemostatic alterations potentially justify variability in response to antiplatelet drugs. Therefore, it is reasonable to add a third, potent antiplatelet agent to the dual therapy regimen to strengthen the effective-

### Table 5. Cumulative Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>Dual therapy (n=1,587)</th>
<th>Triple therapy (n=701)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCU stay (days)</td>
<td>4.5±6.0</td>
<td>4.5±4.7</td>
<td>0.800</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>180 (11.3)</td>
<td>47 (6.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>In-hospital major bleeding</td>
<td>5 (0.3)</td>
<td>2 (0.3)</td>
<td>0.870</td>
</tr>
<tr>
<td>1-month MACE</td>
<td>233 (16.3)</td>
<td>69 (11.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>185 (12.9)</td>
<td>57 (9.1)</td>
<td>0.014</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>24 (1.7)</td>
<td>4 (0.6)</td>
<td>0.062</td>
</tr>
<tr>
<td>MI</td>
<td>11 (0.8)</td>
<td>2 (0.3)</td>
<td>0.238</td>
</tr>
<tr>
<td>Repeat PCI</td>
<td>12 (0.8)</td>
<td>6 (1.0)</td>
<td>0.784</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>0.049</td>
</tr>
<tr>
<td>12-month MACE</td>
<td>357 (28.1)</td>
<td>132 (24.0)</td>
<td>0.069</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>213 (16.8)</td>
<td>72 (13.1)</td>
<td>0.047</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>46 (3.6)</td>
<td>13 (2.4)</td>
<td>0.062</td>
</tr>
<tr>
<td>MI</td>
<td>14 (1.1)</td>
<td>7 (1.3)</td>
<td>0.755</td>
</tr>
<tr>
<td>Repeat PCI</td>
<td>79 (6.2)</td>
<td>39 (7.1)</td>
<td>0.489</td>
</tr>
<tr>
<td>CABG</td>
<td>5 (0.4)</td>
<td>1 (0.2)</td>
<td>0.469</td>
</tr>
</tbody>
</table>

Data given as number (%) or mean±standard deviation. CABG, coronary artery bypass grafting; CCU, coronary care unit; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

### Table 6. MACE-Free Survival Rate for Triple vs. Dual Antiplatelet Therapy

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-month MACE</td>
<td>0.66 (0.50–0.86)</td>
<td>0.002</td>
<td>0.66 (0.15–2.78)</td>
<td>0.565</td>
</tr>
<tr>
<td>12-month MACE</td>
<td>0.81 (0.66–0.99)</td>
<td>0.039</td>
<td>0.65 (0.27–1.61)</td>
<td>0.353</td>
</tr>
</tbody>
</table>

CI, confidence interval; MACE, major adverse cardiac event; OR, odds ratio.

**Figure.** Adjusted major adverse cardiac event (MACE)-free survival at (A) 1 month and (B) 1 year. HR, hazard ratio.
ness of the antiplatelet therapy in patients with renal dysfunction who undergo PCI. Recently, Chen et al reported that triple therapy significantly reduced MACE in patients with STEMI who underwent primary PCI and received drug-eluting stents (DES).14 That study, however, examined only STEMI patients who underwent primary PCI with DES, without analyzing subgroup data according to renal function.

In the present study, KAMIR patients with renal dysfunction (eGFR <60 ml/min · 1.73 m²) were examined to determine whether triple therapy significantly decreased the incidence of in-hospital deaths and 1-month MACE, as compared to dual therapy. The present results suggest that the mortality benefits of triple antiplatelet therapy were obtained mainly within a short period after AMI; the results are similar to other recently reported data.15 A Cox regression analysis, however, performed after adjusting the data with a propensity score, showed that triple therapy did not decrease the incidence of 1-month and 12-month MACE, compared to dual therapy. Moreover, triple therapy did not significantly improve clinical outcomes at 12 months and did not have additional beneficial effects on the incidence of TLR or repeat PCI in the overall study population.

Previous studies suggested that cilostazol is useful for reducing late luminal loss and thrombotic complications after DES implantation.22-24 The primary endpoint of those studies, however, was angiographic late luminal loss, but the present endpoint was short- and long-term clinical outcome. Another difference between the present study and other studies may be related to the subjects. Other previous studies have included a relatively small number of AMI patients and did not conduct subgroup analyses related to renal function impairment. The present study enrolled all patients with AMI and renal dysfunction who underwent PCI and reflected real-world clinical settings, including approximately 40% of the patients having DM; further, it included patients who received both bare-metal stents and DES. Moreover, platelet reactivity significantly increased in AMI patients who underwent PCI.26 Together, these factors may have significant bearing on why the outcome of this study may differ from the outcome of those previously reported.

Recent data showed that adding cilostazol to aspirin and clopidogrel dual therapy was associated with an improvement in platelet response to clopidogrel,27 even in AMI28 or CKD patients.29 Although adjunctive cilostazol reduced the rate of post-treatment platelet reactivity in those trials, the reduced platelet reactivity did not guarantee an improvement in clinical outcome. Suh et al reported that although adjunctive cilostazol is associated with improved platelet responses, triple therapy did not reduce adverse cardiovascular events after DES implantation.30 Similarly, according to the current study, the MACE-free survival curve did not have any beneficial effects of adjunctive cilostazol during short- and long-term follow-up in AMI patients with renal dysfunction. Thus, these results suggest that different response of AMI patients with renal dysfunction to adjunctive cilostazol, compared to patients with normal renal function. More effective and careful antiplatelet therapies are needed, in conjunction with long-term clinical trials, to verify that adjunctive antiplatelet therapy can improve clinical outcomes in these patients.

Study Limitations
The present study has some limitations. First, although this study included a large number of subjects, there were baseline differences in several important prognostic factors between the primary comparison groups. This was because this study was not a prospective, randomized study. Although most confounders were included in the multivariate Cox regression model, including propensity scores to control baseline bias, it is possible that some potential confounders may have been overlooked. Second, the patients were categorized into different antiplatelet therapy groups on the basis of their in-hospital, discharge, and follow-up medical records, but information on adverse reactions to cilostazol or duration of antiplatelet therapy during the follow-up period was not collected. Third, although this study involved a large amount of dual and triple therapy data, the KAMIR has no written record of stent thromboses or any platelet function tests conducted on the patients. Fourth, data regarding the type and dosage of cardioactive medications, which may have induced cytochrome P450 (CYP) 3A4 to show cross-reactivity with clopidogrel, were not collected.

Conclusion
Triple antiplatelet therapy was not superior to dual therapy in reducing MACE, after PCI, in AMI patients with renal dysfunction. Further studies are needed to verify the optimal antiplatelet therapy, according to patient background and underlying conditions.

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Disclosures
Conflict of Interest: None declared.

References


