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Triple Versus Dual Antiplatelet Therapy in Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Kang-Yin Chen, MD; Seung-Woon Rha, MD; Yong-Jian Li, MD; Kanhaiya L. Poddar, MBBS; Zhe Jin, MD; Yoshiyasu Minami, MD; Lin Wang, MD; Eung Ju Kim, MD; Chang Gyu Park, MD; Hong Seog Seo, MD; Dong Joo Oh, MD; Myung Ho Jeong, MD; Young Keun Ahn, MD; Taek Jong Hong, MD; Young Jo Kim, MD; Seung Ho Hur, MD; In Whan Seong, MD; Jei Keon Chae, MD; Myeong Chan Cho, MD; Jang Ho Bae, MD; Dong Hoon Choi, MD; Yang Soo Jang, MD; In Ho Chae, MD; Chong Jin Kim, MD; Jung Han Yoon, MD; Wook Sung Chung, MD; Ki Bae Seung, MD; Seung Jung Park, MD; for the Korea Acute Myocardial Infarction Registry Investigators

Background**—**Whether triple antiplatelet therapy is superior or similar to dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention in the era of drug-eluting stents remains unclear.

Methods and Results**—**A total of 4203 ST-segment elevation myocardial infarction patients who underwent primary percutaneous coronary intervention with drug-eluting stents were analyzed retrospectively in the Korean Acute Myocardial Infarction Registry (KAMIR). They received either dual (aspirin plus clopidogrel; dual group; n=2569) or triple (aspirin plus clopidogrel plus cilostazol; triple group; n=1634) antiplatelet therapy. The triple group received additional cilostazol at least for 1 month. Various major adverse cardiac events at 8 months were compared between these 2 groups. Compared with the dual group, the triple group had a similar incidence of major bleeding events but a significantly lower incidence of in-hospital mortality. Clinical outcomes at 8 months showed that the triple group had significantly lower incidences of cardiac death (adjusted odds ratio, 0.52; 95% confidence interval, 0.32 to 0.84; $P=0.007$), total death (adjusted odds ratio, 0.60; 95% confidence interval, 0.41 to 0.89; $P=0.010$), and total major adverse cardiac events (adjusted odds ratio, 0.74; 95% confidence interval, 0.58 to 0.95; $P=0.019$) than the dual group. Subgroup analysis showed that older (>65 years old), female, and diabetic patients got more benefits from triple antiplatelet therapy than their counterparts who received dual antiplatelet therapy.

Conclusions**—**Triple antiplatelet therapy seems to be superior to dual antiplatelet therapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with drug-eluting stents. These results may provide the rationale for the use of triple antiplatelet therapy in these patients. **(*Circulation*. 2009;119:3207-3214.)**

Key Words: cilostazol ■ myocardial infarction ■ thrombosis ■ platelets

Drug-eluting stents (DES) have drastically changed the landscape of percutaneous coronary intervention (PCI), with significant reductions in the angiographic restenosis rate and need for repeated revascularization.[1] However, several studies showed that DES is associated with a higher incidence of in-stent thrombosis compared with bare metal stents.[2,3] Therefore, the latest guideline for antiplatelet therapy after PCI with DES suggests that the dual antiplatelet therapy (aspirin plus clopidogrel) be administered for at least 12 months.[3] But is it enough for high-risk patients? Some studies showed that as many as 50% of the patients who received PCI did not react positively to aspirin or clopidogrel.[4–6] Furthermore, there is increased platelet activity in acute coronary syndrome, especially in acute myocardial infarction (AMI).[7]

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Cilostazol is a potent inhibitor of type III phosphodiesterase in both platelets and vascular smooth muscle cells.[8–10] The antiplatelet effect of cilostazol is 10 to 30 times more potent than that of aspirin.[9] Antiplatelet therapy with cilostazol after PCI has similar safety and efficacy outcomes

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From the Korea University Guro Hospital, Seoul, Korea.
A complete list of Korea Acute Myocardial Infarction Registry investigators is given in the Appendix.
Correspondence to Seung-Woon Rha, MD, PhD, FACC, FAHA, FESC, FSCAI, Cardiovascular Center, Korea University Guro Hospital, 80, Guro-dong, Guro-gu, Seoul, 152–703, Korea. E-mail swrha617@yahoo.co.kr

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compared with aspirin or clopidogrel.[11–13] A recent study suggested that cilostazol could ameliorate platelet responsiveness to clopidogrel in patients who underwent primary PCI.[14] Furthermore, some other studies showed that the administration of cilostazol after PCI could significantly lower the incidence of in-stent restenosis.[15–18]

Therefore, the present study was designed to evaluate the safety and efficacy of additional administration of cilostazol with aspirin and clopidogrel in a real-world cardiology practice among patients presenting with acute ST-segment elevation myocardial infarction (STEMI) who received primary PCI with DES.

Methods

Korea Acute Myocardial Infarction Registry

The Korea Acute Myocardial Infarction Registry (KAMIR) is a Korean prospective multicenter online registry designed to reflect the "real-world" practice in Asian patients presenting with AMI in the DES era, with support from the Korean Circulation Society since November 2005. Online registry of AMI (at www.kamir.or.kr) has been performed at 41 university or community hospitals that are high-volume centers with facilities for primary PCI and onsite cardiac surgery. Before the initiation of the KAMIR study, several investigator meetings were held, and a practical steering committee from major enrolled hospitals was selected to standardize care given in clinical practice as well as the study protocol to minimize the differences in medical care among the different hospitals and across the different time periods. Data were collected at each site by a trained study coordinator using a standardized case report form. Standardized definitions of all patient-related variables and clinical diagnoses were used. The study protocol was approved by the ethics committee at each participating institution. Data were registered and submitted from individual institutions via password-protected Internet-based electronic case report forms. We enrolled patients who were suffering from AMI, including both STEMI and non-STEMI. Patients were diagnosed with STEMI when they had new or presumed new ST-segment elevation of at least 1 mm seen in any location or new left bundle-branch block on the index or subsequent ECG with at least 1 positive cardiac biochemical marker of necrosis (including creatine kinase-MB and troponin I and T).

Study Population

From November 2005 to December 2007, a total of 13 632 patients were diagnosed with AMI. In the present study, we retrospectively enrolled patients with acute STEMI who underwent primary PCI (PCI performed within 24 hours after the symptom onset) with DES. The criteria for exclusion included non-STEMI, STEMI undergoing primary PCI with bare metal stent or balloon angioplasty only, STEMI undergoing selective PCI or conservative treatment without PCI, Killip grade IV cardiac function, contraindication to antithrombotic agents, known bleeding disorders, thrombocytopenia ($<100\times10^9$/L), administration of oral anticoagulants, administration of thrombolytic or fibrinolytic medications for STEMI, infarction related to the grafted vessel, severe hepatic or renal dysfunction (serum creatinine >2 mg/dL), and estimated life expectancy of <12 months.

Patients were divided into 2 groups: a dual antiplatelet therapy group (aspirin plus clopidogrel; dual group; n=2569) and a triple antiplatelet therapy group (aspirin plus clopidogrel plus cilostazol; the triple group; n=1634). Loading doses of aspirin and clopidogrel were administered immediately after the patients agreed to receive PCI. The loading and maintenance doses were 200 and 100 mg QD for aspirin and 300 to 600 and 75 mg QD for clopidogrel. Cilostazol was given right after the PCI procedure; its loading and maintenance doses were 200 and 100 mg BID, respectively. According to the KAMIR study design, AMI patients when discharged were prescribed medicines for 1 month, after which the first follow-up was performed. Dual antiplatelet therapy was administered to all patients for ≥6 months as per existing guidelines. Cilostazol was administered to the triple antiplatelet therapy group for at least 1 month after the index procedure. After discontinuation of cilostazol, the patients in the triple group received dual antiplatelet therapy.

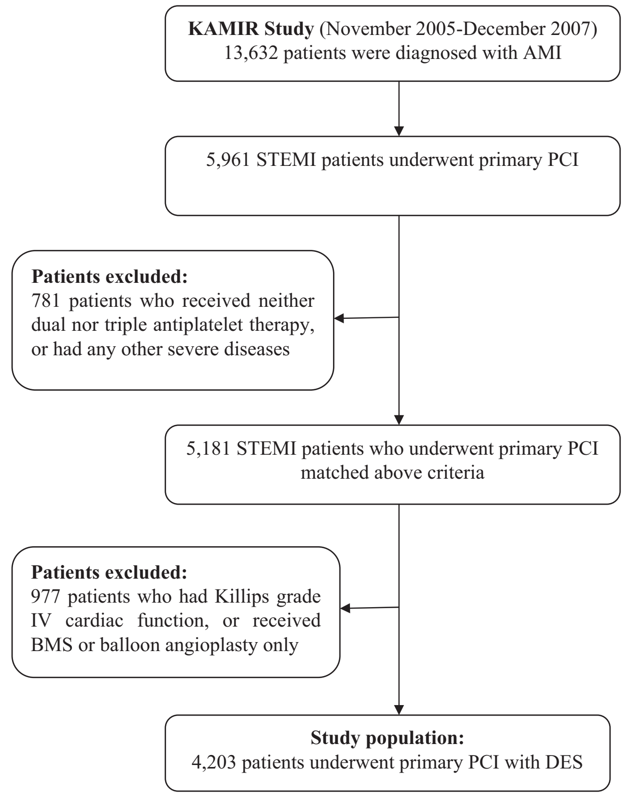

Figure 1. Study flow chart. BMS indicates bare metal stents.

PCI Procedure and Medical Treatment

Diagnostic angiography and PCI were performed after unfractionated heparin (50 to 70 U/kg) was administered. Coronary angiography was performed through the femoral or radial artery. During the procedure, patients received unfractionated heparin to maintain an activated clotting time of >250 seconds. Stents were deployed after prior balloon angioplasty, and the administration of platelet glycoprotein IIb/IIIa receptor blockers was left to the decision of the individual operator. A successful PCI procedure was defined as the achievement of an angiographic minimum stenosis diameter reduction to $<30\%$ in the presence of Thrombolysis in Myocardial Infarction grade III flow.

During the in-hospital period, patients received medical treatment that included β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and statins. After discharge, the patients continued receiving the same kinds of medications that they received in hospital except some intravenous or temporary medications.

Study Definitions and Clinical Follow-Up

The records of cardiovascular risk factors and past history (age, sex, hypertension, dyslipidemia, smoking, diabetes mellitus, family history of coronary heart disease, prior myocardial infarction, chronic heart failure and prior cerebrovascular disease, peripheral arterial disease) 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. All deaths were considered cardiac deaths if noncardiac death could be excluded. Recurrent myocardial infarction was defined as recurrent symptoms with new ST-segment elevation or re-elevation of cardiac markers to at least twice the

Table 1. Baseline Clinical Characteristics

Variables	Dual Therapy (n=2569)	Triple Therapy (n=1634)	*P*
Age, y	62.01±12.91	61.97±12.41	0.928
Body mass index, kg/m^2	24.05±3.18	23.97±3.18	0.442
Male, n (%)	1917 (74.6)	1224 (74.9)	0.834
History, n (%)			
Hypertension	1165 (45.3)	716 (43.8)	0.331
Diabetes mellitus	629 (24.5)	390 (23.9)	0.649
Current smoking	1265 (49.2)	795 (48.7)	0.930
Dyslipidemia	207 (8.1)	116 (7.1)	0.479
Family history of CAD	190 (7.4)	98 (6.0)	0.216
Prior myocardial infarction	107 (4.2)	75 (4.6)	0.509
Chronic heart failure	19 (0.7)	13 (0.8)	0.839
Peripheral arterial disease	30 (1.2)	12 (0.7)	0.169
Cerebrovascular disease	135 (5.3)	81 (5.0)	0.670
Peptic ulcer disease	8 (0.3)	2 (0.1)	0.334
Killip class, n (%)			0.256
I	2019 (78.6)	1314 (80.4)	
II	393 (15.3)	220 (13.5)	
III	157 (6.1)	100 (6.1)	
Onset to PCI (IQR), h	4.08 (1.75–9.00)	4.08 (1.71–9.01)	0.937

CAD indicates coronary artery disease; IQR, interquartile range.

Table 2. Baseline Angiographic and PCI Procedural Characteristics

Variables	Dual Therapy (n=2569)	Triple Therapy (n=1634)	*P*
Target lesion, n (%)			0.215
LAD	1387 (54.0)	866 (53.0)	
RCA	919 (35.1)	576 (35.3)	
LCx	242 (9.4)	169 (10.3)	
Left main	21 (0.8)	23 (1.4)	
Diseased vessels, n (%)			0.005
Single	1207 (47.1)	808 (49.4)	
Double	790 (30.8)	471 (28.8)	
Triple	540 (21.0)	316 (19.4)	
Left main disease	30 (1.2)	39 (2.4)	
Preprocedure TIMI flow grade, n (%)			0.170
0	1536 (59.8)	962 (58.9)	
I	288 (11.2)	167 (10.2)	
II	329 (12.8)	248 (15.2)	
III	416 (16.2)	257 (15.7)	
Stent type, n (%)			<0.001
Sirolimus eluting	1335 (52.0)	638 (39.0)	
Paclitaxel eluting	674 (26.2)	765 (46.8)	
Zotarilimus eluting	205 (8.0)	92 (5.6)	
Other drug eluting	355 (13.8)	139 (8.5)	
Stent diameter, mm	3.17±0.41	3.18±0.38	0.351
Stent length, mm	25.27±6.03	25.65±6.39	0.052
Total stents per patient, n	1.35±0.67	1.53±0.81	<0.001
Postprocedure TIMI flow grade			0.703
0	26 (1.0)	18 (1.1)	
I	17 (0.7)	8 (0.5)	
II	117 (4.6)	65 (4.0)	
III	2409 (93.8)	1543 (94.4)	

LAD indicates left anterior descending artery; RCA, right coronary artery; LCx, left circumflex; and TIMI, Thrombolysis in Myocardial Infarction.

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 major adverse cardiac events (MACEs) were defined as the composite of all-cause death, nonfatal myocardial infarction, and repeated PCI or coronary artery bypass grafting. Major bleeding was defined as any intracranial bleeding, bleeding associated with the need for blood transfusion, or any other clinically relevant bleeding as judged by the investigator.

Patients were required to visit the outpatient clinic of the cardiology department at the end of the first month, every 6 months after the PCI procedure, and when angina-like symptoms occurred. The 6-month clinical follow-up was done at a median of 173 days (interquartile range, 147 to 206 days). Therefore, in the present study, we collected the clinical follow-up data at 8 months (240 days) to ensure that all patients finished their 6-month follow-up. The incidences of major bleeding events and various MACEs, in hospital and at 8 months, were evaluated between the dual and triple groups.

Statistical Analysis

For continuous variables, differences between groups were evaluated by unpaired *t* test or Mann-Whitney rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analyzed with χ^2 (or Fisher exact) test between groups as appropriate. To adjust for potential confounders, a propensity score analysis was performed 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, diabetes mellitus, family history of coronary heart disease), prior myocardial infarction, chronic heart failure and prior cerebrovascular disease, peripheral arterial disease, stent type, number of diseased vessels, and cardiovascular medications (glycoprotein IIb/IIIa receptor blockers, heparins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, and statins). The logistic model by which the propensity score was estimated showed good predictive value (C statistic=0.753). Multivariable Cox regression analysis was then performed using the propensity score, antiplatelet therapies (triple versus dual), and the aforementioned variables to determine the impact of the different antiplatelet therapies on in-hospital and 8-month clinical outcomes. In addition, the effects of the different antiplatelet therapies on 8-month clinical outcomes were further evaluated in different subgroups of patients, including old (≥65 years of age), young (<65 years of age), male, female, diabetic, and nondiabetic patients. Cox regression models adjusted for propensity score and the aforementioned variables were used to assess odds ratios for various MACEs in these different subgroups of patients. All continuous variables were described as mean±SD. All analyses were 2-tailed, with clinical significance defined as values of $P<0.05$. All statistical processes were done with SPSS 13.0 (Statistical Package for the Social Sciences, SPSS-PC Inc, Chicago, Ill).

Results

Eligibility is reported in Figure 1. A total of 4203 eligible STEMI patients who underwent primary PCI with DES were enrolled, and they represented 71.1% of the 5961 STEMI patients who underwent primary PCI. As shown in Table 1, The triple and dual groups had similar baseline clinical

Table 3. In-Hospital Medications

Variables	Dual Therapy (n=2569), n (%)	Triple Therapy (n=1634), n (%)	*P*
Glycoprotein IIb/IIIa receptor blocker*	290 (11.3)	369 (22.6)	<0.001
Low–molecular-weight heparin*	864 (33.6)	553 (33.8)	0.888
Unfractionated heparin*	1705 (66.4)	1081 (66.2)	0.888
β-Blockers	1970 (76.7)	1273 (77.9)	0.357
Angiotensin-converting enzyme inhibitors	1760 (68.5)	1232 (75.4)	<0.001
Angiotensin II receptor blockers	336 (13.1)	220 (13.5)	0.720
Calcium channel blockers	279 (10.9)	129 (7.9)	0.002
Statins	2085 (81.2)	1335 (81.7)	0.660

*Used only during in-hospital period.

characteristics. In addition, these 2 groups also had nearly similar baseline angiographic and PCI procedural characteristics, except that the patients in the triple group were more likely to have single-vessel and left main disease but less likely to have 2- and 3-vessel disease. Moreover, patients in the triple group were more likely to receive paclitaxel-eluting stents but less likely to receive sirolimus-eluting stents than those in the dual group. The triple group also had higher total numbers of stents per patient and longer stents than the dual group (Table 2).

The in-hospital medications are listed in Table 3. Patients in the triple group were more likely to receive glycoprotein IIb/IIIa receptor blockers and angiotensin-converting enzyme inhibitors but less likely to receive calcium channel blockers than those in the dual group.

In-hospital clinical outcomes showed that the triple group had significantly lower incidences of cardiac death and total death than the dual group. The incidences of recurrent myocardial infarction and major bleeding events were similar between these 2 groups (Table 4).

Table 4. Cumulative Clinical Outcomes at 8 Months

Variables	Dual Therapy (n=2569), n (%)	Triple Therapy (n=1634), n (%)	*P*
In-hospital outcomes			
Cardiac deaths	61 (2.4)	21 (1.3)	0.013
Total deaths	88 (3.4)	36 (2.2)	0.022
Recurrent MI	6 (0.2)	6 (0.4)	0.429
Major bleeding events	10 (0.4)	3 (0.2)	0.242
Outcomes at 8 mo			
Cardiac deaths	83 (3.2)	33 (2.0)	0.019
Total deaths	125 (4.9)	51 (3.1)	0.006
Recurrent MI	9 (0.4)	7 (0.4)	0.689
CABG	4 (0.2)	2 (0.1)	1.000
Repeated PCI	101 (3.9)	61 (3.7)	0.745
TLR	29 (1.1)	27 (1.7)	0.149
Total MACEs	240 (9.3)	124 (7.6)	0.049

CABG indicates coronary artery bypass grafting.

Table 5. Adjusted Cumulative Clinical Outcomes at 8 Months of Triple Compared With Dual Antiplatelet Therapy (Cox Regression Analysis Using Propensity Score)

Variables	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
In-hospital outcomes				
Cardiac deaths	0.53 (0.32–0.88)	0.014	0.44 (0.24–0.80)	0.007
Total deaths	0.63 (0.43–0.94)	0.024	0.59 (0.36–0.94)	0.026
Recurrent MI	1.57 (0.51–4.89)	0.433	0.96 (0.28–3.35)	0.954
Outcomes at 8 mo				
Cardiac deaths	0.62 (0.41–0.93)	0.021	0.52 (0.32–0.84)	0.007
Total deaths	0.63 (0.45–0.88)	0.006	0.60 (0.41–0.89)	0.010
Recurrent MI	1.22 (0.45–3.29)	0.689	0.72 (0.24–2.20)	0.565
CABG	0.78 (0.14–4.29)	0.781	0.99 (0.15–6.45)	0.990
Repeated PCI	0.95 (0.68–1.31)	0.745	0.83 (0.59–1.18)	0.312
TLR	1.47 (0.87–2.49)	0.151	1.12 (0.63–1.98)	0.694
Total MACEs	0.80 (0.64–0.99)	0.049	0.74 (0.58–0.95)	0.019

OR indicates odds ratio; CABG, coronary artery bypass grafting.

The clinical outcomes at 8 months also showed that the triple group had a significantly lower incidence of cardiac death, total death, and total MACEs than the dual group. However, the incidences of recurrent myocardial infarction, coronary artery bypass grafting, repeated PCI, and TLR were similar between the 2 groups (Table 4).

Multivariable Cox regression analysis showed that the triple group had significantly lower incidences of in-hospital cardiac death and total death than the dual group. The adjusted clinical outcomes at 8 months also showed that the triple group had significantly lower incidences of cardiac death, total death, and total MACEs (Table 5 and Figure 2).

Subgroup analysis showed that female patients in the triple group had significantly lower incidences of cardiac death, total death, and total MACEs at 8 months compared with the women in the dual group, whereas male patients in the triple group showed only a significantly lower incidence of total death than the dual group. Among ≥65-year-old patients, the triple group had a significantly lower incidence of cardiac death at 8 months and had a trend toward lower incidences of total death and total MACEs than the dual group. However, among <65-year-old patients, the triple group had a trend only toward lower incidence of total death than the dual group. Among diabetics, the triple group had significantly lower incidences of repeated PCI and total MACEs and a trend toward a lower incidence of cardiac death than the dual group. However, in nondiabetic patients, although the triple group had a significantly lower incidence of total death and a trend toward lower incidence of cardiac death than the dual group, the incidences of repeated PCI and total MACE were similar between these 2 groups (Figure 3).

Discussion

The major finding of the present study is that compared with traditional dual antiplatelet therapy, triple antiplatelet therapy with additional cilostazol significantly lowered the incidences

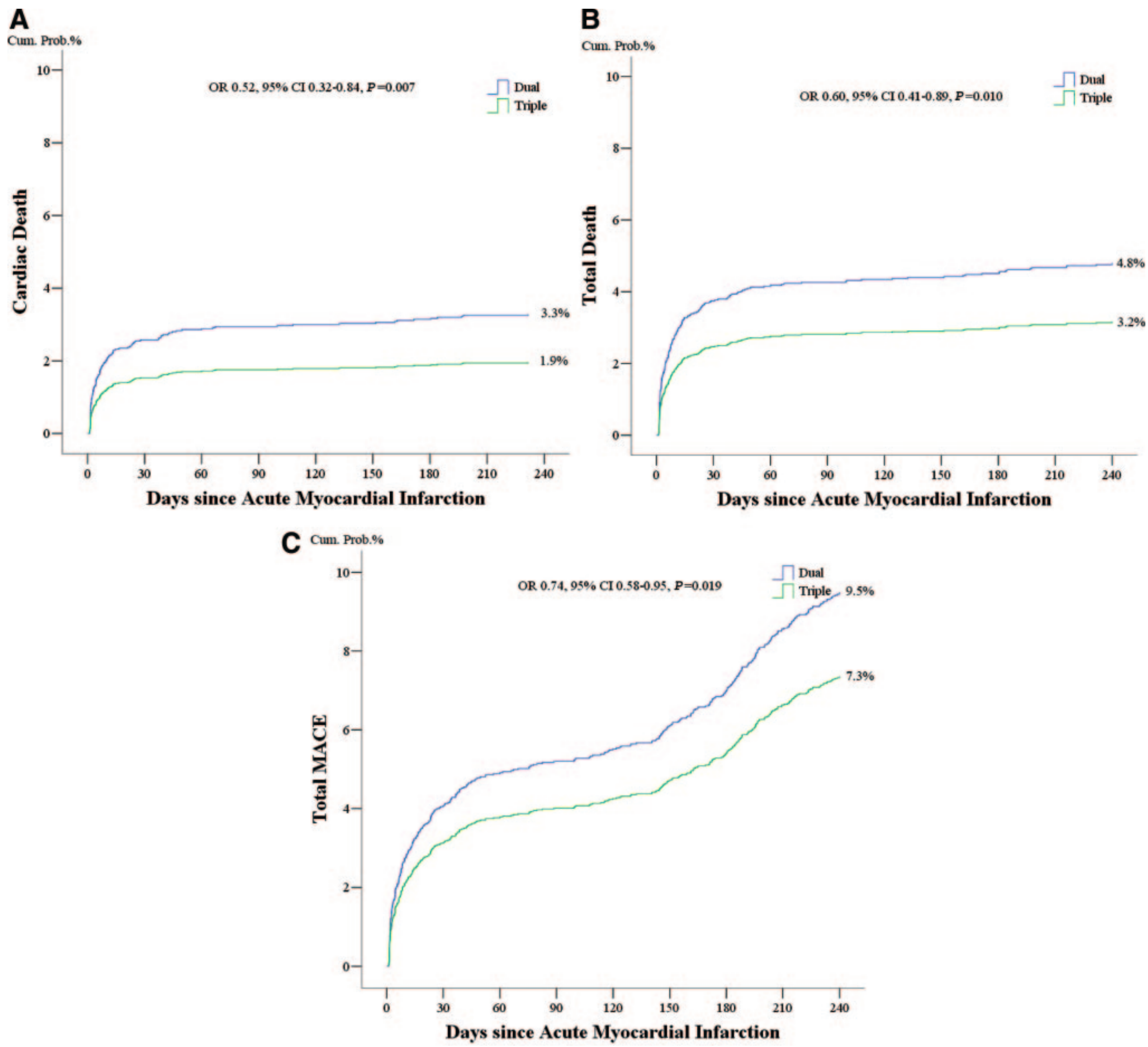

Figure 2. Adjusted cumulative incidence of cardiac death (A), total death (B), and total MACEs (C) at 8 months in patients who received triple or dual antiplatelet therapy. Variables in the multivariable Cox regression analysis included propensity scores, antiplatelet therapy (triple versus dual), age, sex, Killip class on admission, cardiovascular risk factors (hypertension, dyslipidemia, smoking, diabetes mellitus, family history of coronary heart disease), prior myocardial infarction, chronic heart failure and prior cerebrovascular disease, peripheral arterial disease, stent type, number of diseased vessels, and cardiovascular medications (glycoprotein IIb/IIIa receptor blockers, heparins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, and statins). Cum. Prob. indicates cumulative probability; OR, odds ratio.

of cardiac death, total death, and total MACEs at 8 months in patients with acute STEMI who underwent primary PCI with DES.

The recent updated guideline of post-PCI antiplatelet treatment for patients who undergo PCI with DES recommends administration of dual antiplatelet therapy with aspirin and clopidogrel for at least 12 months.[3] But, is it enough, especially in the setting of AMI? Some previous studies suggested that as high as 20% to 50% patients did not react positively to aspirin or clopidogrel and that these patients exhibited significantly higher risks of recurrent cardiovascular events.[4–6,19] Muller and colleagues[20] reported that even a large loading dose (600 mg) of clopidogrel did not inhibit the aggregation and degranulation of platelets by thrombin-related activating peptides in the setting of AMI. In addition, Gawaz et al[21] showed that platelet reactivity significantly increased in AMI patients who underwent PCI. Furthermore, Park et al[22] suggested that primary stenting with sirolimus-eluting or paclitaxel-eluting stents in patients with AMI was an important risk factor for acute and subacute in-stent thrombosis. Therefore, it is reasonable to add a potent antiplatelet agent to aspirin and clopidogrel to strengthen the effectiveness of antiplatelet therapy in patients with acute STEMI undergoing PCI with DES.

The present study showed that compared with dual antiplatelet therapy, triple antiplatelet therapy had a similar

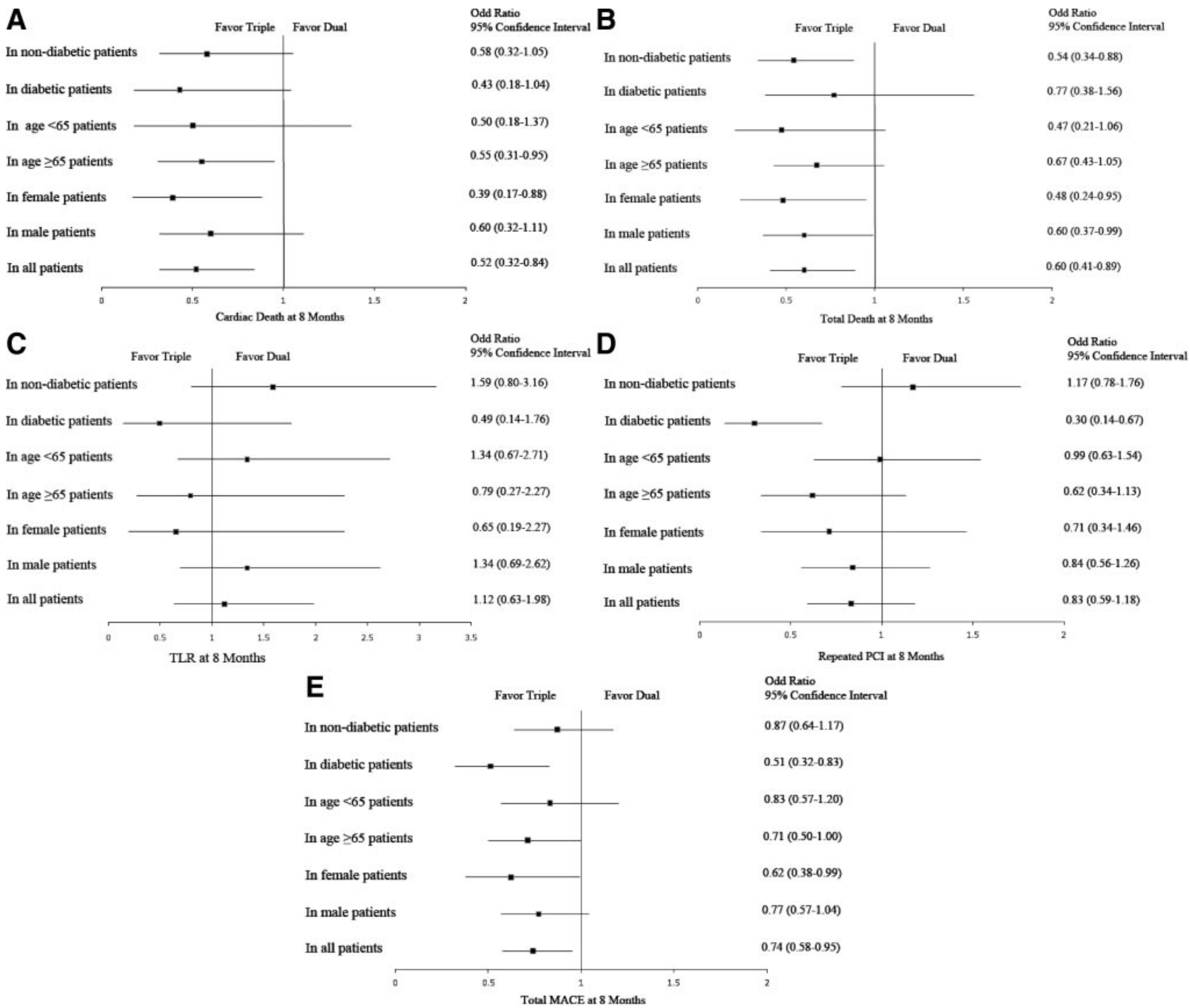

Figure 3. Adjusted odds ratios (ORs) for 8-month incidence of cardiac death (A), total death (B), TLR (C), repeated PCI (D), or total MACEs (E) associated with triple antiplatelet therapy in the entire study population and various subgroups of patients according to sex, age, and diabetes mellitus (DM).

incidence of in-hospital major bleeding events but significantly decreased the incidences of cardiac death, total death, and total MACEs up to 8 months. In addition, it is noted that the event curves including cardiac death and total death separate primarily in the first 30 days and then gradually become linear (Figure 2), suggesting that the mortality benefits of triple antiplatelet therapy were obtained mainly within 30 days after AMI. However, the MACE curve showed that the beneficial effects of triple antiplatelet therapy appeared continuously throughout the 8 months of follow-up (Figure 2), suggesting that the composite beneficial effects of triple antiplatelet therapy were not limited to 30 days but persisted up to 8 months. This result might be attributed to the antirestenotic property of cilostazol and different pharmacological actions with aspirin and clopidogrel as demonstrated in other studies.[14–17] Our results were consistent with a previous study from Lee et al.[23] That study compared the effects of triple antiplatelet and dual antiplatelet strategy on stent thrombosis up to 30 days after the index procedure in all patients who received PCI with both bare metal stents and DES. Their results showed that compared with the dual antiplatelet regimen, triple antiplatelet therapy seemed to be more effective in preventing thrombotic complications after stenting without an increased risk of side effects. However, that study included only a relatively small number of AMI cases (total, 573 AMI cases). Furthermore, they did not provide a subgroup analysis in the patients with AMI. In contrast, we evaluated in a larger scale the safety and efficacy of triple antiplatelet therapy in STEMI patients who underwent primary PCI with DES.

Some previous studies suggested that the administration of cilostazol after PCI significantly lowered the incidence of in-stent restenosis.[15–17] Tsuchikane et al[15] reported that cilostazol significantly reduced the incidences of in-stent restenosis and TLR after successful PCI. Douglas et al[16] also reported that treatment with cilostazol resulted in a significantly larger minimal luminal diameter and a significantly lower binary restenosis rate compared with placebo-treated patients and that these favorable effects were apparent in patients at high risk for restenosis.

However, in the present study, although we found that the treatment of cilostazol significantly improved clinical outcomes at 8 months, we did not find the extra beneficial effects of cilostazol on the TLR and repeated PCI in overall study population. Recently, Lee et al[18] reported a randomized study comparing triple and dual antiplatelet therapy in angina patients with diabetes mellitus who received DES. Their results showed that triple antiplatelet therapy after DES implantation decreased the extent of late loss and the incidence of 9-month TLR. In the present study, the subgroup analysis performed in diabetic patients showed that although the incidence of TLR was similar between the triple and dual groups, the incidence of repeated PCI was significantly reduced in diabetic patients. We speculate that the difference between our study and that of Lee et al[18] might be due to the different study populations and follow-up regimens. In the present study, we routinely performed only clinical follow-up. Some patients with angiographic in-stent restenosis might be asymptomatic and would not be found in routine clinical follow-up. This may be an important reason for the similar incidences of TLR between the triple and dual groups in our study. Cilostazol has pleiotropic effects on preventing the progression of atherosclerosis.[24,25] Nakamura et al[24] reported that treatment with cilostazol in type 2 diabetic patients with peripheral arterial disease could induce some beneficial changes in serum lipid profile and plasma fatty acid composition. These mechanisms might be associated with the reduction in repeated PCI observed in diabetic patients in the present study.

Study Strengths and Limitations

The strengths of the KAMIR study include its prospective design and large multicenter population base. The registry provides a comprehensive view of the contemporary treatments and outcomes in the Asian patients with AMI in the era of DES.

The present study has some limitations. First, although there is a large number of subjects in the present study, because of the nonrandomized nature of the registry study, there were baseline differences in several important prognostic factors between our primary comparison groups. Although we included most confounders in the multivariable Cox regression model, including propensity score to control the baseline biases, it is possible that some potential confounders might have crept in. However, this multicenter registry may help complete the picture gained from randomized trials, which usually have highly selected patients treated in a nonroutine setting. Second, in the present study, we divided patients into different antiplatelet therapies on the basis of their in-hospital, discharge, and follow-up medical records, but we did not collect information on adverse reactions to cilostazol during the follow-up period. However, we have detailed information on the major and minor bleeding events, mortality, and recurrent myocardial infarction, which also are very important components of safety profiles and can help us understand the main safety profiles of cilostazol.[26] Fortunately, a recent study showed that the adverse reactions in patients who received triple antiplatelet therapy were similar to those who received dual therapy.[18] Third, because we did not collect data on cardioactive medications, including β-blockers, statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers, during the follow-up period, this also might be a confounding factor.

Conclusions

The present study showed that aggressive antiplatelet treatment with aspirin, clopidogrel, and cilostazol not only had a good safety profile but also improved midterm clinical outcomes in acute STEMI patients who underwent primary PCI in the era of DES. Notably, female patients, old patients, and diabetic patients seemed to get more benefits from the triple antiplatelet therapy. Therefore, these results might provide the rationale for the use of triple antiplatelet therapy in these patients. Because of the limitations of the registry study, a randomized trial designed to compare triple and dual antiplatelet therapy in these patients is needed.

Appendix

KAMIR Investigators

The complete list of KAMIR Investigators follows: Myung Ho Jeong, MD; Young Jo Kim, MD; Chong Jin Kim, MD; Myeong Chan Cho, MD; Young Keun Ahn, MD; Jong Hyun Kim, MD; Shung Chull Chae, MD; Seung Ho Hur, MD; In Whan Seong, MD; Taek Jong Hong, MD; Dong Hoon Choi, MD; Jei Keon Chae, MD; Jae Young Rhew, MD; Doo Il Kim, MD; In Ho Chae, MD; Jung Han Yoon, MD; Bon Kwon Koo, MD; Byung Ok Kim, MD; Myoung Yong Lee, MD; Kee Sik Kim, MD; Jin Yong Hwang, MD; Seok Kyu Oh, MD; Nae Hee Lee, MD; Kyoung Tae Jeong, MD; Seung Jea Tahk, MD; Jang Ho Bae, MD; Seung Woon Rha, MD; Keum Soo Park, MD; Kyoo Rok Han, MD; Tae Hoon Ahn, MD; Moo Hyun Kim, MD; Ju Young Yang, MD; Chong Yun Rhim, MD; Hyeon Cheol Gwon, MD; Seong Wook Park, MD; Young Youp Koh, MD; Seung Jae Joo, MD; Soo Joong Kim, MD; Dong Kyu Jin, MD; Jin Man Cho, MD; Jeong Gwan Cho, MD; Wook Sung Chung, MD; Yang Soo Jang, MD; Ki Bae Seung, MD; and Seung Jung Park, MD.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Drug-eluting stent implantation in acute myocardial infarction is associated with an increased risk for acute and subacute in-stent thrombosis. Increased platelet activity also has been observed in acute myocardial infarction. Therefore, more aggressive antiplatelet therapy rather than conventional dual antiplatelet therapy may offer extra benefits for acute myocardial infarction patients undergoing primary percutaneous coronary intervention with drug-eluting stents. This article retrospectively evaluates the safety and efficacy of triple antiplatelet therapy (aspirin plus clopidogrel plus cilostazol; n=1634) and dual antiplatelet therapy (aspirin plus clopidogrel; n=2569) in 4203 ST-segment elevation myocardial infarction patients who underwent primary percutaneous coronary intervention with drug-eluting stents. Selection of patients for treatment with triple antiplatelet therapy was left to the physician's discretion. Compared with dual antiplatelet therapy, triple antiplatelet therapy had a similar incidence of major bleeding events but a significantly lower incidence of in-hospital mortality. After adjustment for known confounders, triple antiplatelet therapy had significantly lower incidences of cardiac death (adjusted odds ratio, 0.52; 95% confidence interval, 0.32 to 0.84; $P=0.007$), total death (adjusted odds ratio, 0.60; 95% confidence interval, 0.41 to 0.89; $P=0.010$), and total major adverse cardiac events (adjusted odds ratio, 0.74; 95% confidence interval, 0.58 to 0.95; $P=0.019$) at 8 months than dual antiplatelet therapy. In this large, real-world clinical study in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention with drug-eluting stents, triple antiplatelet therapy not only had a good safety profile but also improved midterm clinical outcomes. Randomized trials are needed to compare the safety and efficacy of the triple and dual antiplatelet therapies in these patients.