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# Late Reperfusion with Sirolimus-eluting for ST-segment Elevated Myocardial Infarction

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*ABSTRACT*

Objective : Long-term outcomes in patients with ST-segment elevation myocardial infarction (STEMI) presenting 12 to 48 hours after symptom onset and who underwent an emergent procedure (late reperfusion) with implantation of a sirolimus-eluting stent (SES) were compared with those of bare metal stent (BMS).

Methods and Results : This retrospective, nonrandomized, and single-center study was performed in October 2012. The crude incidence of the primary endpoint (composite of cardiac death, nonfatal recurrent myocardial infarction, definite stent thrombosis, and target lesion revascularization) in the SES group ($n$=106 ; 13.2% ; mean follow-up period, 1,702±746 days ; from September 2004 through July 2010) was significantly lower than that in the BMS group ($n$=88 ; 26.1% ; 1,338±1,128 days ; from April 2003 to September 2011) ($p$=0.022). The baseline adjustment with a propensity score matching analysis produced a similar result : primary endpoint incidences in the SES and BMS groups were 10.1% and 27.5% ($n$=69, $p$=0.023), and the cumulative clinical endpoint-free rate in the SES group was significantly higher than that in the BMS group ($p$=0.004, log-rank test).

Conclusion : SES for late reperfusion in patients with STEMI was safe and effective.

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Key words : myocardial infarction, sirolimus-eluting stent, late reperfusion

## INTRODUCTION

The short-term and midterm safety and efficacy of primary stenting (treatment within 12 hours from symptom onset) with sirolimus-eluting stents (SES ; Cypher Bx Velocity, Cordis Corp., Fremont, CA, USA) for patients with ST-segment elevated myocardial infarction (STEMI) have been reported in Japan[1,2]. In addition to primary stenting with drug-eluting stents (DESs), invasive treatment with an emergent procedure for patients with STEMI presenting between 12-48 hours from symptom onset (late reperfusion) has been widely performed in Japan. A recent study has shown that late reperfusion with SES in patients with STEMI achieves long-term clinical and angiographic outcomes similar to those of primary stenting with SES[2] and supports previous studies that have shown the safety, efficacy, and benefits of late reperfusion[1,3-5]. However, because Japanese Circulation Society guidelines[6] and American College of Cardiology/American Heart Association guidelines[7] do not recommend invasive therapy for patients with STEMI presenting after 12 hours, long-term outcomes of late reperfusion with DES in patients with STEMI re-

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ceiving routine clinical practice should be further examined.

Therefore, the safety (statistically equivalent clinical outcomes) and efficacy (better angiographic outcomes) of late reperfusion with SES for patients with STEMI in Japan, where the incidence of severe cardiac events including stent thrombosis[8] is lower than that in Western countries[9], were retrospectively examined. For this purpose, in the present study, the long-term clinical and angiographic outcomes of late reperfusion with SES were retrospectively and historically compared with those of BMS by adjusting baselines with the use of a propensity score matching analysis.

## METHODS

*Study design*

This retrospective, nonrandomized, single-center study was performed at the Saitama Cardiovascular Respiratory Center. The rationale was approved by the ethics committee at Saitama Cardiovascular Respiratory Center in March 2011. The retrospective examination was performed with the permission of the ethics committee, and the clinical follow-up was performed with hospital visits, telephone calls, and letters in October 2012. The following were not prospectively randomized : stent selection (DES or bare-metal stent (BMS), after SES approval was obtained in August 2004) ; reperfusion methods used to achieve a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, such as distal protection methods and thrombosuction with thrombectomy catheters to prevent the development of slow-reflow or no-reflow phenomena ; the duration of thienopyridine agent administration ; assignment to follow-up coronary angiography (follow-up CAG) ; and drugs administered for secondary prevention[10]. All patients were informed of the intensive therapy of STEMI, including reperfusion, and consent was obtained from patients or their families or both in the Emergency Department.

*Population*

In April 2003, databases were established to collect the baseline information and variables of patients with myocardial infarction and of percutaneous coronary intervention (PCI). Consecutive patients who had STEMI and were treated with an emergent procedure with either SES or BMS implantation were enrolled, and their clinical and angiographic outcomes were evaluated. From April 2003 through September 2011, 88 patients presenting 12 to 48 hours after an initial STEMI who had not received a previous coronary artery bypass graft were treated with BMS in the native coronary arteries (BMS group). From September 2004 through July 2010, 106 patients were treated with SES for late reperfusion (SES group). Findings of follow-up CAG until April 2012 were included. The follow-up CAG was usually planned between from 6 to 12 months after BMS placement and between from 10 to 18 months after SES placement. However, because we aimed to compare long-term outcomes, all patients who underwent follow-up CAG were included, and the last CAG was considered to be follow-up CAG. The percentages of patients who had follow-up CAG were 75.0% (78 of 104 patients) in the SES group and 65.8% (52 of 79 patients) in the BMS group ($p=0.18$).

*Antiplatelet therapy*

Periprocedural antiplatelet therapy was performed as previously reported[1,2]. Before primary PCI was performed, aspirin (162-200 mg) and ticlopidine (200 mg) were immediately administered orally in the emergency department. After PCI, ticlopidine (200 mg/day) was prescribed for at least 2 weeks for the BMS group and 12 weeks for the SES group. If ticlopidine showed adverse effects, cilostazol (200-300 mg/day) or clopidogrel (75 mg/day) was administered at the physician's discretion.

*Endpoints*

The primary endpoint (cardiac events) was the composite of 1) deaths without definite noncardiac death, 2) nonfatal recurrent myocardial infarction, 3) all (early, late, and very late) definite stent thromboses as defined by the Academic Research Consortium)[8], and 4) the incidence of target lesion revascularization (TLR). The TLR observed with follow-up CAG was defined as elective, emergency repeated PCI or coronary artery bypass grafts, performed for definite ST and in-stent restenosis, including both the 5-mm proximal and distal stent margins. The need for TLR was determined on the basis of visual angiographic outcomes as in our previous studies[1,2]. Additional clinical outcomes of interest were in-hospital mortality and all-cause death. An additional angiographic outcome of inter-

est was the frequency of binary restenosis described below.

*Quantitative coronary artery angiography*

The quantitative coronary angiography variables were measured with the Cardiovascular Angiography Analysis Systems (Pie Medical Imaging BV, Maastricht, The Netherlands) as described previously[2]. Values were obtained at 3 points : before PCI (preprocedural), immediately after successful PCI (postprocedural), and at the chronic phase (follow-up). Minimal lumen diameter (MLD), percent diameter stenosis (%DS), reference diameter, and lesion length were measured. In addition, acute gain (postprocedural MLD minus preprocedural MLD) and late luminal loss (postprocedural MLD minus follow-up MLD) were calculated. Binary in-stent restenosis (binary restenosis) was defined as %DS of <50% at the chronic phase. In the occluded lesion, %DS was defined as 100 and MLD was defined as 0 mm.

*Estimated variables*

The definitions of the variables used as baseline characteristics, in particular, patient characteristics, clinical characteristics, lesion characteristics, and procedure at discharge, were as follows : the percentage of age at primary stenting more than 75 years (age ≥ 75 years) ; male sex ; diabetes mellitus status (diabetes) ; Killip classification of 3 or 4 (Killip classification 3-4) ; cardiac dysfunction (left ventricle ejection fraction of <40 as evaluated with ultrasonography, left ventriculogram, or scintigraphy) ; serum hematocrit (serum hematocrit at presentation) level, serum lactate dehydrogenase (serum LDH at presentation) level, and serum creatinine (serum creatinine at presentation) level at the emergency care unit at presentation ; culprit lesion location in the left anterior descending artery or right coronary artery ; final TIMI grade flow 2 or 3 (postprocedural TIMI grade 2 or 3 flow) ; number of stents (number of implanted stents per lesion) ; diameter of stent (maximum diameter of the balloon used to dilate the stent) ; length of stent (calculated by adding the length of each stent, regardless of overlap) ; and the clinical observational interval (duration in days until being censored after stenting).

*Statistical analyses*

Baseline characteristic variables are expressed as the mean value±standard deviation (SD). Variables and endpoints in the SES group were compared with those in the BMS group through the use of unpaired *t*-tests for continuous values and of $\chi^2$ or Fisher's tests for categorical values. A propensity score matching analysis was used to adjust the baseline values in the 2 groups, because the present study was a retrospective, nonrandomized study and a historical comparison. A propensity score matching analysis was performed using the STATA PSMATCH2 program (StataCorp LP, College Station, TX, USA) by matching 11 variables (age ≥75 years, cardiac dysfunction, Killip classification 3-4, final TIMI grade flow 2-3, serum hematocrit and LDH at presentation, left anterior descending, length of stent, postprocedural %DS and reference diameter, and acute gain) that were clinically related to the primary endpoints (11) among 18 variables shown in Table 1 with the nearest neighbor matching approach within caliper width of 0.02. The propensity for BMS use was determined with multivariable logistic regression analysis. A propensity score for BMS use was then calculated from the logistic equation for each patient. This model yielded a c statistic of 0.51 using the STATA ROCTAB program (StataCorp LP). After the baseline values were adjusted, variables and endpoints in the SES group were compared with those in the BMS group by using the Wilcoxon signed-rank test for continuous values, and McNemar's Chi-squared test for categorical values (Table 2). The cumulative primary endpoint-free rate expressed with Kaplan-Meier curves in the SES group was compared with that in the BMS group by a log-rank test after baseline adjustment (Fig. 1). A p value of less than 0.05 was considered to be statistically significant. The Stata for Windows version 13 software program (StataCorp LP) was used for the statistical analyses.

## Results

*Crude baseline characteristics of patients with STEMI after late reperfusion with either SES or BMS and outcomes*

Table 1 shows the crude baseline characteristics of patients and the clinical and angiographic outcomes in the SES group (106 patients) and the BMS group (88 patients). Among the 18 variables, the mean serum hematocrit and LDH at presentation and the length of stent in the SES group were significantly different from those in the BMS group ($p<0.001$, 0.050, and 0.022, respectively).

Table 1. Crude baseline characteristics and clinical outcomes

| (*n*) | Bare metal stent (*n*=88) | Sirolimus-eluting stent (*n*=106) | *p* Value |
|---|---|---|---|
| Age ≥75 year (%) | 30.7 | 28.3 | 0.717 |
| Male sex (%) | 80.7 | 75.5 | 0.384 |
| Diabetes mellitus (%) | 42.0 | 38.7 | 0.634 |
| Killip classification 3-4 (%) | 10.2 | 7.5 | 0.511 |
| Cardiac dysfunction (%) | 26.1 | 29.2 | 0.631 |
| Serum hematocrit at presentation (%) | 40.7±5.0 | 44.6±4.7 | <0.001 |
| Serum left anterior descending at presentation (IU/L) | 498±257 | 593±386 | 0.050 |
| Serum creatinine at presentation (mg/dL) | 0.96±0.82 | 0.89±0.40 | 0.464 |
| Left anterior descending artery (%) | 53.4 | 40.6 | 0.074 |
| Right coronary artery (%) | 29.5 | 33.0 | 0.603 |
| Final TIMI grade flow 2-3 (%) | 96.6 | 98.1 | 0.505 |
| Number of stents | 1.22±0.44 | 1.31±0.54 | 0.178 |
| Diameter of stent (mm) | 3.34±0.53 | 3.22±0.47 | 0.106 |
| Length of stent (mm) | 27.2±10.9 | 31.8±15.8 | 0.022 |
| Postprocedural minimal lumen diameter (mm) | 2.55±0.54 | 2.50±0.47 | 0.496 |
| Postprocedural % diameter stenosis | 10.4±11.1 | 13.2±8.8 | 0.055 |
| Postprocedural reference diameter (mm) | 2.84±0.54 | 2.89±0.54 | 0.521 |
| Acute gain (mm) | 2.15±0.65 | 2.19±0.61 | 0.661 |
| Number performing follow-up CAG (n) | (*n*=52) | (*n*=78) | |
| Interval for follow-up CAG (days) | 372±579 | 542±430 | 0.070 |
| Follow-up minimal lumen diameter (mm) | 1.60±0.81 | 2.31±0.85 | <0.001 |
| Follow-up % diameter stenosis (mm) | 41.2±24.7 | 28.2±22.8 | 0.002 |
| Late loss (mm) | 1.00±0.76 | 0.23±0.79 | <0.001 |
| Binary restenosis (%) | 28.8 | 12.8 | 0.023 |
| Clinical observation interval (days) | 1,338±1,128 | 1,702±746 | <0.01 |
| Cardiac events (%) | 26.1 | 13.2 | 0.022 |
| Cardiac death (%) | 6.8 | 4.7 | 0.529 |
| Nonfatal recurrent myocardial infarction (%) | 0 | 0.9 | 0.361 |
| All definite stent thrombosis (%) | 0 | 0.9 | 0.361 |
| Target lesion revascularization (%) | 19.3 | 6.6 | 0.007 |
| In-hospital mortality (%) | 3.4 | 1.9 | 0.505 |
| All-cause death (%) | 13.6 | 9.4 | 0.358 |

Abbreviations : TIMI, Thrombolysis in Myocardial Infarction ; CAG, coronary angiography

In the angiographically follow-up data in the SES (*n*=78) and BMS (*n*=52) groups, the mean follow-up MLD, follow-up %DS, and late loss and the incidence of binary restenosis in the SES group were significantly different from those in the BMS group ($p<0.001$, $=0.002$, $<0.001$, and $=0.023$, respectively).

In the endpoint-related data, the mean clinical observational interval and the frequencies of cardiac events (primary endpoint) and target lesion revascularization in the SES group were significantly different from those in the BMS group ($p<0.01$, $=0.022$, and $=0.007$, respectively).

*Baseline characteristics and outcomes after propensity score matching analysis*

Table 2 shows the baseline and outcomes in the SES and BMS groups after propensity score matching analysis (*n*=69, respectively). In the endpoint-related data, the mean clinical observational interval, and the frequencies of cardiac events (primary endpoint) and target lesion revascularization in the SES group were significantly different from those in the BMS group ($p=0.004$, 0.023, and 0.013, respectively).

Table 2. Baseline characteristics and clinical outcomes after propensity score matching analysis

| (*n*) | Bare metal stent (*n*=69) | Sirolimus-eluting stent (*n*=69) | *p* Value |
|---|---|---|---|
| Age ≥75 years (%) | 29.0 | 36.2 | 0.511 |
| Male sex (%) | 81.2 | 73.9 | 0.442 |
| Diabetes mellitus (%) | 43.5 | 34.8 | 0.345 |
| Killip classification 3-4 (%) | 7.2 | 4.3 | 0.727 |
| Cardiac dysfunction (%) | 24.6 | 26.1 | 0.853 |
| Serum hematocrit at presentation (%) | 41.0±4.6 | 42.5±5.3 | 0.052 |
| Serum lactate dehydrogenase at presentation (IU/L) | 504±244 | 541±404 | 0.917 |
| Serum creatinine at presentation (mg/dL) | 0.89±0.47 | 0.86±0.47 | 0.315 |
| Left anterior descending artery (%) | 53.6 | 58.0 | 0.736 |
| Right coronary artery (%) | 29.0 | 29.0 | 1.000 |
| Final TIMI grade flow 2-3 (%) | 98.6 | 97.1 | 0.317 |
| Number of stents | 1.20±0.44 | 1.15±0.36 | 0.450 |
| Diameter of stent (mm) | 3.35±0.49 | 3.42±0.49 | 0.529 |
| Length of stent (mm) | 26.4±10.5 | 27.1±8.9 | 0.600 |
| Postprocedural minimal lumen diameter (mm) | 2.56±0.54 | 2.52±0.64 | 0.532 |
| Postprocedural % diameter stenosis | 10.6±10.9 | 9.9±7.8 | 0.967 |
| Postprocedural reference diameter (mm) | 2.83±0.54 | 2.77±0.62 | 0.420 |
| Acute gain (mm) | 2.13±0.69 | 2.27±0.64 | 0.211 |
| Clinical observation interval (days) | 1,339±1,109 | 1,839±733 | 0.004 |
| Cardiac events (%) | 27.5 | 10.1 | 0.023 |
| Cardiac death (%) | 5.8 | 1.4 | 0.375 |
| Nonfatal recurrent myocardial infarction (%) | 0 | 1.4 | 0.317 |
| All definite stent thrombosis (%) | 0 | 1.4 | 0.317 |
| Target lesion revascularization (%) | 21.7 | 5.8 | 0.013 |
| In-hospital mortality (%) | 1.4 | 1.4 | 1.000 |
| All-cause death (%) | 13.0 | 5.8 | 0.267 |

Abbreviations : TIMI, Thrombolysis in Myocardial Infarction ; CAG, coronary angiography

*Cumulative clinical endpoint-free rates after propensity score matching analysis*

The cumulative clinical endpoint-free rate in the SES group after propensity score matching analysis was significantly higher than that in the BMS group ($p=0.004$, log-rank test) (Fig. 1).

## Discussion

A recent study with patients with STEMI showed that long-term clinical and angiographic outcomes of late reperfusion with SES were statistically equivalent with those of primary stenting[2]. Therefore, the present study was performed because the previous study did not compare long-term outcomes of late reperfusion with DES with those of BMS. Furthermore, although several reports of the safety and efficacy of late reperfusion for patients with STEMI were available[1,3-5], Japanese Circulation Society guidelines[6] and American College of Cardiology/American Heart Association guidelines[7] do not recommend invasive therapy for patients with STEMI presenting after 12 or 24 hours with stable hemodynamics. Lack of recommendation in those guidelines might be because of a lack of recent reports of late reperfusion with either BMS or DES. In the present study, late reperfusion with SES for patients with STEMI achieved a statistically better long-term (an approximately 5-year interval) clinical outcome than did late reperfusion with BMS (Table 2, Fig. 1), with SES achieving significantly lower incidences of TLR and binary restenosis than did BMS (Tables 1 and 2). Thus, the present study is the first to show that SES is superior to BMS for late reperfusion for patients with STEMI, in terms of lower rates of TLR and binary restenosis without associated safety concerns.

The benefits of late reperfusion for patients with STE-

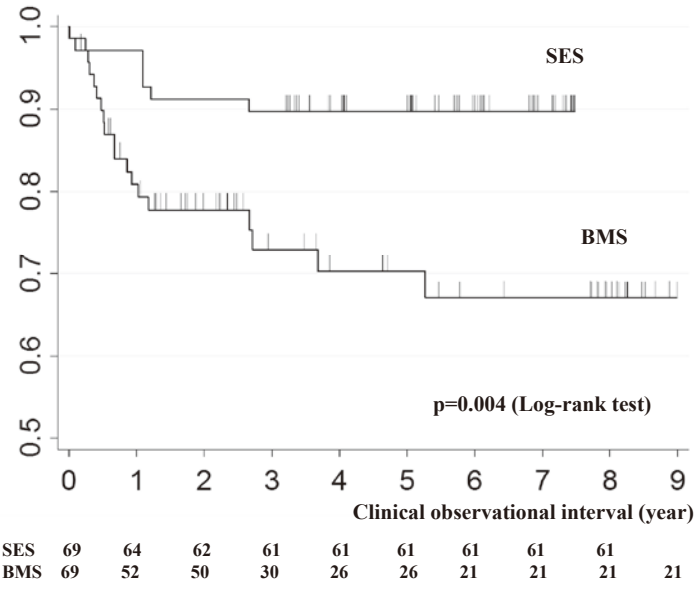


Fig. 1. Cumulative clinical endpoint-free rates
The cumulative primary endpoint-free rate in the SES group was compared with that in the BMS group. The difference was statistically significant by the log-rank test. The numbers of patients at risk during the annual follow-up period are described at the bottom.

MI were relief from persistent myocardial ischemia, myocardial salvage, electrophysiological stabilization, and decreased cost because of shortened hospitalization[4]. On the basis of recent advances in PCI modalities and the increase in operator skill, reevaluation of the safety and efficacy of late reperfusion for patients with STEMI is necessary. The present study reflects the clinical setting and included high-risk patients with complex lesion-related cardiac events and binary restenosis, such as those with cardiac dysfunction, Killip 3-4 classifications, and longer stents than those used in previous prospective randomized studies (Table 1)[3,5]. In addition, nonuse of glycoprotein IIb/IIIa inhibitors and a high rate of diabetic (as high as 40%) were other characteristics of the cohort in Japan. The incidences of total severe cardiac events in patients treated with late reperfusion with SES (6.5% during approximately 5 years) (Table 1) were slightly lower than those in previous randomized studies of primary stenting (6.9% in 155 patients with STEMI during 5 years in the Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute Myocardial Infarction (SEAMI) trial[12] and 7.6% in 355 patients with STEMI during 4 years in the Trial to Assess the Use of the CYPher Sirolimus-Eluting Coronary Stent in Acute Myocardial Infarction Treated with BallOON Angioplasty (TYPHOON)[13]. Therefore, the clinical outcome of the present STEMI cohort treated with late reperfusion with SES was as good as the well-known prospective randomized studies worldwide of primary stenting with SES, despite the many disadvantageous baselines. In addition, the incidence of cardiac death in patients treated with late reperfusion with SES (4.7%) was half of that in the invasive treatment group in the Beyond 12 hours Reperfusion Alternative Evaluation (BRAVE-2) study[3], despite the presence of high-risk patients in the daily practice environment. Therefore, the present study showed the comparable long-term safety of late reperfusion with either SES or BMS by an emergent procedure including invasive therapy, in routine Japanese clinical practice (Tables 1 and 2, Fig. 1).

In addition to the favorable long-term safety of SES with that of BMS for the present Japanese patients with STEMI treated with late reperfusion as mentioned above, it was essential to show the potent antirestenotic effect of SES compared with BMS because the benefit of SES on the angiographic outcome was consistently reported in any baselines[14]. After the baselines were adjusted in the present study, a significantly better angiographic outcome (lower TLR rate) after late reperfusion with SES for patients with STEMI was consistently observed (Table 2). Thus, the advantage of SES over BMS, in terms of better angiographic outcomes not associated with safety concerns, was con-

sistently observed in the present patients with STEMI treated with late reperfusion.

The present study has several limitations. First, the choice of stents was not randomized between BMS or SES from August 2004 through May 2007 (the time before paclitaxel-eluting stent approval ; TAXUS Express ; Boston Scientific Corp., Natick, MA, USA) and between SES and other DESs after May 2007. Second, the enrolled populations for late reperfusion with either SES or BMS were small. After the baseline adjustment, the number of patients with STEMI in each arm was further reduced (Table 2). Because approximately 80% of patients with STEMI presented within 12 hours of symptom onset[2], it was difficult to examine, on a large scale, patients with STEMI presenting 12 to 48 hours from symptom onset. Previously, we compared the outcomes after primary stenting with SES versus BMS[15] and the outcomes after primary stenting versus late reperfusion with SES[2]. Therefore, by evaluating these interrelations, the present study could reach a conclusion despite the small population. A third limitation is that the value of the c statistic of the present propensity-score matching analysis was 0.51. Similarly, as above, this c statistic would be due to the very small cohort. A fourth limitation was that the outcomes of patients with STEMI who did not undergo emergent PCI could not be fully evaluated in this nonrandomized study. The outcomes could not be fully evaluated because the number of patients who did not receive mechanical reperfusion was very small[2] and because several age-associated factors are known to play a role in the indication for an emergent procedure in patients with STEMI and stable hemodynamics[16]. A fifth limitation is that the standard deviations of the interval for follow-up CAG were wide. The standard deviations were wide because the last CAG was considered to be the follow-up CAG. Finally, the duration of dual antiplatelet therapy depended on the physician's judgment, particularly in the SES group. However, the frequency of definite stent thrombosis was extremely low in the present cohort (Tables 1 and 2).

## Conclusion

The present small, retrospective, and nonrandomized study in Japanese patients with STEMI has shown the long-term clinical safety and angiographic efficacy of SES for late reperfusion after late reperfusion, including an invasive strategy with the emergent procedure, in a daily practice environment.

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