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Original article

Retrospective comparison of clinical and angiographic outcomes after primary stenting using sirolimus-eluting and bare-metal stents in nonrandomized consecutive 568 patients with first ST-segment elevated myocardial infarctions

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Summary
Background and purpose: The long-term safety and efficacy of primary stenting using drug-eluting stents (DES) in patients with ST-segment elevation myocardial infarction (STEMI) are not fully understood in Japan. Therefore, we retrospectively examined the midterm clinical and angiographic outcomes in STEMI patients after primary stenting using sirolimus-eluting stents (SES) in a clinical setting through a historical comparison with those of bare-metal stents (BMS).
Methods and results: The study design was a retrospective, nonrandomized, and single-center study. The clinical outcomes for 568 consecutive patients who presented within 12 h of their first STEMI and who were treated with BMS ($n = 198$; 184 STEMIs from June 2003 to August 2004 and 14 STEMIs from September 2004 to May 2007) or SES ($n = 370$; from August 2004 to May

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2007) at our medical center in Japan were retrospectively investigated in February 2010. The incidence of post-discharge events (comprising cardiac death and nonfatal recurrent MI) after SES placement (3.9%) was not significantly different from that after BMS placement (6.7%). SES was not related to the risk of post-discharge events (mean follow-up for SES, 1327 ± 415 days; BMS, 1818 ± 681 days) (hazard ratio of 0.369 at 95% CI, 0.119—1.147, $p = 0.085$). The incidence of definite stent thromboses after SES placement (0.54%) was not significantly higher than that after BMS placement (0%). The incidence of binary in-stent restenosis (% diameter stenosis of more than 50% at secondary angiography) after SES placement (8.3%) was significantly lower than that after BMS placement (25.7%; $p < 0.001$).

Conclusions: From the present historical comparison of SES and BMS, we conclude that primary stenting using SES in a clinical setting has favorable clinical and angiographic outcomes in Japanese STEMI patients.

Introduction

Several randomized prospective studies have compared the safety and efficacy of primary stenting using sirolimus-eluting stents (SES) (Cypher; Cordis Corp., Miami, FL, USA) and bare-metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) [1—3]. However, because of the exclusion criteria in these studies [1—3], the safety and efficacy of SES required to support the routine clinical use of primary stenting in all STEMI patients, including high-risk STEMI patients, are not completely understood [4]. Therefore, the long-term durability of primary stenting using SES in clinical practice remains to be examined.

In Japan, only a few studies have investigated the short-term safety after primary stenting using SES in STEMI patients [5,6]. The guideline set forth by the Japanese Circulation Society [7] states that the long-term safety and efficacy of primary stenting using SES in a relatively large patient population with STEMI have not been fully investigated in Japan. SES was not used in patients with STEMI because of the major risk of stent thrombosis (ST) associated with primary stenting using drug-eluting stents (DES) [8], i.e. the incidence of ST, was not fully understood. However, the percentage of ST in Japan is significantly lower than that in Western countries [9—11]. Therefore, the evaluation of long-term safety after primary stenting using SES in Japanese STEMI patients is important; furthermore, the incidence of ST after SES placement in Japanese patients should be compared with that from western countries [1—4].

In this study, to examine the midterm safety and efficacy of primary stenting using SES in a routine clinical setting in Japan, we retrospectively investigated the clinical and angiographic outcomes after primary stenting using SES in STEMI patients. The 568 consecutive patients presenting within 12 h of their first STEMI were retrospectively compared for the incidences of (A) post-discharge events composite of death without definite non-cardiac death and nonfatal recurrent MI (re-MI); (B) angiographic binary in-stent restenosis [% diameter stenosis (DS) of more than 50% at the follow-up angiogram (fu CAG)]; and (C) the incidences of all (early, late, and very late) definite ST, as defined by the Academic Research Consortium (ARC) [12], after SES placement and after BMS placement under ticlopidine.

Methods

Population

The rationale of almost unrestricted use of DES, including their use in STEMI patients, has been previously reported [5,11]. From June 2003 to August 2004 (before SES was approved in Japan), 184 patients, presenting within 12 h [13] of their first STEMI without prior coronary artery bypass grafts (CABG), were treated using BMS in the native coronary arteries. From August 2004 to May 2007 [before the paclitaxel-eluting stent (TAXUS Express; Boston Scientific, Natick, MA, USA) was approved in Japan], 14 patients were treated using BMS and 370 patients were treated using SES. The placement of SES or BMS after SES approval was not prospectively randomized. However, 14 patients were treated using BMS for the following reasons: 3 patients with known malignancies and 2 patients with severe anemia needed further investigations; 2 patients received BMS due to their preoperative states; in 2 patients, SES could not be delivered to the culprit lesion; 2 patients, a large reference in the ectatic right coronary artery (RCA); 2 patients presented with an unknown clinical course (psychologically instability and unconsciousness); and 1 patient showed low compliance with drug continuation. Thus, we enrolled 568 consecutive patients who had their first occurrence of STEMI [BMS group ($n = 198$) and SES group ($n = 370$)]. The ratio of SES use was 96.4% in all primary stenting performed after SES approval. We retrospectively investigated the clinical outcomes in the 568 patients in February 2010. The incidences of in-hospital mortality (comprising cardiac death and nonfatal recurrent MI) after SES placement ($n = 9$, 2.4%) were not significantly different from those after BMS placement ($n = 4$, 2.0%) (mean follow-up interval for SES 13.0 ± 20.8 days; BMS 13.4 ± 10.4 days). Thus, in the present study, the clinical and angiographic outcomes in patients with SES placement who were discharged alive ($n = 361$) were compared with those with BMS placement ($n = 194$). Angiographic outcomes at the fu CAG up to February 2010 were included. The fu CAG was planned approximately 6—12 months after primary stenting for the BMS group and approximately at 10—18 months for the SES group. The percentage patient follow-up for the fu CAG in the BMS group was 78.4% (152 patients of 194 patients), and in the SES group was 73.1% (264 of 361, no significant change). After primary stenting, all patients were encour-

aged to undergo optimal medical therapy according to the guidelines for the management and secondary prevention of MI, as outlined by the Japanese Circulation Society [7,14]. Oral beta-blockers as well as angiotensin-converting enzyme inhibitors or angiotensin receptor-blockers were administered as soon as possible by checking for a contraindication (Table 1). A lipid-lowering therapy using HMG-CoA reductant (statin) was also administered by checking the level of serum low-density lipoprotein (Table 1). These drugs were continuously administered after discharge.

Table 1 Post-discharge baseline characteristics of patients receiving primary stenting with SES or BMS.

	SES $n = 361$	BMS $n = 194$
Age (years)	67.0 ± 11.6	65.5 ± 12.4
Male gender (%)	71.7	78.9
Diabetes (%)	40.7	38.1
Smoking (%)	56.2	58.8
Elapsed time (h)	3.73 ± 2.67	4.04 ± 2.53
Killip classification	1.29 ± 0.68	1.22 ± 0.63
Killip 3—4 (%)	6.1	7.2
Cardiac dysfunction (%)	20.5	7.7***
First TIMI-grade 2—3 flow (%)	34.1	32.5
Rentrop-grade 2—3 (%)	12.2	13.9
Number of diseased vessels	1.65 ± 0.73	1.57 ± 0.66
LAD/RCA/LMT	47.6/35.5/1.1	43.3/44.3*/0
Calcification (%)	3.9	4.6
Bifurcation (%)	29.4	8.2***
Thrombus (%)	14.7	22.7*
Number of stents	1.36 ± 0.56	1.23 ± 0.47**
Diameter of stent (mm)	3.29 ± 0.46	3.44 ± 0.61**
Length of stent (mm)	32.7 ± 15.8	25.0 ± 11.2***
Maximum pressure (atm)	19.6 ± 3.2	14.6 ± 2.7***
IVUS use (atm)	93.9	37.6***
Distal protection (%)	80.9	65.5***
Thrombectomy (%)	89.2	75.3***
Final TIMI-grade 2—3 flow (%)	98.1	97.9
Peak CK-MB (IU/dl)	372 ± 269	312 ± 249**
Medication at discharge		
β-Blocker (%)	69.3	68.9
ACE-I/ARB (%)	90.9	90.7
Statin (%)	69.3	68.0
Total endpoint (*n*, %)	14, 3.9	13, 6.7
Death (*n*, %)	12, 3.3	13, 6.7
Non-fatal re-MI (*n*, %)	2, 0.6	0
Post-discharge observational duration (days)	1327 ± 415	1818 ± 681***

Thirty-three baseline variables related to patients, clinical condition, lesions, and procedure and endpoint are shown. The definitions of the variables are described in the text.

* The significance of the differences between the BMS and SES groups is shown as $p < 0.05$.

** The significance of the differences between the BMS and SES groups is shown as $p < 0.01$.

*** The significance of the differences between the BMS and SES groups is shown as $p < 0.001$.

Procedures for primary stenting and antiplatelet therapy

The choice of the device used to restore a good coronary flow was subject to the doctor's discretion (nonrandomized study). Stents were implanted by visual angiographic estimation to cover the entire baseline lesion, and after SES approval, were implanted largely under the guidance of intravascular ultrasonography (IVUS-guide) (Table 1). When further stent dilation was needed, high-pressure ballooning using a non-compliant balloon [15,16] was typically carried out (Tables 1 and 3). Because the culprit lesions in STEMI may develop through a slow- or no-reflow phenomenon, a distal protection method using the PercuSurge GuardWire® (Medtronic, Santa Rosa, CA, USA) device [17] was preferred.

Periprocedural antiplatelet therapy was conducted, as previously reported [5,9,11]. At the emergency care unit, before performing primary percutaneous coronary intervention (PCI), aspirin (162—200 mg) and ticlopidine (200 mg) were immediately given orally. After the procedure, ticlopidine (200 mg/day) was prescribed for at least 2 weeks for the BMS group and 12 weeks for the SES group. Although these prescriptions were not prospectively randomized, ticlopidine was prescribed for about 1 year in accordance with the recommended guidelines [18]. Cilostazol (200—300 mg/day) or clopidogrel (75 mg/day) was administered at the doctor's discretion if ticlopidine administration showed adverse effects.

Follow-up angiography and quantitative coronary artery angiography

The details of the duration for which fu CAG was performed are given under ''Methods.'' The quantitative coronary artery angiography (QCA) parameters were measured using the TCS cardiovascular network system, as described previously [19]; their values were obtained at 3 points: before PCI (preprocedural), immediately after successful PCI (postprocedural), and at the chronic phase (follow-up) (*CAAS II system*, Pie Medical, Maastricht, The Netherlands). Minimal lumen diameter (MLD), %DS (described above), reference diameter (RD), and lesion length were measured. In addition, acute gain (postprocedural MLD minus preprocedural MLD) and late luminal loss (postprocedural MLD minus MLD at chronic phase) were calculated. Binary in-stent restenosis (binary restenosis) was defined as %DS of <50% at the chronic phase. Mehran et al. [20] reported that in-*stent* restenosis (ISR) was divided into focal (lesion length at chronic phase $\geq$10 mm) (type 1) and diffuse (<10 mm) (types 2, 3, 4) types. The ratio of type 1 (focal type) ISR in the SES group was compared with that in the BMS group. Target lesion revascularization (TLR) observed on the fu CAG was defined as any (elective or emergency) repeated PCI or CABG performed, including ISR, at the 5-mm proximal and distal stent margins [20]. The need for TLR was decided primarily on the basis of visual angiographic outcome [21], although the patient's

symptoms and the outcomes indicated by stress electrocardiograms, cardiac ultrasonography, and radionuclide images were also considered.

Endpoints

The safety endpoints of the clinical outcomes were (A) post-discharge events composite of death without definite non-cardiac death and nonfatal re-MI. The efficacy endpoint of the angiographic outcome was (B) the incidence of binary restenosis (defined above). An additional outcome of interest was (C) definite (early, late, and very late) ST, as defined by the ARC [12].

Estimated variables

The definitions of the variables used as baseline characteristics, namely, patient, clinical, lesion, and procedure at discharge, were as follows: age (age at primary stenting); male gender; diabetes (patients with diabetes mellitus); smoking (smoker at the time of primary stenting); elapsed time (interval after onset until arrival); Killip classification [22]; Killip 3—4 (Killip classification 3 or 4); cardiac dysfunction (ejection fraction of left ventricle less than 40 as evaluated by ultrasonography or left ventriculogram); first TIMI-grade 2—3 flow (TIMI-grade 2 or 3 flow at the first angiogram); Rentrop grade 2—3 (Rentrop grade 2 or 3 for collateral flow); number of diseased vessels (number of diseased vessels of the native coronary artery); location of the culprit lesion in the left anterior descending (LAD) artery, RCA, or left main trunk (LMT); calcification (calcified lesions, estimated using an angiogram and IVUS); bifurcation (bifurcative lesions requiring any treatment of the side branch); thrombus (thrombus-containing lesion; the previous 4 variables have been defined according to the American College of Cardiology/American Heart Association classification of lesions); 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 (length of the stented segment, calculated by adding the length of each stent, regardless of overlap); maximum pressure (maximum pressure at the maximum inflation diameter of the balloon); IVUS use (availability of IVUS during PCI); distal protection (lesions treated with the PercuSurge GuardWire device); thrombectomy (performing thrombectomy using any thrombosuction catheter); final TIMI-grade 2—3 flow (postprocedural TIMI-grade 2 or 3 flow); peak CK-MB (peak serum level of myocardial creatine kinase isoenzyme measured every 3 h); and post-discharge observational duration (duration in days until censored after discharge).

Statistics

Baseline characteristic variables are expressed as a mean value $\pm$ standard deviation (SD). Comparisons of variables between the BMS and SES groups were conducted using unpaired t-tests for continuous values and χ^2 tests for categorical values. Predictors of binary restenosis were analyzed using logistic regression analysis by including 27 related variables, as shown in Tables 3 and 4. Cumulative post-discharge endpoint-free and binary restenosis-free ratios were expressed using Kaplan—Meier curves. The Cox proportional hazard model was used to analyze the predictors of post-discharge events by including 22 related variables. A difference was considered significant when the p-value was less than 0.05. Stata for Windows version 8 (StataCorp, College Station, TX, USA) was used for statistical analysis.

Results

Post-discharge baseline characteristics

Table 1 shows the post-discharge baseline characteristics of patients receiving primary stenting with SES ($n = 361$) and BMS ($n = 194$). Thirteen variables in the SES group were significantly different from those in the BMS group. Among patient and clinical characteristics, the percentage of cardiac dysfunction (20.5%) and the mean peak level of CK-MB (372 ± 269 IU/dl) in the SES group were significantly different from those in the BMS group ($p < 0.001$ and $p < 0.01$, respectively). Among the lesion characteristics, the percentages of bifurcation lesions (29.4%), thrombus lesions (14.7%), and RCA lesions (35.5%) in the SES group were significantly different from those in the BMS group ($p < 0.001$, $p < 0.05$, and $p < 0.05$, respectively). Among the procedural characteristics, IVUS use (93.9%), distal protection (80.9%), thrombectomy (89.2%), mean number of stents (1.36 ± 0.56), diameter of stents (3.29 ± 0.46), length of stents (32.7 ± 15.8), and maximum pressure (19.6 ± 3.2) in the SES group were significantly different from those of the BMS group ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.01$, $p < 0.01$, $p < 0.001$, and $p < 0.001$, respectively). The ratios of three types of medicines for the secondary prevention at discharge were not significantly different in both groups. The mean post-discharge observational duration in the SES group (1327 ± 415 days) was significantly shorter than that in the BMS group (1818 ± 681 days, $p < 0.001$). The percentages of endpoints were not significantly different between the 2 groups.

Clinical endpoint after discharge

The cumulative post-discharge endpoint-free ratio for the SES group was not significantly different from that for the BMS group ($p = 0.44$, by the log-rank test) (Fig. 1), although the cumulative post-discharge endpoint-free ratio for the SES group was approximately 500 days less than that for the BMS group. Using the Cox proportional hazard model, age [hazard ratio (HR) of 1.090, 95% CI, 1.031—1.153, $p < 0.01$], Killip classification (HR of 1.833, 95% CI, 1.124—2.990, $p < 0.05$), and calcification (HR of 3.794, 95% CI, 1.090—13.20, $p < 0.05$) were the significant predictors of post-discharge endpoints. SES was not related to the post-discharge endpoint (HR of 0.369, 95% CI, 0.119—1.147, $p = 0.085$) (Table 2).

Table 2 Predictors of post-discharge endpoint.

	Hazard ratio	95% CI		*p*-Value
		Lower limb	Upper limb	
Age	1.090	1.031	1.153	<0.01
Killip classification	1.833	1.124	2.990	<0.05
Calcification	3.794	1.090	13.200	<0.05
Diabetes	2.453	0.931	6.464	0.070
⋮				⋮
SES	0.369	0.119	1.147	0.085
⋮				⋮

Predictors of post-discharge endpoint analyzed by the Cox proportional hazard model are shown. The definitions of the variables are described in the text. The first 3 variables were significant predictors, but the others including SES were not related to the post-discharge endpoint.

Angiographic outcomes

Table 3 shows the baseline characteristics of patients after performing fu CAG. As shown in Table 1, 13 variables were significantly different between the SES ($n = 264$) and BMS ($n = 152$) groups.

Table 4 shows the results from the serial QCA after performing fu CAG. Eight variables were significantly different in both groups, excluding pre and postprocedural RD. Although the mean value of acute gain in the SES group was not significantly different from that in the BMS group, that of late luminal loss in the SES group (0.201 ± 0.658 mm) was significantly lower than that in the BMS group (0.818 ± 0.705 mm) ($p < 0.001$). The incidences of binary restenosis (8.2%) and TLR (9.4%) in the SES group were significantly lower than those in the BMS group (24.7% and 23.3%, $p < 0.001$ and $p < 0.001$, respectively). The incidence of mild in-stent stenosis (%DS of more than 45% at the chronic phase) in the SES group (9.8%) was also significantly lower than that in the BMS group (32.2%, $p < 0.001$). The incidence of type-1 (focal) ISR among all the binary restenoses in the SES group (61.9%) was significantly higher than that in the BMS group (36.1%, $p < 0.001$). The mean observation interval for follow-up secondary angiograms taken after primary stenting in the SES group (455 ± 269 days) was significantly longer than that for the BMS group (308 ± 394 days, $p < 0.001$).

Fig. 2 shows that the cumulative binary restenosis-free ratio for the SES group was significantly higher than that for the BMS group ($p < 0.01$, by the log-rank test).

Table 5 shows the predictors of binary restenosis using logistic regression analysis. By a multivariate analysis, SES [odds ratio (OR) of 0.231, 95% CI 0.129—0.413, $p < 0.001$] and diameter of stent (OR of 0.475, 95% CI 0.266—0.851, $p < 0.05$) were the predictors of binary restenosis in 416

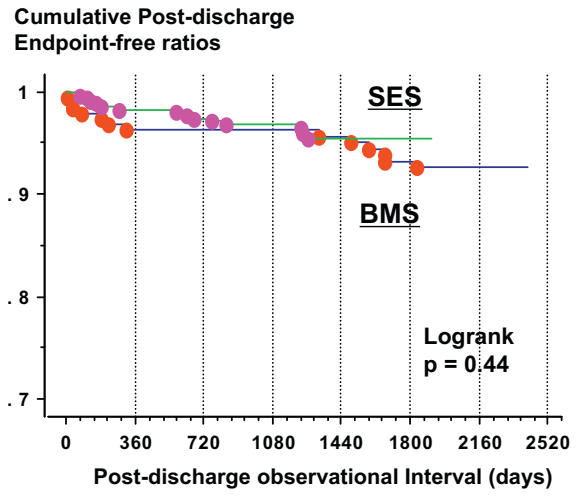

Figure 1 Cumulative post-discharge endpoint-free ratios for the bare-metal stents (BMS) and sirolimus-eluting stents (SES) groups. The vertical axis expresses the cumulative post-discharge endpoint-free ratio (%) and the horizontal axis expresses the interval after discharge (days).

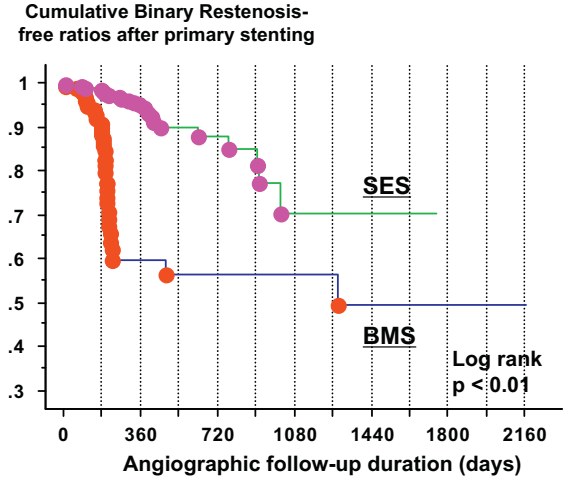

Figure 2 Cumulative binary restenosis-free ratios for the bare-metal stents (BMS) and sirolimus-eluting stents (SES) groups. The vertical axis expresses the cumulative binary restenosis-free ratio (%) and the horizontal axis expresses the interval after primary stenting until secondary angiogram (days).

Table 3 Baseline characteristics of patients after follow-up secondary angiography.

	SES $n=264$	BMS $n=152$
Age (years)	64.2 ± 10.4	63.9 ± 10.7
Male gender (%)	75.4	80.9
Diabetes (%)	41.3	40.8
Smoking (%)	59.1	61.8
Elapsed time (h)	3.60 ± 2.64	4.01 ± 2.60
Killip classification	1.22 ± 0.59	1.12 ± 0.46
Killip 3—4 (%)	4.2	3.3
Cardiac dysfunction (%)	19.3	7.2***
First TIMI-grade 2—3 flow (%)	29.9	29.6
Rentrop-grade 2—3 (%)	15.1	12.5
Number of diseased vessels	1.59 ± 0.68	1.49 ± 0.61
LAD/RCA/LMT	49.6/33.0/0.8	41.4/46.1**/0
Calcification (%)	2.3	4.1
Bifurcation (%)	29.2	6.6***
Thrombus (%)	12.5	21.7*
Number of stents	1.38 ± 0.59	1.25 ± 0.49*
Diameter of stent (mm)	3.28 ± 0.45	3.45 ± 0.59*
Length of stent (mm)	33.5 ± 16.3	25.2 ± 11.4***
Maximum pressure (atm)	19.5 ± 3.1	14.6 ± 2.8***
IVUS use (%)	93.2	38.8***
Distal protection (%)	82.2	67.1***
Thrombectomy (%)	90.2	75.0***
Final TIMI-grade 2—3 flow (%)	97.3	98.0
Peak CK-MB (IU/dl)	377 ± 269	318 ± 253*

Twenty-six baseline variables related to patients, clinical condition, lesions, and procedure are shown. The definitions of the variables are described in the text.
* The significance of the differences between the BMS and SES groups is shown as $p < 0.05$.
** The significance of the differences between the BMS and SES groups is shown as $p < 0.01$.
*** The significance of the differences between the BMS and SES groups is shown as $p < 0.001$.

Table 4 Serial quantitative coronary angiography findings after follow-up secondary angiography.

	SES $n=264$	BMS $n=152$
Pre-procedural		
MLD (mm)	0.296 ± 0.428	0.521 ± 0.676***
%DS	88.8 ± 15.7	82.9 ± 22.1**
RD (mm)	2.85 ± 0.535	2.88 ± 0.623
Lesion length (mm)	19.5 ± 9.53	15.3 ± 8.99***
Post-procedural		
MLD (mm)	2.52 ± 0.441	2.65 ± 0.540**
%DS	14.7 ± 9.25	11.3 ± 12.8*
RD (mm)	2.97 ± 0.500	3.03 ± 0.633
Follow-up		
MLD (mm)	2.32 ± 0.712	1.83 ± 0.813***
%DS	25.0 ± 18.7	36.7 ± 23.9***
RD (mm)	3.10 ± 0.564	2.86 ± 0.665***
Lesion length (mm)	4.83 ± 3.92	13.3 ± 9.39***
Acute gain (mm)	2.22 ± 0.588	2.13 ± 0.775
Late luminal loss (mm)	0.201 ± 0.658	0.818 ± 0.705***
Binary restenosis (%)	8.2	24.7***
Follow-up %DS ≥ 45 (%)	9.8	32.2***
Type-1 ISR/total ISR (%)	61.9	36.1***
TLR (%)	9.4	23.3***
Angiographic follow-up duration (days)	455 ± 269	308 ± 394***

Seventeen variables related to angiographic outcomes are shown. The definitions of the variables are described in the text: angiographic followed-up duration (duration until performing latest followed-up angiogram after primary stenting).
* The significance of the differences between the BMS and SES groups is shown as $p < 0.05$.
** The significance of the differences between the BMS and SES groups is shown as $p < 0.01$.
*** The significance of the differences between the BMS and SES groups is shown as $p < 0.001$.

STEMI patients after performing primary stenting with BMS or SES. The length of stent was a significant predictor of binary restenosis, as determined by a univariate analysis.

Incidence of definite stent thrombosis after primary stenting

The incidence of total definite ST events in the SES group (0.54%) (2 cases in 370 STEMIs) was not significantly different from that in the BMS group (0%). No definite ST was observed in the BMS group after stent placement in 198 patients. In the SES group, no definite early and late ST was observed; however, 2 cases of definite, very late ST were implicated in cardiac death and nonfatal re-MI during the post-discharge observational interval.

Discussion

This study mainly indicated a favorable midterm (a mean follow-up period of more than 1300 days) post-discharge clinical and angiographic outcomes of primary stenting using SES in a routine clinical setting in Japanese STEMI patients with very low incidence of definite ST under aspirin plus ticlopidine therapy (Tables 2, 4 and 5; Figs. 1 and 2). The present study included the high-risk patients with complex lesion-related cardiac events, ST events, and binary restenosis, such as those with Killip 3—4 classifications [22], bifurcation [23], calcification [24], thrombus lesions [25], and LMT lesions [22]; higher mean peak values of CK-MB >300 (IU/dl) [26], and longer stents [27] compared to those in previous prospective randomized studies [1—3] (Table 1). In addition, no use of glycoprotein IIb/IIIa inhibitors [28], a proportion of diabetic patients as high as 40% [29], and a

Table 5 Predictors of in-stent binary restenosis.

	Univariate analysis				Multivariate analysis			
	Odds ratio	95% CI		*p*-Value	Odds ratio	95% CI		*p*-Value
		Lower limb	Upper limb			Lower limb	Upper limb	
SES	0.095	0.037	0.243	<0.001	0.231	0.129	0.413	<0.001
Diameter of stent	0.313	0.117	0.838	<0.05	0.475	0.266	0.851	<0.05
Length of stent	3.395	0.838	13.800	0.087				

Predictors of in-stent binary restenosis (BR) analyzed by logistic regression analysis are shown. The definitions of the variables are described in the text.

relatively high percentage of cardiac dysfunction [30] were some of the other characteristics of the cohort.

The long-term safety of SES use for STEMI patients has been an unresolved issue in the DES era [4] and also in Japan [7]. Particularly, stent thromboses [early, late, and very late STs (VLST)] implicated in the devastating outcomes have been the major concern for DES use for STEMI [4], because STEMI was a powerful predictor of ST [8,10]. In the present cohort, the composite incident ratio of cardiac death and re-MI (6.3%) with mean follow-up periods (approximately 3.5 years) was acceptable compared to the previous reports from western countries after primary stenting using SES for more than 150 STEMI patients [1—3]: 5.7—10.1% at 3—4 years, although the predictors of mortality listed above were partially excluded in those studies. In addition, the incidence ratio of definite ST events (0.54%) at the present mean follow-up periods were particularly lower than those in previous reports after primary stenting using SES in more than 150 STEMI patients [1—3]: 1.9—3.6% at 3—4 years, although the predictors of ST listed above were partially excluded in those studies. This low incidence of definite STs was attributable to the acceptable low incident ratio of post-discharge cardiac event in this clinical practice setting. First of all, in the present cohort of 568 consecutive Japanese STEMI patients, none of the incidences of early definite ST events was one of the major reasons for the lower incidence of total definite ST events after primary stenting, because the incident ratio of early definite ST occurred in 0.6—1.3% in other studies after SES treatment [1—3]. This advantage of the present cohort would be primarily due to optimal stenting techniques (technical factors) [31], such as better high-pressure dilation (close to the rated value in the present study) compared to previous reports (close to the nominal value) [1]; high-pressure ballooning [15,16] to prevent no-/slow-flow phenomenon with an efficient utilization of distal protection using the PercuSurge GuardWire system [17], one of the predictors of ST [31]; and efficient use of IVUS-guidance [32], particularly in the SES group (Table 1). None of the late ST events in the present cohort might be due to this technical benefit or due to the performing ratio of fu CAG (more than 70%), because the late ST events were considered to be related to the aggressive restenosis process [33]. The very low incidence of VLST (0.54%) in the present Japanese STEMI patients compared to those western reports [1—3] should be estimated in a larger scale cohort with further longer intervals, because many factors: persistent inflammation (hypersensitivity), incomplete endothelialization, late malapposition, and persistent contrast stains are considered to relate to VLST [33].

The angiographic efficacy of SES was primarily due to a significant decrease in the mean value of late luminal loss and the incidences of binary restenosis and TLR (approximately 60% reduction) after the fu CAG compared to those of BMS (Table 4). This efficacy of SES in primary stenting is consistent with previous prospective reports [1—4]. The high incidences of binary restenosis and TLR have been a limitation in using BMS for the treatment of STEMI [4]. On the other hand, SES was a protective predictor of binary restenosis in STEMI (Table 5), although the adverse baseline characteristics, as described above, were present in the SES group (Table 3). In addition, Fig. 2 shows the midterm efficacy of SES in the treatment of STEMI. Thus, the present study indicates the midterm favorable safety and efficacy of primary stenting using SES in a routine clinical setting in patients with STEMI. The study also determines the adverse baseline characteristics of the SES group through a historical comparison with those in the BMS group. Thus, a large-scale, long-term, randomized controlled trial is needed to clarify the durability of primary stenting using DES in Japanese STEMI patients.

Several limitations must be taken into account. First, the present study was a retrospective, non-randomized, and single-center analysis. The SES use ratio after SES approval (96.4%) was very high. Thus, the outcomes of SES were compared with those of BMS through a historical comparison. Second, the duration of dual antiplatelet therapy was dependent on the doctor's judgment, particularly for the SES group. The number of patients who discontinued the medical therapy, including the dual antiplatelet therapy, due to surgical and bleeding complications, was not fully examined nor was low compliance. However, there was no increase in the number of post-discharge events or definite ST events (Table 1). Third, other consistent predictors for cardiac events in STEMI patients, such as medicines, renal dysfunction, and anemia, were not fully estimated. Fourth, since TLR was decided mainly by our visual estimation, the occulo-stenotic reintervention after fu CAG was included, particularly in the SES group. The percentage of TLR was similar to that of intermediate stenosis (%DS more than 45%) in the SES group (Table 4). This was due to the benefit of patency of the infarcted-related artery [21,34]. This issue involving the long-term outcome of reintervention after primary stenting using DES or BMS along

with cost-effectiveness [35] of the procedure should be further investigated.

Conclusions

The midterm (mean interval, 3.5 years) clinical and angiographic outcomes of primary stenting using SES in Japanese STEMI patients in a clinical practice setting were favorable, as determined by a historical comparison with those of BMS.

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