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Original article

Relation between stent thrombosis and calcium channel blocker after drug-eluting stent implantation
Kumamoto Intervention Conference Study (KICS) registry

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ABSTRACT

Background: Stent thrombosis (ST) has emerged as a severe complication of percutaneous coronary intervention (PCI). Since the occurrence of ST is lower in Japan than Western countries, there are few data to predict ST after drug-eluting stent (DES) implantation in Japan. We examined the independent predictors of ST incidence after DES implantation in Japanese patients, including the use of calcium channel blockers (CCBs).

Methods and results: We used data from the Kumamoto Intervention Conference Study registry. There were 6286 consecutive patients enrolled from June 2008 to March 2011. Among them, we analyzed 3493 patients who underwent DES implantation. The incidence of definite/probable ST throughout a median follow-up period of 364 days was 0.57% (20 patients). There were 8 patients with early ST (within 30 days), 8 patients with late ST (between 31 and 365 days), and 4 patients with very late ST (after 1 year). The frequency of CCB use was significantly lower in ST than non-ST patients (25.0% versus 51.4%, respectively, $p = 0.016$). Multiple regression analysis showed that longer stent length ($p = 0.034$), acute coronary syndrome ($p = 0.039$), and the absence of CCB use ($p = 0.046$) were significant and independent predictors of ST within 1 year.

Conclusions: These results suggest that CCB use may be associated with a decreased risk of ST after DES implantation within 1 year in Japanese patients.

Introduction

Percutaneous coronary intervention (PCI) is an established treatment for coronary heart disease (CHD) [1]. Stent thrombosis (ST) has emerged as a severe complication of PCI with stenting [2]. Regardless of the drug-eluting stent (DES) or bare metal stent (BMS), concern about ST has been raised including the timing, such as early, late, and very late phases, especially in acute coronary syndrome (ACS) patients [3,4]. Although DES implantation is reported to be associated with very late stent thrombosis [5,6], recent studies demonstrate that there is no concern about stent thrombosis regarding second generation DESs [7]. The occurrence of ST is lower in Japan than Western countries [3,4]; therefore, there are few data to predict ST after DES implantation in Japanese patients. Dual antiplatelet therapy (DAPT) is currently recommended for the prevention of adverse cardiovascular events in patients undergoing PCI and patients with ACS [8–10]. However, ST also may occur in patients who are taking DAPT. It remains unknown whether any other drug therapy affects the occurrence of ST after DES implantation. The present study was therefore conducted to examine the independent predictors of ST after DES implantation in Japanese patients, including prescription drug therapy.

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Methods

Study population

We used data from the Kumamoto Intervention Conference Study (KICS) registry. KICS is a physician-initiated, non-company-sponsored, multicenter registry enrolling consecutive procedures undergoing PCI in 16 centers in Japan. Written informed consent was obtained from all patients. There were 6286 consecutive patients who underwent PCI between June 2008 and March 2011. The exclusion criteria were: (1) percutaneous balloon angioplasty or thrombus aspiration without coronary stent implantation, (2) unsuccessful PCI, and (3) in-hospital death. We excluded in-hospital death because we would like to examine the effect of any prescriptions for ST. We excluded 2 in-hospital deaths by ST because both cases occurred before stable conditions. The selection of treatment was left to the discretion of the attending physicians at each hospital. After excluding 557 patients based on the criteria above, there were 5729 patients who underwent stent implantation. Among these patients, 3493 had successful DES implantation and were used in the final analysis (Fig. 1).

Clinical outcomes and definitions

The endpoint of this study was the occurrence of definite/probable ST. ST was defined according to the Academic Research Consortium criteria [11]. Cardiovascular (CV) events were defined as CV death, non-fatal myocardial infarction (MI), and ischemic stroke. CV death was defined as death from MI, congestive heart failure or documented sudden cardiac death. The universal definition of MI was used [12]. We performed a follow-up survey to evaluate clinical outcomes throughout a median follow-up period of median 364 days (261–523 days).

Statistical analysis

Continuous variables are expressed as the mean ± SD. Categorical variables are expressed as frequencies and percentages. Continuous variables were compared between groups using a Student's *t*-test, and categorical variables were compared using a chi-square test. Univariate and multivariate logistic regression analyses were performed to determine the predictors of ST. The odds ratios (ORs) and 95% confidence intervals (CIs) were determined from the logistic regression analysis. A p-value <0.05 was regarded as significant. We performed all statistical analyses with SPSS 19 (Chicago, IL, USA).

Results

Subject characteristics

In 3493 patients who underwent DES implantation, the incidence of definite/probable ST throughout a median follow-up period of 364 days was 0.57% (20 patients). There were 18 (90%) definite and 2 (10%) probable ST. There were 8 patients with early ST (EST, within 30 days), 8 patients with late ST (LST, from 31 to 365 days), and 4 patients with very late ST (VLST, after 1 year). The longest duration until ST occurrence was 810 days after PCI. Table 1A shows the clinical characteristics according to ST incidence. The rate of ACS was significantly higher in the ST than the non-ST group (65.0% versus 36.3%, respectively, $p = 0.009$). When we replaced ACS with unstable angina pectoris or acute MI, the results were similar. Other parameters, such as general health status and classical risk factors, were similar between the two groups. Table 1B shows the angiographic characteristics of each group. The presence of emergency PCI, severe pre-stenosis, and acute occlusion (as a complication) was significantly higher in the ST than non-ST group. In the ST group, the mean stent diameter was significantly smaller (2.5 ± 0.7 mm versus 2.9 ± 0.8 mm, $p = 0.033$) and stent length was significantly longer (23.8 ± 4.5 mm versus 20.6 ± 6.7 mm, $p = 0.001$) than in the non-ST group. Lesion complexity, the use of mechanical supports, and the complication rate were similar between the two groups. Fig. 2 shows the occurrence of ST based on the actual number of DESs implanted (5371) rather than the number of patients (3493). Sirolimus-eluting (SES) (26.4%), paclitaxel-eluting (PES) (27.6%), and everolimus-eluting (EES) (25.8%) stents were the major stent types used in this study. The occurrence of ST was 0.49% in SES, 0.40% in PES, 0.35% in zotarolimus-eluting stent (ZES), and 0.25% in EES. EES showed lower rate of ST occurrence compared with any other stents, especially first-generation DES (SES and PES). These results corresponded with a previous study [7]. The occurrence of ST after 1 year (VLST) was lower in second-generation DES (ZES and EES) (14.3%) compared with first-generation DES (SES and PES) (23.1%).

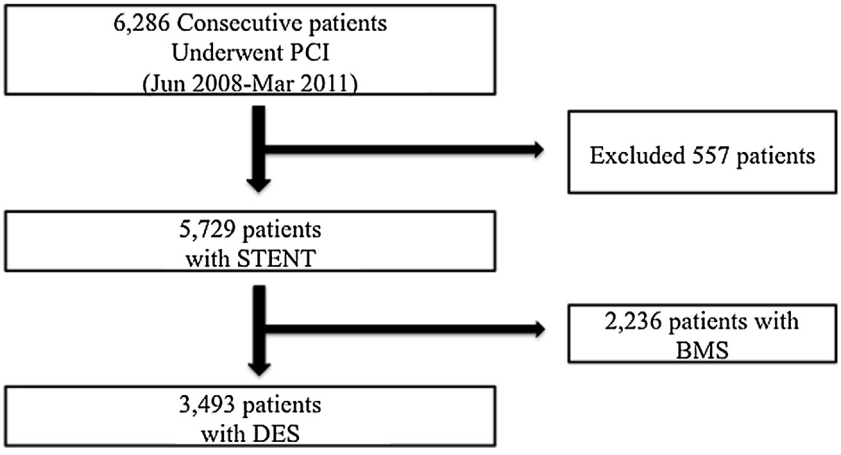

Fig. 1. Study population. There were 6286 consecutive patients who underwent PCI between June 2008 and March 2011. After excluding 557 patients based on the criteria above, there were 5729 patients who underwent stent implantation. Among these patients, 3493 had successful DES implantation and were used in the final analysis. PCI, percutaneous coronary intervention; DES, drug-eluting stent; BMS, bare metal stent.

Table 1A
Comparison of clinical characteristics between non-stent thrombosis and stent thrombosis.

	All ($n=3493$)	Non-ST ($n=3473$)	ST ($n=20$)	p
Male	2492 (71.3%)	2478 (71.4%)	14 (70.0%)	0.529
Age (years)	69.8 ± 10.2	69.8 ± 10.2	68.0 ± 9.9	0.425
BMI (kg/m^2)	24.0 ± 3.6	24.0 ± 3.6	23.0 ± 3.2	0.210
HbA1c (%)	6.2 ± 1.3	6.2 ± 1.3	6.6 ± 1.1	0.266
Prior MI	860 (24.6%)	855 (24.6%)	5 (25.0%)	0.570
Prior CABG	218 (6.2%)	215 (6.2%)	3 (15.0%)	0.125
Prior stroke	491 (14.1%)	486 (14.0%)	5 (25.0%)	0.139
Prior PAD	327 (9.4%)	326 (9.4%)	1 (5.0%)	0.429
Hypertension	2840 (81.3%)	2823 (81.3%)	17 (85.0%)	0.470
Dyslipidemia	2349 (67.2%)	2337 (67.3%)	12 (60.0%)	0.318
Diabetes mellitus	1298 (46.3%)	1288 (46.2%)	10 (50.0%)	0.147
Hemodialysis	198 (5.7%)	197 (5.7%)	1 (5.0%)	0.685
Current smoker	745 (21.3%)	741 (21.4%)	4 (20.0%)	0.571
ACS	1275 (36.5%)	1262 (36.3%)	13 (65.0%)	0.009
Killip ≧ 2	210 (8.4%)	210 (8.4%)	0 (0%)	0.188

ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; HbA1c, glycated hemoglobin A1c; MI, myocardial infarction; PAD, peripheral artery disease; ST, stent thrombosis.

Table 1B
Comparison of angiographic characteristics between non-stent thrombosis and stent thrombosis.

	All ($n=3493$)	Non-ST ($n=3473$)	ST ($n=20$)	p
Emergent PCI	574 (17.0%)	584 (16.8%)	10 (50.0%)	<0.001
IVUS	2472 (70.8%)	2466 (71.0%)	6 (30.0%)	<0.001
Distal protection	87 (2.5%)	87 (2.5%)	0 (0%)	0.603
Thrombus aspiration	324 (9.3%)	320 (9.2%)	4 (20.0%)	0.108
Disease vessel ≧ 2	1737 (50.5%)	1730 (50.5%)	7 (35.0%)	0.227
Left main lesion	227 (6.5%)	225 (6.5%)	2 (10.0%)	0.377
Lesion morphology B2 or C	2059 (60.0%)	2045 (59.9%)	14 (70.0%)	0.094
Mean stent diameter (mm)	3.2 ± 0.5	2.9 ± 0.8	2.5 ± 0.7	0.033
Mean stent length (mm)	29.2 ± 5.9	20.6 ± 6.7	23.8 ± 4.5	0.012
Post dilatation	2386 (68.3%)	2377 (68.4%)	10 (50.0%)	0.067
Rotational atherectomy	234 (6.7%)	232 (6.7%)	2 (10.0%)	0.392
IABP	102 (2.9%)	101 (2.9%)	1 (5.0%)	0.448
Cardiac ECMO	4 (0.1%)	4 (0.1%)	0 (0%)	0.977
Pre-stenosis ≧ 99%	1174 (33.7%)	1161 (33.5%)	13 (65.0%)	0.004
Post stenosis > 50%	349 (9.5%)	336 (9.5%)	3 (15.0%)	0.296
Procedural complications				
Slow flow or no reflow	142 (4.1%)	142 (4.1%)	0 (0%)	0.433
Acute occlusion	18 (0.5%)	16 (0.5%)	2 (10.0%)	0.005
Emergent CABG	5 (0.1%)	5 (0.1%)	0 (0%)	0.972
Stroke	12 (0.3%)	12 (0.3%)	0 (0%)	0.933
Bleeding	26 (0.7%)	26 (0.7%)	0 (0%)	0.927

CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; IABP, intra aortic balloon pumping; IVUS, intravascular ultrasonography; PCI, percutaneous coronary intervention; ST, stent thrombosis.

Prescriptions

We also compared the rate of prescription drug use between the ST and non-ST groups in EST, LST, and VLST, respectively (Table 2). In 3493 patients who underwent DES implantation, 1790 patients (51.2%) received a calcium channel blocker (CCB). Patients who were relatively stable following DES implantation, without congestive heart failure and with hypertension, tended to be administered CCB after DES implantation. However, there was no difference in patients' background and lesion characteristics between with and without CCB. Patients who were relatively stable following DES implantation, without congestive heart failure, ACS, and no classical risk factors, tended to be administered CCB after DES implantation (Table 3A), while patients who were relatively severe conditions, with multi-vessel disease and left main trunk stenosis, had a tendency to avoid CCB (Table 3B). There were 1459 (81.7%) patients who received a dihydropyridine agent, 314 (17.5%) who received a non-dihydropyridine agent, and 17 (0.8%) who received an unknown type of CCB. Nifedipine (all agents were long-acting type) was the most commonly used agent (571 patients, 31.9%). The rates of use of other prescription drugs were similar between the two groups. The frequency of CCB use was significantly lower in the ST than the non-ST group (25.0% versus 51.4%, respectively, $p = 0.016$). This tendency was prominent in patients with both EST (12.5% versus 51.3%, $p = 0.030$) and LST (12.5% versus 51.3%, $p = 0.030$). There was no significant difference in the use of aspirin and thienopyridine derivative between ST and non-ST.

Clinical outcomes

We analyzed clinical outcomes according to CCB use (Table 3C). The occurrence of all ST was lower in patients with than without CCB use (0.3% versus 0.9%, $p = 0.016$). This tendency was observed in cases of EST and LST, but not VLST. Moreover, there was less CV death in patients who received a CCB (0.6% versus 1.4%, $p = 0.020$). There were no significant differences in all-cause death, non-CV death, non-fatal MI, non-fatal stroke or bleeding due to any cause.

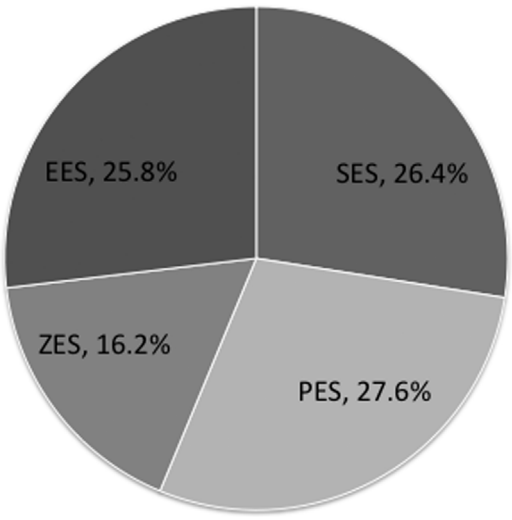

Fig. 2. Occurrence of stent thrombosis based on actual number of DES implanted. Total 5371 DESs were implanted. SES (26.4%), PES (27.6%), and EES (25.8%) were the major stent types used in this study. The occurrence of ST was 0.49% in SES, 0.40% in PES, 0.35% in ZES, and 0.25% in EES. EES showed lower rate of ST occurrence compared with any other stents, especially first-generation stent (SES and PES). DES, drug-eluting stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent; EES, everolimus-eluting stent.

Univariate and multivariate regression analysis

We examined predictors of ST using both univariate and multivariate Cox regression models. In univariate analysis, ACS, severe pre-stenosis (>99%), longer stent length (>20 mm), and the non-use of CCB were predictors of all ST (EST + LST + VLST). In multivariate analysis, only longer stent length was an independent predictor of all ST (OR, 7.142; 95% CI, 1.604–31.801; $p = 0.01$) (Table 4A). Given that there may be a relation between non-use of CCB and ST within 1 year, we performed multivariate analysis for ST within 1 year (Table 4B) or more than 1 year (Table 4C). For ST within 1 year, ACS, longer stent length, and lack of CCB use were predictors in univariate analysis. In multivariate analysis, ACS (OR, 3.715; 95% CI, 1.069–12.909; $p = 0.039$), longer stent length (OR, 5.239; 95% CI, 1.132–24.252; $p = 0.034$), and lack of CCB use (OR, 0.209; 95% CI, 0.045–0.973; $p = 0.046$) were independent predictors of ST within 1 year (Table 4B). For ST more than 1 year, multivariate analysis showed there were no independent predictors of ST (Table 4C).

Table 3A
Comparison of clinical characteristics between CCB and non-CCB.

	CCB (−) ($n = 1703$)	CCB (+) ($n = 1790$)	p
Male	1231 (72.3%)	1261 (70.5%)	0.127
Age (years)	69.5 ± 10.8	70.2 ± 9.7	0.039
BMI (kg/m^2)	23.7 ± 3.7	24.4 ± 3.4	<0.001
HbA1c (%)	6.2 ± 1.4	6.2 ± 1.2	0.178
Prior MI	453 (26.6%)	407 (22.7%)	0.005
Prior CABG	111 (6.5%)	107 (6.0%)	0.278
Prior stroke	239 (14.0%)	252 (14.1%)	0.505
Prior PAD	133 (7.8%)	194 (10.8%)	0.001
Hypertension	1226 (72.0%)	1614 (90.2%)	<0.001
Dyslipidemia	1140 (66.9%)	1209 (67.5%)	0.366
Diabetes mellitus	599 (44.3%)	699 (48.2%)	0.02
Hemodialysis	70 (4.1%)	128 (7.2%)	<0.001
Current smoker	387 (22.7%)	358 (20.0%)	0.027
ACS	704 (41.3%)	571 (31.9%)	<0.001
Killip ≧ 2	123 (9.5%)	87 (7.2%)	0.023

ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CCB, Ca-channel blocker; HbA1c, glycated hemoglobin A1c; MI, myocardial infarction; PAD, peripheral artery disease; ST, stent thrombosis.

Table 3B
Comparison of angiographic characteristics between CCB and non-CCB.

	CCB (−) ($n = 1703$)	CCB (+) ($n = 1790$)	p
Emergent PCI	413 (24.3%)	181 (10.1%)	<0.001
IVUS	1183 (69.5%)	1289 (72.0%)	0.053
Distal protection	40 (2.3%)	47 (2.6%)	0.339
Disease vessel ≧ 2	891 (53.3%)	846 (47.8%)	0.001
Left main lesion	127 (7.5%)	100 (5.6%)	0.015
Lesion morphology B2 or C	980 (58.8%)	1079 (61.1%)	0.086
Mean stent diameter (mm)	3.0 ± 0.9	2.9 ± 0.7	0.536
Mean stent length (mm)	21.0 ± 6.7	20.2 ± 6.6	0.001
Post dilatation	1133 (66.5%)	1253 (70.0%)	0.015
Rotablator	99 (5.8%)	135 (7.5%)	0.024
IABP	76 (4.5%)	26 (1.5%)	<0.001
Cardiac ECMO	3 (0.2%)	1 (0.1%)	0.294
Pre-stenosis ≧ 99%	673 (39.6%)	501 (28.1%)	<0.001
Post stenosis > 50%	1525 (90.0%)	1619 (90.9%)	0.204
Procedural complications			
Slow flow or no reflow	87 (5.1%)	55 (3.1%)	0.001
Acute occlusion	7 (0.4%)	11 (0.6%)	0.274
Emergent CABG	3 (0.2%)	2 (0.1%)	0.477
Stroke	9 (0.5%)	3 (0.2%)	0.061
Bleeding	13 (0.7%)	13 (0.7%)	0.992

CABG, coronary artery bypass graft; CCB, Ca-channel blocker; ECMO, extracorporeal membrane oxygenation; IABP, intra aortic balloon pumping; IVUS, intravascular ultrasonography; PCI, percutaneous coronary intervention; ST, stent thrombosis.

Discussion

ST is a rare, but severe complication after coronary stenting. Although especially, VLST has come to the front in the DES era, ST through 1 year (i.e. EST and LST) is also a problem needing to be solved irrespective of DES or BMS [13]. We demonstrated that ACS, longer stent length, and lack of CCB use were associated with an increased risk of ST after DES implantation within 1 year in

Table 2
Comparison of prescription drug use among early, late, and very late stent thrombosis groups.

	All ST ($n = 20$)			EST ($n = 8$)			LST ($n = 8$)			VLST ($n = 4$)		
	Non-ST	ST	p	Non-EST	EST	p	Non-LST	LST	p	Non-VLST	VLST	p
Aspirin	3439 (99.0%)	19 (95.0%)	0.183	3451 (99.0%)	7 (87.5%)	0.077	3450 (99.0%)	8 (100%)	0.923	3454 (99.0%)	4 (100%)	0.961
Thienopyridine	3380 (97.3%)	19 (95.0%)	0.421	3392 (97.3%)	7 (87.5%)	0.196	3391 (97.3%)	8 (100%)	0.804	3395 (97.3%)	4 (100%)	0.897
Nitrate	680 (19.6%)	3 (15.0%)	0.431	683 (19.6%)	0 (0%)	0.175	681 (19.5%)	2 (25.0%)	0.484	682 (19.5%)	1 (25.0%)	0.302
Statin	2524 (72.7%)	13 (65.0%)	0.294	2530 (72.6%)	7 (87.5%)	0.311	2533 (72.7%)	4 (50.0%)	0.149	2535 (72.7%)	2 (50.0%)	0.581
Beta-blocker	1364 (39.3%)	8 (40.0%)	0.558	1367 (39.2%)	5 (62.5%)	0.162	1370 (39.3%)	2 (25.0%)	0.330	1371 (39.3%)	1 (25.0%)	0.488
CCB	1785 (51.4%)	5 (25.0%)	0.016	1789 (51.3%)	1 (12.5%)	0.030	1789 (51.3%)	1 (12.5%)	0.030	1787 (51.2%)	3 (75.0%)	0.331
ACEI/ARB	2393 (68.9%)	15 (75.0%)	0.376	2401 (68.9%)	7 (87.5%)	0.235	2402 (68.9%)	6 (75.0%)	0.525	2406 (69.0%)	2 (50.0%)	0.367
Insulin	165 (4.8%)	1 (5.0%)	0.623	166 (4.8%)	0 (0%)	0.677	165 (4.7%)	1 (12.5%)	0.323	166 (4.8%)	0 (0%)	0.823

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; EST, early stent thrombosis; LST, late stent thrombosis; MI, myocardial infarction; ST, stent thrombosis; VLST, very late stent thrombosis.

Table 3C
Comparison of clinical outcomes according to calcium channel blocker use.

	CCB (−) $n=1703$ (43.7%)	CCB (+) $n=1790$ (55.1%)	p
All-cause death	41 (2.4%)	41 (2.3%)	0.453
Cardiovascular death	23 (1.4%)	11 (0.6%)	0.020
Non-cardiovascular death	18 (1.1%)	30 (1.7%)	0.076
Non-fatal MI	12 (0.7%)	11 (0.6%)	0.452
Non-fatal stroke	10 (0.6%)	14 (0.8%)	0.312
Any bleeding	9 (0.5%)	11 (0.6%)	0.456
All ST	15 (0.9%)	5 (0.3%)	0.016
EST	7 (0.4%)	1 (0.1%)	0.030
LST	7 (0.4%)	1 (0.1%)	0.030
VLST	1 (0.1%)	3 (0.2%)	0.331

CCB, calcium channel blocker; EST, early stent thrombosis; LST, late stent thrombosis; MI, myocardial infarction; ST, stent thrombosis; VLST, very late stent thrombosis.

Japanese patients. In Asian countries including Japan, the occurrence of ST is lower than in Western countries. Kimura et al. assessed the incidence of ST in 10,778 patients who underwent SES implantation in Japan, and they reported an incidence of 0.34% at 30 days, 0.54% at 1 year, and 0.77% at 2 years [3]. Daemen et al. assessed the incidence of ST in 8146 patients who underwent SES or PES implantation in the Netherlands. The incidence of ST was 1.2% at 30 days, 1.7% at 1 year, and 2.3% at 2 years [5]. If subjects were limited to those with ACS who underwent PCI, this tendency was more prominent [14]. Therefore, there are limited data to predict ST occurrence in Japan.

It is thought that the frequency of coronary spastic angina is higher in Japan than Western countries. Pristipino et al. performed a provocation test for coronary spasm in patients with recent MI, and examined the differences between Japanese and Italian patients [15]. They reported that Japanese patients exhibited a 3-fold greater incidence of spasm and more vasoconstriction of non-spastic segments after intracoronary injection of acetylcholine compared with Caucasians. Because of a higher incidence of spasm, Japanese patients with ischemic heart disease tend to receive CCBs rather than beta-blockers (BBs). The use of CCBs was higher than BBs in our subjects (51.4% versus 39.3%, respectively). We previously compared the effects of BBs on cardiovascular events with those of CCBs in Japanese post-MI patients [16]. That study demonstrated that the incidences of heart failure and coronary spasm were significantly higher in the BBs group than in the CCBs group, and there were no significant differences in any other CV events between both groups. Although we could not determine whether patients in this study had coronary spasm, there is a possibility that coronary spasm may be associated with ST occurrence because several patients had chest pain at rest. We do not recommend the use of CCBs in all patients following DES implantation, and coronary spasm may be one of the etiologies of ST, so CCB use may be considered in patients with a history of chest pain at rest.

In multivariate regression analysis, the lack of CCB use was an independent predictor of ST within 1 year. There is some concern that ST could be caused by coronary spasm in patients not receiving a CCB. In this study, ACS accounted for 65% of primary illness in the ST group. For patients with ACS, it was sometimes

Table 4A
Multiple logistic regression analysis for all stent thrombosis.

All ST	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age > 75 years	0.748	(0.287–1.951)	0.552	–	–	–
Disease vessel > 1	0.623	(0.241–1.610)	0.329	–	–	–
Acute coronary syndrome	3.254	(1.295–8.176)	0.009	2.129	(0.761–5.953)	0.15
Dyslipidemia	0.729	(0.297–1.789)	0.490	–	–	–
HbA1c > 6.5%	2.381	(0.863–6.571)	0.072	–	–	–
Serum creatinine > 1.3 mg/dL	1.819	(0.658–5.026)	0.249	–	–	–
Pre-stenosis ≧ 99%	3.684	(1.466–9.258)	0.004	2.703	(0.940–7.774)	0.065
Smaller stent diameter (<3 mm)	2.495	(0.851–7.315)	0.072	–	–	–
Longer stent length (>20 mm)	8.473	(1.922–37.345)	0.001	7.142	(1.604–31.801)	0.01
Aspirin	0.188	(0.024–1.443)	0.108	–	–	–
Beta blocker	1.031	(0.420–2.528)	0.558	0.688	(0.245–1.930)	0.477
Calcium channel blocker	0.315	(0.114–0.869)	0.016	0.483	(0.164–1.424)	0.187

CI, confidence interval; HbA1c, glycated hemoglobin A1c; OR, odds ratio; ST, stent thrombosis.

Table 4B
Multiple logistic regression analysis for stent thrombosis within 1 year.

ST within 1 year	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age > 75 years	0.793	(0.275–2.289)	0.669	–	–	–
Disease vessel > 1	0.587	(0.213–1.619)	0.304	–	–	–
Acute coronary syndrome	5.259	(1.693–16.340)	0.002	3.715	(1.069–12.909)	0.039
Dyslipidemia	0.811	(0.294–2.237)	0.686	–	–	–
HbA1c > 6.5%	1.901	(0.658–5.496)	0.235	–	–	–
Serum creatinine > 1.3 mg/dL	1.817	(0.584–5.656)	0.302	–	–	–
Pre-stenosis ≧ 99%	2.542	(0.944–6.842)	0.053	1.335	(0.409–4.363)	0.632
Smaller stent diameter (<3 mm)	2.179	(0.637–7.460)	0.215	–	–	–
Longer stent length (>20 mm)	6.035	(1.320–27.589)	0.008	5.239	(1.132–24.252)	0.034
Aspirin	0.148	(0.019–1.153)	0.068	–	–	–
Beta blocker	1.203	(0.447–3.239)	0.714	0.776	(0.242–2.489)	0.67
Calcium channel blocker	0.135	(0.031–0.595)	0.002	0.209	(0.045–0.973)	0.046

CI, confidence interval; HbA1c, glycated hemoglobin A1c; OR, odds ratio; ST, stent thrombosis.

Table 4C
Multiple logistic regression analysis for stent thrombosis more than 1 year.

ST more than 1 year	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age > 75 years	0.582	(0.060–5.602)	0.640	–	–	–
Disease vessel > 1	0.981	(0.061–15.696)	0.989	–	–	–
Acute coronary syndrome	0.58	(0.060–5.577)	0.637	0.49	(0.049–4.858)	0.542
Dyslipidemia	0.487	(0.068–3.459)	0.472	–	–	–
HbA1c > 6.5%	–	–	0.988	–	–	–
Serum creatinine > 1.3 mg/dL	1.813	(0.188–17.461)	0.607	–	–	–
Pre-stenosis ≧ 99%	–	–	0.985	–	–	–
Smaller stent diameter (<3 mm)	3.732	(0.388–35.913)	0.254	–	–	–
Longer stent length (>20 mm)	–	–	0.987	–	–	–
Aspirin	–	–	0.998	–	–	–
Beta blocker	0.515	(0.054–4.956)	0.566	0.434	(0.044–4.304)	0.476
Calcium channel blocker	2.857	(0.063–3.200)	0.363	2.932	(0.290–29.649)	0.362

CI, confidence interval; HbA1c, glycated hemoglobin A1c; OR, odds ratio; ST, stent thrombosis.

necessary to implant stents on plaque and thrombus-rich endothelium. The underlying plaque morphology may affect the rate of healing when stent struts penetrate deeply into a necrotic core and are not in contact with cellular areas [17]. Inflammatory cells, such as macrophages and T-cell lymphocytes, may accumulate more on these foundations. Coronary spasm on such foundations might easily lead to plaque rupture to ST. Moreover, there is no direct evidence or report that inhibition of coronary spasm by use of CCBs might reduce the risk of ST, although DAPT is reported to lead to a decreased risk of ST in the early phase after DES implantation. However, this study might suggest the efficacy of CCBs for suppression of coronary spasm. It is thought that inflammation may have an important role in the pathogenesis of coronary spasm [18,19]. Given that there was a decreased risk of ST with CCB use, although the relation between coronary spasm and ST is unclear, there is a possibility that coronary spasm may be associated with the pathogenesis of ST as well as pathophysiology of ischemic heart diseases. Although it has been said that BBs have adverse effects for coronary spasm, the use of BBs was not associated with increased risk of ST in this study. BBs with beta-1 selectivity, which have little effect on vasodilation, were prescribed for many BB users (516 patients; 37.9%). Therefore, it was thought that BB use was not associated with ST occurrence. Nitrate agents have effects on vasodilatation according to nitric oxide production and tolerance should occur in long-term use. In this study, although the frequency of nitrate agent use tended to be lower in the EST group than in the non-EST group, there were no differences between LST and non-LST groups or VLST and non-VLST groups.

In this study, ACS was also an independent predictor of ST. It is thought that patients who undergo PCI during ACS are exposed to a higher risk of ST than those who undergo elective stenting. Previous studies reported that the incidence of ST in ACS patients was higher (2.2–4.4%) than in patients who undergo elective stenting [4,20,21]. In this study, the incidence of ST was 1.02% in ACS patients but only 0.32% in non-ACS patients, and these results are consistent with previous data.

Longer stent length was also an independent predictor of ST in the present study. Caputo et al. reported that a longer DES length was associated with increased adverse events (major adverse cardiac events including MI and target lesion revascularization). Although DES length was not an independent predictor of adverse events in that study, there was a tendency for an increased risk ($p = 0.1$) [22]. Stent length could well be associated with any CV event, including ST.

Although diabetes mellitus (DM) has emerged as a strong risk factor of cardiovascular events, DM was not an independent predictor for ST incidence in this study. Billinger et al. analyzed clinical outcomes according to diabetic status in patients who underwent DES implantation. They reported that DM contributed increasing risk for mortality, but DM was not associated with an increased risk of ST and target-lesion revascularization [23]. These results were similar to those of the present study.

We examined the rate of any prescription drug use according to the presence of ST. ST patients had a lower frequency of CCB use compared with non-ST patients. On the other hand, patients in both groups received DAPT. DAPT, especially aspirin and thienopyridine, are currently used as standard medical therapy after PCI. Previous studies reported that thienopyridine, clopidogrel, and CCBs are all metabolized by hepatic cytochrome 450 3A4, so it has been controversial whether there is interaction between these agents [24,25]. In this study, patients who received a CCB had a lower occurrence of ST and CV death than patients without a CCB; however, the majority of patients were receiving thienopyridines. It is possible that the vasodilatory effects of CCBs were more important than their interaction with other drugs.

Limitations

This study was implemented as an observational study rather than an interventional study, and it is therefore not clear if patient management during and after PCI could have influenced the incidence of ST. Buonamici et al. reported that non-responsiveness to clopidogrel was a strong independent predictor of ST in patients who received DESs [26]. Thus, it might be useful to investigate the role of platelet reactivity in the occurrence of ST in this population. Although we suggested the possibility of decreased risk of ST by use of CCBs, we have no data on comparison of actual blood pressure levels between patients with and without taking CCBs. We could not examine the impact of lowering blood pressure on ST occurrence.

In this study, a total of 5371 drug-eluting stents were implanted. SES (26.4%), PES (27.6%), and EES (25.8%) were the major stent types implanted. The occurrence of ST was similar among these three stent types (about 0.3% with each stent type). Palmerini et al. reported that the cobalt–chromium EES had a lower rate of ST than any other stent (BMS, PES, ZES, or SES) in a meta-analysis of multiple, randomized, controlled trials [7]. Variation in stent type could possibly influence ST occurrence. The small sample size and low incidence of ST in this study made it impossible to determine if stent type was a predictor of ST occurrence.

Conclusions

These results suggest that CCB use may be associated with a decreased risk of ST after DES implantation within 1 year in Japanese patients.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Members of KICS

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