Effect of Cytochrome P450 2C19 Polymorphism on Target Lesion Outcome After Drug-Eluting Stent Implantation in Japanese Patients Receiving Clopidogrel

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Background: Cytochrome P450 (CYP) 2C19 polymorphism is associated with reduced responsiveness to clopidogrel and poor clinical outcome after drug-eluting stent (DES) implantation, but its contribution to lesion outcome after DES implantation is unclear.

Methods and Results: The study included 160 Japanese patients who received clopidogrel and underwent DES implantation with follow-up angiography. Patients were divided into 3 groups by CYP2C19 polymorphism: extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM). The incidence of major adverse cardiac events (MACE) and target lesion revascularization (TLR) were compared among the 3 groups. Optical coherence tomography (OCT) was performed for 120 patients to evaluate the incidence of intra-stent thrombi. Of the 160 patients, the proportion of EM, IM, and PM was 37.5%, 48.1%, and 14.4%, respectively. The incidence of TLR and MACE was more frequent in IM and PM than EM (TLR: 18.2% and 26.1% vs. 3.3%, $P=0.008$, MACE: 22.1% and 30.4% vs. 5.0%, $P=0.005$). Among the 120 patients who underwent follow-up OCT, intra-stent thrombi were more frequently detected in IM and PM than in EM (45.6% and 63.2% vs. 20.5%, $P=0.005$). The incidence of TLR was significantly higher in patients with than in those without intra-stent thrombi (27.7% vs. 6.8%, $P=0.003$).

Conclusions: CYP2C19 loss-of-function polymorphism might be associated with the incidence of MACE and TLR in association with intra-stent thrombi. (*Circ J* 2012; **76**: 2348–2355)

Key Words: CYP2C19; Intra-stent thrombi; Major adverse cardiac events; Optical coherence tomography; Target lesion revascularization

Dual antiplatelet therapy with aspirin plus a thienopyridine derivative is recommended for the prevention of thrombotic events in patients with coronary artery disease who have undergone drug-eluting stent (DES) implantation.¹ Clopidogrel, a thienopyridine derivative, is a pro-drug that is converted into an active metabolite in the liver and the metabolite irreversibly inhibits the adenosine diphosphate P2Y₁₂ receptor.² Because the conversion is achieved by the hepatic cytochrome P450 (CYP) system in a 2-step oxidative process and CYP2C19 is involved in both of these steps, polymorphisms of the genes encoding CYP2C19 are considered to

influence clopidogrel's efficacy by affecting the activity of its metabolite.^{3–5} Among the single nucleotide polymorphisms of CYP2C19, the CYP2C19*2 polymorphism (mutation of guanine to adenine at position 681 in exon 5) and the CYP2C19*3 polymorphism (mutation of guanine to adenosine at position 636 in exon 5) are considered to be important loss-of-function polymorphisms. Previous studies demonstrated that the CYP2C19*2 and CYP2C19*3 polymorphisms increase the risk of stent thrombosis,^{6–8} but only limited data are available regarding the association between the presence of CYP2C19 polymorphisms and future lesion outcomes after DES therapy.

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We previously suggested that the frequency of subclinical thrombus detected by optical coherence tomography (OCT) is increased in association with the CYP2C19*2 polymorphism.⁹ Based on recent pathologic and clinical studies suggesting a role of thrombus formation in DES restenosis,^{10,11} we hypothesized that the presence of CYP2C19 polymorphisms is associated with lesion outcomes after DES treatment. Therefore, in the present study, we evaluated the effect of CYP2C19 loss-of-function polymorphisms on long-term target lesion outcome after DES implantation.

Methods

Patients

This study was approved by the ethics committee of Kobe University, and all enrolled study patients provided written informed consent to participate in the clinical trial and genetic study. Between June 2008 and June 2010, 302 patients at Kobe University Hospital underwent percutaneous coronary intervention (PCI) with a DES (sirolimus-eluting stent [SES]: Cypher™; Cordis Corp, Miami Lakes, FL USA; paclitaxel-eluting stent [PES]: TAXUS Express™ or TAXUS Liberté™; Boston Scientific Corporation, Natick, MA, USA). All PCIs were performed with intravascular ultrasound guidance (Boston Scientific Corporation or Volcano Corporation, Rancho Cordova, CA, USA). Follow-up angiography was planned at 8–10 months after the index procedure as routine follow-up practice. Recurrence of chest symptoms and evidence of myocardial ischemia on a stress test were also considered to be indications for repeat angiography. All patients were encouraged to undergo OCT examination at the time of the follow-up angiography. Of the 302 patients, 212 patients underwent follow-up angiography and of these, 160 patients agreed to the CYP2C19 polymorphism analysis and were enrolled in the study.

The patients' characteristics, including age, sex, body mass index, and the presence of coronary risk factors (hypertension, dyslipidemia, diabetes mellitus, and smoking) were assessed. Additional drug usage was also assessed, because the prognosis after PCI and the response to clopidogrel is potentially influenced by concomitant medications, such as proton-pump inhibitors, calcium-channel blockers, statins, β -blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and warfarin.^{12,13}

All patients treated with a DES received dual antiplatelet therapy with aspirin and clopidogrel. The loading dose of clopidogrel (300 mg) was administered at least 24 h before the procedure, followed by a maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day) until at least 1 year after the procedure. A longer duration of clopidogrel use was permitted at the discretion of the treating physician.

Blood Sampling and Genotyping Methods

We obtained blood samples from the arterial sheath at the time of follow-up angiography. Genomic DNA was extracted from whole blood using the commercially available QIAamp™ DNA Blood Mini kit (QIAGEN N.V., Venlo, The Netherlands) according to the manufacturer's instructions. The CYP2C19*2 (681G>A) or *3 (636G>A) polymorphism was genotyped using TaqMan™ Drug Metabolism Genotyping Assays (Applied Biosystems, Foster City, CA, USA) with the Applied Biosystems 7500 Real-Time PCR System. CYP2C19*2 and *3 are considered to account for more than 99% of alleles generating the null-activity enzyme protein in the Japanese population.¹⁴ Thus, CYP2C19 genotypes were classified into 3 phenotypes: (1) extensive metabolizers (EM) carrying normal function al-

Figure 1. Representative case of an intra-stent thrombus (white arrow), defined as a mass protruding beyond the stent strut into the lumen with remarkable attenuation behind the mass.

les (CYP2C19*1/*1); (2) intermediate metabolizers (IM) carrying 1 loss-of-function allele (*1/*2, *1/*3); and (3) poor metabolizers (PM) carrying 2 loss-of-function alleles (*2/*2, *2/*3, *3/*3).

Angiographic Analysis

Cineangiograms were analyzed with a computer-assisted, automated edge detection algorithm (CMS-Medis Medical Imaging Systems, Leiden, The Netherlands). The outer diameter of the contrast-filled catheter was used for calibration and the minimal lumen diameter (MLD) was obtained from the single worst view. Acute gain was defined as the difference between the MLD pre- and post-PCI. In-stent late loss was defined as the difference between the MLD immediately after the procedure and the MLD at the follow-up date. The traditional lesion type was also assessed according to the American Heart Association/American College of Cardiology classification.¹⁵

OCT Substudy

OCT Examination To assess the relationship between CYP2C19 polymorphism and local vessel reaction after DES implantation, we performed OCT in some of the enrolled patients at the time of follow-up angiography. Among the overall population of 160 patients, patients with left main trunk disease, ostial disease, and severe 3-vessel disease (n=18) were excluded from the OCT examination to ensure the safety of the patients during the OCT procedure. Patients with severe tortuous lesions and severely calcified vessels (n=11) were also excluded because of anticipated difficulties in advancing the OCT catheters. In addition, patients with vessels greater than 4.0 mm in diameter on angiography (n=6) were excluded, because these vessels were too large for blood flow to be occluded. A total of 125 patients were enrolled in the OCT substudy.

In this study, because frequency-domain OCT was not yet approved for clinical use in Japan, time-domain OCT with coronary artery occlusion was used, as previously reported.¹⁶

Table 1. Baseline Characteristics of Patients

	EM (n=60)	IM (n=77)	PM (n=23)	P value
Age (years)	69.4±10.3	69.8±8.9	70.6±7.3	0.87
Sex (male; n)	43 (71.7)	62 (80.5)	17 (73.9)	0.46
Body mass index (kg/m ²)	24.5±2.8	23.6±3.6	23.8±3.6	0.31
Acute coronary syndrome (n)	6 (10.0)	8 (10.4)	2 (8.7)	0.97
Hypertension (n)	52 (86.7)	60 (77.9)	20 (87.0)	0.34
Dyslipidemia (n)	40 (66.7)	52 (67.5)	16 (69.6)	0.97
Diabetes (n)	27 (45.0)	39 (50.6)	9 (39.1)	0.58
Smoker (n)	21 (35.0)	33 (42.9)	9 (39.1)	0.65
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	59.6±18.9	60.5±20.9	56.8±25.0	0.76
Medications				
PPI (n)	29 (48.3)	40 (51.9)	10 (43.5)	0.76
Omeprazole (n)	3 (5.0)	6 (7.8)	2 (8.7)	0.75
CCB (n)	28 (46.7)	36 (46.8)	11 (47.8)	0.99
Statin (n)	43 (71.7)	54 (70.1)	16 (69.6)	0.89
β-blocker (n)	25 (41.7)	39 (50.6)	10 (43.4)	0.55
ACEI or ARB (n)	45 (75.0)	57 (74.0)	18 (78.3)	0.92
Warfarin (n)	3 (5.0)	4 (5.2)	1 (4.3)	0.99

Data are presented as mean±SD or n (%).

EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; PPI, proton-pump inhibitor.

Briefly, a 0.016-inch OCT wire (ImageWire, LightLab Imaging, Westford, MA, USA) was advanced to the distal end of the stented lesion through an occlusion balloon catheter (HeliosTM, LightLab Imaging). The occlusion balloon was inflated to 0.5 atm at the proximal site of the stented lesion, followed by an infusion of lactated Ringer's solution into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s, serving as a flush to clear the area of blood. The entire stented length was then imaged using an automatic pullback system moving at 1 mm/s.

OCT Analysis Cross-sectional images were analyzed at 1-mm (15 frames) intervals. Bifurcation lesions with major side branches were excluded from the study. All images were analyzed by 2 independent observers blinded to the clinical presentation and lesion characteristics. Neointimal thickness inside each stent strut was measured on each cross-section. Stent diameters (maximum and minimum) and area were also measured manually. A stent strut with a measured thickness of 0 μm was defined as an uncovered strut and a maximum distance of more than 170 μm between the center reflection of the strut and adjacent vessel surface was defined as stent malapposition. This criterion was determined by adding the actual strut thickness and polymer thickness to the OCT resolution limit (140 μm + 10 μm + 20 μm for the SES; 130 μm + 14 μm + 20 μm for the PES).^{17,18} The numbers of uncovered struts and malapposed struts were calculated and described as the frequency (number of malapposed struts divided by total number of struts). A stent eccentricity index and a neointimal unevenness score were calculated, because these parameters are reported to be predictive factors for intra-SES thrombus.¹⁹ The stent eccentricity index was calculated as the minimum stent diameter divided by the maximum stent diameter in each cross-section. The neointimal unevenness score was calculated as the maximum neointimal thickness in 1 cross-section divided by the mean neointimal thickness of the same cross-section. Intra-stent thrombus was defined as a mass protruding beyond the stent strut into the lumen with significant attenua-

tion behind the mass.²⁰ A representative case of an intra-stent thrombus is shown in [Figure 1](#). To quantify the intra-stent thrombi, the maximum area of intra-stent thrombi was measured and the prevalence of intra-stent thrombi was calculated as percentage of cross-sections with intra-stent thrombi (number of cross-sections with intra-stent thrombi × 100/total cross-sections for the stent).

Clinical Follow-up

In the present study, clinical follow-up data (up to 3 years after the index procedure) were obtained from outpatient record reviews or telephone interviews. Death, cardiac death, myocardial infarction (MI, defined according to the WHO definition based on creatine kinase and creatine kinase-MB rise),²¹ clinically-driven target lesion revascularization (TLR, defined as repeat PCI or coronary artery bypass graft to the target lesion), stent thrombosis (adjudicated according to the Academic Research Consortium classification),²² and the composite end-points of major adverse cardiac events (MACE: cardiac death, MI, TLR, stent thrombosis) were evaluated during the follow-up period.

Statistical Analysis

All statistical analyses were performed using Medcalc (version 12.1; Medcalc Software, Mariakerke, Belgium). Continuous variables are presented as the mean±SD. Differences in continuous parameters between the 3 groups were calculated using a 1-way ANOVA. Categorical variables are presented as frequency counts. Comparison of categorical variables between the 3 groups was performed using the chi-square test. Values were considered statistically significant at P<0.05. Cumulative incidences were analyzed from time of DES implantation to the first event according to the Kaplan-Meier method, and the differences were calculated by the log-rank test.

Table 2. Quantitative Coronary Angiography and PCI Data				
	EM (n=60)	IM (n=77)	PM (n=23)	P value
Lesion location				
LAD (n)	27	40	11	0.61
LCX (n)	15	18	8	
RCA (n)	25	24	6	
Type of lesion				
A/B1 (n)	32	42	10	0.64
B2/C (n)	28	35	13	
CTO (n)	11 (18.3)	17 (22.1)	5 (21.7)	0.84
Bifurcation lesion (n)	18 (30.0)	29 (37.7)	8 (34.8)	0.61
Procedural characteristics				
Total no. of stents (n)	1.92±1.06	1.74±0.77	1.65±0.89	0.38
SES (n)	1.13±1.05	1.12±0.87	1.17±0.78	0.97
PES (n)	0.80±0.92	0.62±0.84	0.48±0.59	0.29
Total stent length (mm)	36.6±22.8	38.0±23.3	29.8±14.7	0.29
Stent diameter (mm)	2.89±0.39	2.81±0.36	2.75±0.33	0.26
Post dilatation (n)	31 (51.7)	44 (57.1)	10 (43.5)	0.37
Max. inflation pressure (atm)	14.7±3.7	13.6±4.3	15.0±2.8	0.23
Overlap stent (n)	17 (28.3)	16 (26.2)	3 (13.0)	0.28
Rotablation (n)	1 (1.7)	8 (10.4)	1 (4.3)	0.08
Quantitative coronary angiography				
Lesion length (mm)	9.2±4.5	9.1±5.0	10.4±5.9	0.56
Reference diameter (mm)	2.22±0.51	2.18±0.70	2.06±0.44	0.59
Minimum lumen diameter				
Before PCI (mm)	0.37±0.30	0.37±0.34	0.37±0.25	0.99
After PCI (mm)	2.36±0.43	2.25±0.44	2.21±0.36	0.21
Follow-up (mm)	1.96±0.55	1.79±0.61	1.82±0.48	0.22
% diameter stenosis				
Before PCI (%)	80.9±14.2	78.0±16.7	83.4±13.8	0.28
After PCI (%)	11.9±5.2	12.8±6.5	13.0±6.4	0.69
Follow-up (%)	22.9±16.0	25.2±19.4	24.4±16.8	0.78
Acute gain (mm)	1.92±0.47	1.85±0.48	1.78±0.54	0.42
Late loss (mm)	0.46±0.34	0.52±0.48	0.43±0.36	0.54

Data are presented as mean±SD or n (%)

PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CTO, chronic total occlusion; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent. Other abbreviations as in Table 1.

	EM (n=60)	IM (n=77)	PM (n=23)	P value
Death (n)	1 (1.7)	2 (2.6)	2 (8.7)	0.24
Cardiac death (n)	0	2 (2.6)	0	0.34
Myocardial infarction (n)	1 (1.7)	1 (1.3)	1 (4.3)	0.69
TLR (n)	2 (3.3)	14 (18.2)*	6 (26.1)**	0.008
Stent thrombosis (n)	1 (1.7)	2 (2.6)	1 (4.3)	0.79
MACE (n)	3 (5.0)	17 (22.1) [†]	7 (30.4) [‡]	0.005

Data are presented as n (%). *P=0.04, **P=0.02, [†]P=0.03, [‡]P=0.02 (compared with EM, using Scheffe's post hoc test). MACE, major adverse cardiac events; TLR, target lesion revascularization. Other abbreviations as in Table 1.

Results

Of the 160 patients who were enrolled in this study, the proportions of EM, IM, and PM were 37.5%, 48.1%, and 14.4%, respectively (*1/*1, 37.5%; *1/*2, 30.6%; *1/*3, 17.5%; *2/*2, 5.6%; *2/*3, 6.3%; *3/*3, 2.5%). Mean age was 69.7±9.2 years and mean follow-up duration was 646.2±255.2 days (median, 692.5 days). The mean duration of clopidogrel treatment

was 475.9±206.1 days in EM, 465.5±223.9 days in IM, and 454.9±213.3 days in PM, and was not statistically different among groups (P=0.92).

The baseline characteristics of the study population are listed in Table 1. Patient characteristics did not differ significantly among the 3 groups. There were no differences in the use of omeprazole or calcium-channel blocker among the groups. The lesion and procedural characteristics are shown in Table 2.

No difference in the quantitative coronary angiography data or procedural characteristics was noted among the 3 groups.

The incidences of MACE and TLR were significantly higher in IM and PM than in EM (Table 3). The incidences of death, MI, and stent thrombosis did not differ among the 3 groups. The Kaplan-Meier cumulative MACE- and TLR-free survival curves with a log-rank test showed that the presence of CYP2C19 loss-of-function polymorphisms was associated with higher incidences of MACE and TLR after PCI, which were sustained for at least 3 years after DES implantation (Figures 2A,2B).

Of the 125 patients enrolled in the OCT subgroup analysis, 5 were excluded because of poor image acquisition. Therefore, the OCT data for 120 patients were analyzed. Baseline

and procedural characteristics did not differ among the 3 metabolizer groups. The mean follow-up duration was 231.5 ± 75.4 days (median, 225.0 days). The percentages of EM, IM, and PM were 36.7%, 47.5%, and 15.8%, respectively. Qualitative OCT analysis revealed that intra-stent thrombi were more frequently observed in IM and PM than in EM (Figure 3). There were no other differences in the quantitative and qualitative OCT analyses among the 3 groups. The maximum area and % cross-sections with intra-stent thrombi were not different among the 3 groups (Table 4). The incidence of TLR was significantly higher in patients with intra-stent thrombi than in those without intra-stent thrombi (Figure 4).

Figure 3. Presence of intra-stent thrombi. Data are presented as n (%). EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Figure 4. Incidence of TLR in patients with and without intra-stent thrombi. Data are presented as n (%). TLR, target lesion revascularization.

	EM (n=44)	IM (n=57)	PM (n=19)	P value
Number of struts (n)	160.1±81.9	193.2±83.7	179.7±75.8	0.15
Frequency of malapposed struts (%)	1.7±1.9	2.0±2.0	1.9±2.0	0.79
Number of malapposed struts (n)	3.2±4.0	4.1±3.9	3.3±3.7	0.54
Frequency of uncovered struts (%)	7.4±7.1	6.8±6.7	7.4±6.3	0.90
Number of uncovered struts (n)	12.6±13.2	12.2±12.5	12.5±13.4	0.99
Minimum stent diameter (mm)	2.89±0.40	2.73±0.42	2.80±0.39	0.15
Stent eccentricity index	0.92±0.04	0.93±0.04	0.92±0.05	0.94
Mean neointimal thickness (mm)	0.12±0.08	0.11±0.07	0.13±0.13	0.86
Neointimal unevenness score	1.94±0.33	1.90±0.31	1.89±0.17	0.71
Mean stent area (mm ²)	7.42±1.96	6.74±1.87	7.02±1.84	0.22
Minimum stent area (mm ²)	5.81±1.82	5.56±1.63	5.53±1.68	0.74
Maximum area of intra-stent thrombi (mm ²)*	0.29±0.22	0.61±1.01	0.89±1.53	0.47
% cross-sections with intra-stent thrombi (%)*	4.88±3.00	6.61±14.36	9.87±19.64	0.72

Data are presented as mean±SD.

OCT, optical coherence tomography. Other abbreviations as in Table 1.

*Maximum area and % cross-sections with intra-stent thrombi were calculated only in the patients with intra-stent thrombi.

Discussion

In this study, the proportions of EM, IM, and PM were 37.5%, 48.1%, and 14.4%, respectively. During the median follow-up of 692.5 days, the incidence of MACE and TLR was significantly higher in IM and PM than in EM. In a subgroup analysis of 120 patients who underwent follow-up OCT (median, 225.0 days), intra-stent thrombi were more frequently observed in IM and PM than in EM, although there were no significant differences in other quantitative or qualitative OCT parameters. In this OCT subgroup population, the incidence of TLR was significantly higher in patients with intra-stent thrombi than in those without intra-stent thrombi.

Previous studies have consistently reported a relatively high incidence of CYP2C19 loss-of-function carriers in Asian populations. The frequency of CYP2C19*2 is higher in Asians (30–50%) than in Western people (20–30%), and the CYP2C19*3 allele is frequent in Asians (10–20%) and rare in Caucasians

(approximately 0.5%).^{3,23–26} In the present study, the proportions of EM, IM, and PM were 37.5%, 48.1%, and 14.4%, respectively, which is consistent with previous studies in Japanese populations.^{27–29} Because the population of CYP2C19 loss-of-function carriers is not small, not only in the Japanese but also in the Western population, clarifying the effect of CYP2C19 loss-of-function on future clinical events is vital.

In this study, patients with CYP2C19 loss-of-function polymorphisms had a higher incidence of TLR and MACE compared with patients without the polymorphisms. Several studies of DES restenosis and pathologic examinations of human specimens have demonstrated that neointimal tissues after DES implantation comprises heterogeneous components, including proteoglycan-rich tissue, organized thrombus, smooth muscle cells, atheroma, inflammatory cells, and fibrinoid.³⁰ Among these components, previous investigators implied that thrombus formation has an important role in the process of DES restenosis. A pathologic analysis of recent human SES

restenosis demonstrated the presence of fibrin deposition and a myxomatous extracellular matrix within restenotic tissue.¹⁰ Also, based on their analysis of restenotic tissue collected through directional coronary atherectomy, Oikawa et al reported that the tissues comprising human SES restenosis are frequently associated with thrombus components.¹¹ Similarly, in the present study, the incidence of TLR was higher in patients with intra-stent thrombi than in those without intra-stent thrombi and the incidence of intra-stent thrombi increased with an increase in the number of CYP2C19 polymorphisms. Therefore, we speculate that the presence of CYP2C19 loss-of-function polymorphisms might increase the possibility for TLR because of an increased incidence of DES restenosis through insufficient suppression of thrombus formation by clopidogrel. Interestingly, the difference in the incidence of TLR and MACE occurred mostly in the early phase, mainly up to 1 year after the index PCI. Oh et al⁷ reported that the CYP2C19*2 allele carrier status was associated with an increased incidence of adverse clinical events, including stent thrombosis up to 1 year after stenting. Such association, however, no longer existed after 1 year, at which time most of the patients in their study population had discontinued clopidogrel,⁷ which was similar to our present study population, in which most of the patients (66.9%) discontinued clopidogrel intake 1 year after stenting. These results support our speculation.

Although previous studies have described a highly significant association of CYP2C19 loss-of-function polymorphisms and stent thrombosis,^{3,6,31,32} in our study population the incidence of stent thrombosis was not significantly different among the 3 metabolizer groups. We speculate that this is mainly related to the small sample size of our study and the relatively short duration of the follow-up period under clopidogrel treatment. On the other hand, we demonstrated a possible association between CYP2C19 loss-of-function polymorphisms and TLR, although most previous studies failed to show such a finding.⁹ Although still speculative, we currently consider that mandatory mid-term angiographic follow-up with detailed OCT assessment performed for more than 75% of enrolled patients might help detect such tiny differences observed in the present study. Although the rationale for mid-term follow-up angiography is controversial, this practice might help to detect severe luminal narrowing before the development of late stent thrombosis.

Study Limitations

Because only the patients who revisited hospital for follow-up angiography were enrolled in this study, some selection bias is likely. Also, because of the observational study design based on a limited sample size, it remains unclear whether the CYP2C19 loss-of-function polymorphisms increase the incidence of stent thrombosis. Further, this study only examined SES and PES and there was no comparison with bare metal stents and other DES. Residual platelet reactivity was not evaluated in this study. The relationship between the incidence of intra-stent thrombi and residual platelet reactivity is unclear and further study is warranted.

Conclusions

Our results suggest that CYP2C19 loss-of-function polymorphisms are associated with an increased incidence of MACE, especially because of the increased incidence in early-phase TLR (within 1 year) after DES implantation in Japanese patients receiving clopidogrel.

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