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ORIGINAL RESEARCH

Stent-Related Adverse Events as Related to Dual Antiplatelet Therapy in First- vs Second-Generation Drug-Eluting Stents

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ABSTRACT

BACKGROUND There are limited data on the long-term stent-related adverse events as related to the duration of dual antiplatelet therapy (DAPT) in second-generation (G2) drug-eluting stents (DES) compared with first-generation (G1) DES.

OBJECTIVES This study sought to compare the long-term stent-related outcomes of G2-DES with those of G1-DES.

METHODS The study group consisted of 15,009 patients who underwent their first coronary revascularization with DES from the CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Grafting) Registry Cohort-2 (first-generation drug-eluting stent [G1-DES] period; n = 5,382) and Cohort-3 (second-generation drug eluting stent [G2-DES] period; n = 9,627). The primary outcome measures were definite stent thrombosis (ST) and target vessel revascularization (TVR).

RESULTS The cumulative 5-year incidences of definite ST and TVR were significantly lower in the G2-DES group than in the G1-DES group (0.7% vs 1.4%; $P < 0.001$; and 16.2% vs 22.1%; $P < 0.001$, respectively). The lower adjusted risk of G2-DES relative to G1-DES for definite ST and TVR remained significant (HR: 0.53; 95% CI: 0.37-0.76; $P < 0.001$; and HR: 0.74; 95% CI: 0.68-0.81; $P < 0.001$, respectively). In the landmark analysis that was based on the DAPT status at 1 year, the lower adjusted risk of on-DAPT status relative to off-DAPT was significant for definite ST beyond 1 year in the G1-DES stratum (HR: 0.42; 95% CI: 0.24-0.76; $P = 0.004$) but not in the G2-DES stratum (HR: 0.66; 95% CI: 0.26-1.68; $P = 0.38$) ($P_{interaction} = 0.14$).

CONCLUSIONS G2-DES compared with G1-DES were associated with a significantly lower risk for stent-related adverse events, including definite ST and TVR. DAPT beyond 1 year was associated with a significantly lower risk for very late ST of G1-DES but not for that of G2-DES. (JACC: Asia 2021;1:345–356) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ARC = Academic Research Consortium

ARC-HBR = Academic Research Consortium High Bleeding Risk

BMS = bare-metal stent

CABG = coronary artery bypass grafting

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

G1 = first-generation

G2 = second-generation

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

TVR = target vessel revascularization

ZES = zotarolimus-eluting stent(s)

Stent-related adverse events are lifelong risks after percutaneous coronary intervention (PCI) (1,2). In particular, stent thrombosis (ST) is a rare but life-threatening adverse event after PCI with stent implantation (3,4). The introduction of coronary stents coated with antiproliferative drugs such as sirolimus and paclitaxel, known as first-generation (G1) drug-eluting stents (DES), markedly reduced the rate of restenosis within 1 year as compared with bare-metal stents (BMS). However, G1-DES were associated with a higher risk for very late ST and restenosis beyond 1 year as compared with BMS (1,5). To overcome the stent-related adverse events associated with G1-DES, second-generation (G2) DES were developed and replaced G1-DES in daily clinical practice because of the substantial reduction in ST reported in observational studies with 3 to 4 years of follow-up (6,7). However, the results of the 4 randomized trials comparing everolimus-eluting stents (EES) with sirolimus-eluting stents (SES) were not consistent for significant reduction in ST (8-10). In addition, the favorable effect of G2-DES compared with G1-DES for restenosis has not yet been confirmed in observational studies (6,7) and in randomized trials (8-17). Moreover, there is a scarcity of data on the association between ST and the duration of dual antiplatelet therapy (DAPT) in patients who received G2-DES as compared with patients who received G1-DES (18-21). ST risk tends to be lower in Asian populations than in European or North American populations, and this may lead to differences in risk-to-benefit trade-off of antithrombotic treatment between these groups (22). Therefore, we sought to assess comprehensively the 5-year incidences of stent-related adverse events and other clinical outcomes, as well as the relationship of stent stent-related adverse events with DAPT duration after G1-DES and G2-DES implantation, in a setting of Japanese real-world clinical practice.

METHODS

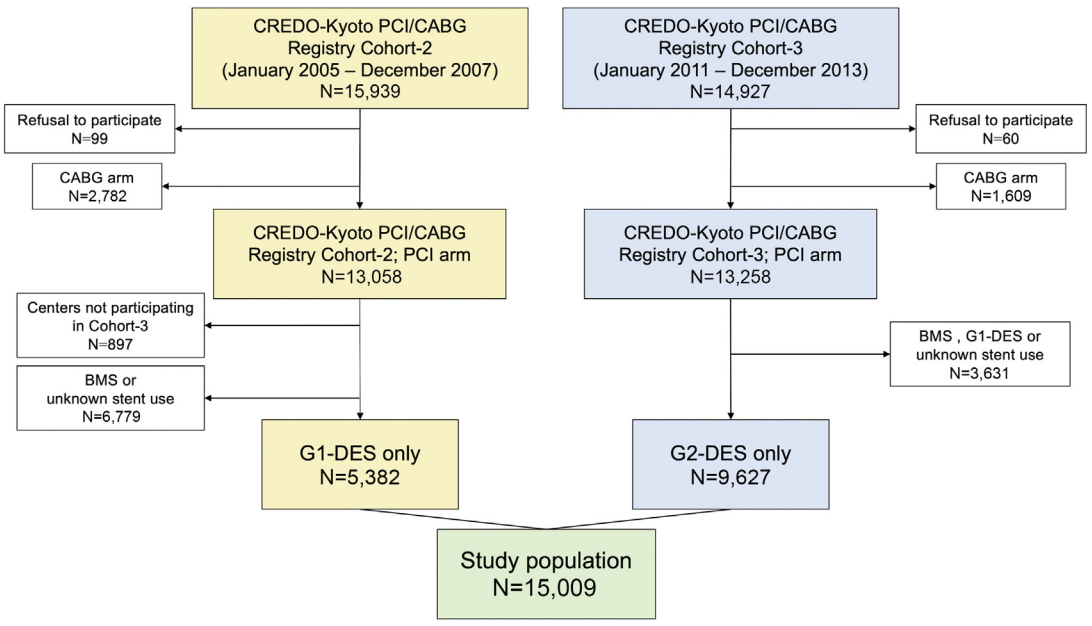
STUDY GROUP AND DATA COLLECTION. The study group consisted of a series of large Japanese registries: the CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Grafting) Registry Cohort-2 and Cohort-3. These physician-initiated non-company-sponsored multicenter registries consecutively enrolled patients who underwent their first coronary revascularization with PCI or isolated CABG: Cohort-2 in 26 centers between January 2005 and December 2007 (after approval of G1-DES) and Cohort-3 in 22 centers between January 2011 and December 2013 (after approval of G2-DES) (Supplemental Appendix) (23,24).

The relevant Institutional Review Boards at all participating hospitals approved the study protocols, and we performed the studies in accordance with the Declaration of Helsinki. Written informed consent was waived in both registries because of the retrospective study designs; however, we excluded those patients who refused participation in the study when they were contacted at follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor, and Welfare.

From both registries (n = 15,939 in Cohort-2 and n = 14,927 in Cohort-3), we excluded those patients who refused to participate in the study and who underwent CABG. Among 13,058 patients treated with PCI in Cohort-2, we excluded those patients who underwent PCI with BMS and/or unknown stent types. Similarly, among 13,258 patients treated with PCI in Cohort-3, we excluded those patients who underwent PCI with BMS, G1-DES, and/or unknown stent types. To make the groups comparable, we excluded those patients from the 4 centers in Cohort-2 who did not participate in Cohort-3. Thus, we obtained the data set to make a historical comparison between G1-DES and G2-DES (5,382 patients in the G1-DES group and 9,627 patients in the G2-DES group) (**Figure 1**). The median durations of follow-up were 5.3 years (25th to 75th percentile: 4.6-6.0 years) in the G1-DES group and 5.9 years (25th to 75th percentile: 5.1-6.7 years) in the G2-DES group, respectively. The follow-up of patient survival status in the G1-DES group was completed in 99.3% of patients at 1 year and 69.6% at 5 years, and in the G2-DES group it was completed in 98.2% of patients at 1 year and 82.0% at 5 years. To standardize the follow-up duration, we censored the follow-up at 5 years after PCI.

Independent experienced clinical research coordinators from a clinical research organization (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix) collected baseline clinical, angiographic, and procedural characteristics from hospital charts or hospital databases. They also collected follow-up information mainly from hospital charts and contacted patients, relatives, and/or referring physicians by sending questionnaires regarding vital status, subsequent hospitalizations, and status of antiplatelet therapy.

FIGURE 1 Study Flowchart



A total of 15,009 patients were included in this study from the CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Grafting) Registry Cohort-2 and Cohort-3. BMS = bare-metal stent(s); DES = drug-eluting stent(s); G1 = first-generation; G2 = second-generation.

BASELINE CHARACTERISTICS AND MEDICATIONS. We used the identical definitions of patient characteristics in the 2 cohorts. Medication status was assessed at discharge from the index hospitalization. On the basis of patient-backgrounds, we also assessed the Academic Research Consortium (ARC) High Bleeding Risk (ARC-HBR) (25) and DAPT score (26).

In this study, we defined SES and paclitaxel-eluting stents (PES) as G1-DES and EES, biolimus-eluting stents, and zotarolimus-eluting stents (ZES) as G2-DES.

ANTIPLATELET THERAPY. There was no specific protocol-recommended antiplatelet therapy in both cohorts because of the retrospective observational study designs. The actual duration of DAPT was left to the discretion of each attending physician. The status of antiplatelet therapy was evaluated throughout the follow-up period. Discontinuation of DAPT (discontinuation of either aspirin or a thienopyridine) was defined to be persistent when withdrawn for ≥2 months (26). The follow-up rates for DAPT status at 1 year, 3 years, and 5 years were 95.3%, 90.1%, and 73.9% in Cohort-2, and 94.7%, 91.0%, and 85.4% in Cohort-3, respectively.

CLINICAL OUTCOME MEASURES AND DEFINITIONS. The primary outcome measures of this study were stent-related adverse events, including definite ST defined by ARC consensus criteria and target vessel revascularization (TVR) (27). The secondary outcome measures were exploratory and included definite or probable ST, clinically driven TVR, any coronary revascularization, myocardial infarction, death, stroke, and major bleeding. Detailed definitions of clinical outcome measures are described in the Supplemental Appendix. The clinical event committee adjudicated ST, myocardial infarction, death, stroke, and major bleeding (Supplemental Appendix).

STATISTICAL ANALYSIS. We presented categorical variables as numbers and percentages and continuous variables as mean ± SD or median (25th to 75th percentiles) according to their distributions. We compared categorical variables with the chi-square test when appropriate; otherwise, we used the Fisher exact test. We compared continuous variables with Student's *t*-test or the Wilcoxon rank sum test on the basis of their distributions.

We estimated cumulative incidences with the Kaplan-Meier method and assessed the between-group differences with the log-rank test. We used a 1-year landmark analysis to assess the very late outcomes beyond 1 year. We adjusted for baseline characteristics and medications (Supplemental Table 1)

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TABLE 1 Baseline Characteristics and Medications

	G1-DES (n = 5,382)	G2-DES (n = 9,627)	*P* Value
Patient characteristics			
Age, y	68.5 ± 10.3	69.9 ± 10.7	<0.001
≥75 y	1,640 (30)	3,459 (36)	<0.001
BMI, kg/m^2	23.8 ± 3.4	23.8 ± 3.6	0.42
<25 kg/m^2	3,516 (67)	6,364 (67)	0.73
Women	1,544 (29)	2,679 (28)	0.26
PCI indication			<0.001
STEMI	716 (13)	2,177 (23)	
NSTEACS	509 (9.5)	953 (9.9)	
Stable CAD	4,157 (77)	6,497 (67)	
Acute coronary syndrome	1,225 (23)	3,130 (33)	<0.001
Hypertension	4476 (83)	8,019 (83)	0.84
Diabetes mellitus	2,185 (41)	3,812 (40)	0.23
On insulin therapy	541/2,185 (25)	875/3,812 (23)	0.11
Current smoking	1,440 (27)	2,432 (25)	0.07
History of heart failure	265 (4.9)	461 (4.8)	0.71
History of myocardial infarction	728 (14)	1,153 (12)	0.006
History of atrial fibrillation	426 (7.9)	917 (9.5)	<0.001
History of stroke	621 (12)	1,277 (13)	0.002
Peripheral vascular disease	310 (5.8)	716 (7.4)	<0.001
Hemodialysis	249 (4.6)	479 (5.0)	0.34
COPD	184 (3.4)	374 (3.9)	0.15
Liver cirrhosis	124 (2.3)	253 (2.6)	0.22
Malignant disease	464 (8.6)	1,117 (12)	<0.001
Laboratory and echocardiographic tests			
Hemoglobin, g/dL	13.3 ± 2.0	13.3 ± 2.0	0.58
<11 g/dL	627 (12)	1,136 (12)	0.95
Platelet count, 10^4/μL	21.4 ± 6.3	20.7 ± 6.3	<0.001
<10	78 (1.5)	186 (1.9)	0.03
Creatinine, mg/dL	0.86 [0.70-1.05]	0.85 [0.70-1.06]	0.08
eGFR, mL/min/1.73 m^2	63.8 [51.2-76.5]	64.7 [50.6-77.9]	0.12
<30 mL/min/1.73 m^2	452 (8.5)	867 (9.0)	0.27
Moderate CKD[a]	1,701 (32)	3,056 (32)	0.87
Severe CKD[a]	458 (8.6)	874 (9.1)	0.31
LVEF, %	61.1 [52.0-68.7]	62.0 [52.0-68.0]	0.77
<40%	376 (8.4)	744 (8.9)	0.36
ARC-HBR	2,332 (43)	4,541 (47)	<0.001
DAPT score			0.27
<2	3,763 (70)	6,648 (69)	
≥2	1,619 (30)	2,979 (31)	

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with inverse probability of treatment weights (IPTW) (6,28). We developed multivariable logistic regression models to calculate the propensity scores for IPTW. We estimated HRs and their 95% CIs of the G2-DES group relative to the G1-DES group for each outcome measure with crude Cox proportional hazards models and Cox models with IPTW as analytic weights. In the multivariable models, we regarded the missing values of dichotomized variables as negative values because data should have been available if abnormalities were suspected (Supplemental Table 2). Subgroup analyses were conducted for acute coronary syndrome (ACS), intracoronary imaging use, and the patients with only SES or only EES (the majority of the G1-DES and G2-DES groups). We examined the interactions with the product terms in the Cox proportional hazards models. We also sought to evaluate the association between prolonged DAPT (>1 year) and the outcomes in each DES stratum. We divided the patients of each DES stratum into the 2 groups according to their DAPT status at 1 year (on-DAPT and off-DAPT at 1 year) (26). In each DES stratum, we compared the on-DAPT group with the off-DAPT group for definite ST and TVR by using Cox proportional hazards model with IPTW. Additionally, we performed a sensitivity analysis using Cox proportional hazards models with DAPT status as a time-updated covariate (26) and estimated the risk of on-DAPT status relative to off-DAPT for definite ST and TVR.

The statistical analyses were performed with R software version 3.6.3 (R Foundation for Statistical Computing) and SPSS software version 25 (IBM Corporation). The reported *P* values were 2-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS AND MEDICATIONS. Among the total 15,009 patients in this study, there were 5,382 patients in the G1-DES group from Cohort-2 and 9,627 patients in the G2-DES group from Cohort-3 (Figure 1).

Patients in the G2-DES group as compared with those in the G1-DES group were older and more often presented with ACS and ST-segment elevation myocardial infarction (Table 1). The G2-DES group more often included patients with a higher bleeding risk according to the ARC-HBR criteria than the G1-DES group, whereas the DAPT score was similarly distributed in the 2 groups. Because of the availability specific to the study periods, clopidogrel was mostly prescribed as the thienopyridine treatment in the G2-DES group, whereas ticlopidine was the main thienopyridine treatment in the G1-DES group. Anticoagulant agents were more often prescribed in the G2-DES group than in the G1-DES group. Statins were much more often prescribed in the G2-DES group than in the G1-DES group. PCI was more frequently performed as an emergency procedure in the G2-DES group than in the G1-DES group. High-risk features for stent-related adverse events, such as total stent length >60 mm, ≥3 stents implanted, and ≥3 lesions treated, were more frequently seen in the G2-DES group. Intracoronary imaging was much more frequently used in the G2-DES group than in the G1-DES group.

LONG-TERM CLINICAL OUTCOMES. The cumulative 5-year incidence and the adjusted risk for definite ST were significantly lower in the G2-DES group than in the G1-DES group (0.7% vs 1.4%; $P < 0.001$; adjusted HR: 0.53; 95% CI: 0.37-0.76; $P < 0.001$) (**Figure 2A, Table 2**). The 1-year landmark analysis demonstrated that the difference in the 5-year outcome for definite ST was largely attributable to the outcome in the late phase (>1 year) after PCI (adjusted HR: 0.34; 95% CI: 0.20-0.57; $P < 0.001$) (**Figure 2B, Table 3**). The annual incidence of very late ST beyond 1 year was 0.25%/y in the G1-DES group, and it was 0.08%/y in the G2-DES group.

The cumulative 5-year incidence and adjusted risk for TVR were also significantly lower in the G2-DES group than in the G1-DES group (16.2% vs 22.1%; $P < 0.001$; adjusted HR: 0.74; 95% CI: 0.68-0.81; $P < 0.001$) (**Figure 2C, Table 2**). In the 1-year landmark analysis, the lower adjusted risk of G2-DES relative to G1-DES was significant for TVR both within and beyond 1 year (**Figure 2D, Table 3**). The annual incidence of very late TVR beyond 1 year was 3.1%/y in the G1-DES group and 2.1%/y in the G2-DES group. The results of the subgroup analysis comparing the 2 groups of patients treated with SES or EES were fully consistent with the main results (Supplemental Table 3, Supplemental Figure 1).

In the subgroup analysis, the cumulative 5-year incidences of definite ST in the ACS subgroup were approximately twice as high as those in the non-ACS subgroup regardless of the type of DES (Supplemental Figure 2). The results in the subgroup analyses that were based on ACS and intracoronary imaging were consistent with the main results both for definite ST and TVR (Supplemental Figures 2 and 3). Nevertheless, significant interaction was present between intracoronary imaging and the effect of G2-DES relative to G1-DES for TVR ($P_{interaction} = 0.003$), with greater risk reduction in TVR by G2-DES than G1-DES in patients without intracoronary imaging than in those with intracoronary imaging (Supplemental Figure 3).

Regarding the secondary outcome measures, G2-DES compared with G1-DES was associated with a lower risk for stroke but a higher risk for GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate to severe bleeding. There was no difference in adjusted mortality risk between G2-DES and G1-DES (**Table 2**).

DAPT STATUS AND STENT-RELATED ADVERSE EVENTS. Persistent discontinuation of DAPT was more frequent in the G1-DES group than in the

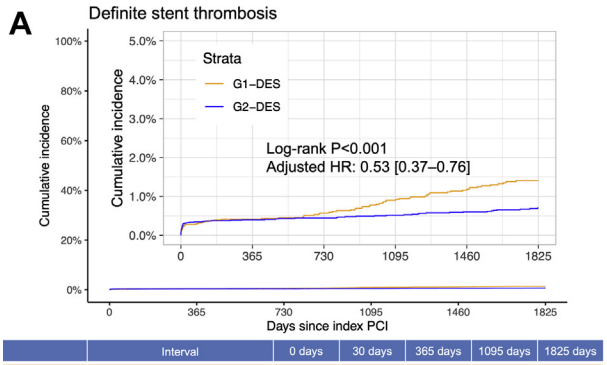
TABLE 1 Continued

	G1-DES (n = 5,382)	G2-DES (n = 9,627)	*P* Value
Medications at the time of discharge			
Aspirin	5,313/5,382 (98.7)	9,571/9,627 (99.4)	<0.001
Thienopyridine	5,366/5,382 (99.7)	9,594/9,627 (99.7)	0.64
Ticlopidine	4,680/5,366 (87)	238/9,594 (2.5)	<0.001
Clopidogrel	678/5,366 (13)	9,281/9,594 (97)	<0.001
Cilostazol	859 (16)	271 (2.8)	<0.001
Anticoagulation therapy	434 (8.1)	931 (9.7)	0.001
Warfarin	434/434 (100)	798/931 (86)	NA
DOACs	0/434 (0)	133/931 (14)	NA
Statins	2,919 (54)	7,512 (78)	<0.001
ACE inhibitors or ARBs	2,974 (55)	6,073 (63)	<0.001
Beta-blockers	1,496 (28)	3,553 (37)	<0.001
Calcium-channel blockers	2,507 (47)	4,154 (43)	<0.001
Nitrates	1,994 (37)	2,068 (21)	<0.001
Nicorandil	1,118 (21)	1,367 (14)	<0.001
PPIs	1,305 (24)	6,367 (66)	<0.001
H_2-blockers	1,270 (24)	1,120 (12)	<0.001
PPIs or H_2-blockers	2,568 (48)	7,428 (77)	<0.001
PCI procedural characteristics			
Radial artery approach	1,846 (34)	4,571 (47)	<0.001
Brachial artery approach	627 (12)	1,183 (12)	0.30
Femoral artery approach	3,272 (61)	4,807 (50)	<0.001
Emergency procedure	997 (19)	3,043 (32)	<0.001
Extent of CAD			<0.001
LMCA	179 (3.3)	526 (5.5)	
3 VD	1,217 (23)	2,121 (22)	
2 VD	1,849 (34)	3,061 (32)	
1 VD	2,137 (40)	3,919 (41)	
Multivessel disease	3,257 (61)	5,709 (59)	0.15
CTO lesions	1,125 (21)	1,922 (20)	0.17
Treated lesions ≥3	542 (10)	1,162 (12)	<0.001
3 vessels treated	259 (4.8)	527 (5.5)	0.081
PCI for unprotected LMCA	185 (3.4)	491 (5.1)	<0.001
PCI for CTO lesions	731 (14)	1,052 (11)	<0.001
PCI for bifurcation lesions	2,162 (40)	4,320 (45)	<0.001
PCI with side branch stenting	269 (5.0)	474 (4.9)	0.84
Implanted stents ≥3	1,271 (24)	2,471 (26)	0.005
Total length of stents, mm	33 [20-56]	33 [20-56]	0.98
>28	2,883 (54)	5,205 (54)	0.56
>60	1,131 (21)	2,190 (23)	0.01
Minimum stent diameter <3.0 mm	2,731 (51)	5,649 (59)	<0.001
PCI with intracoronary imaging	3,148 (58)	7,551 (78)	<0.001
PCI with IVUS	3,148 (58)	7,463 (78)	<0.001
PCI with OCT	0 (0)	236 (2.5)	NA
Sirolimus-eluting stents	5,065 (94)	0 (0)	NA
Paclitaxel-eluting stents	466 (8.7)	0 (0)	NA
Everolimus-eluting stents	0 (0)	6,953 (72)	NA
Biolimus-eluting stents	0 (0)	2,712 (28)	NA
Zotarolimus-eluting stents	0 (0)	939 (9.8)	NA

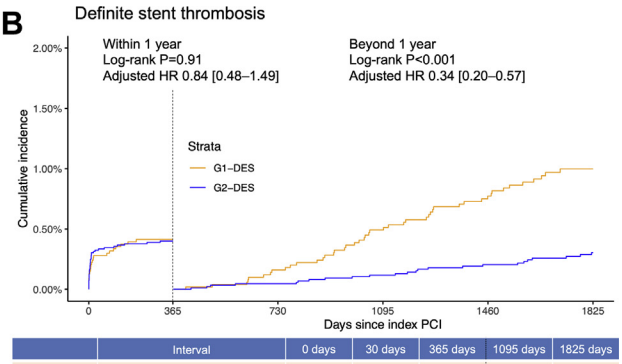
Values are mean ± SD, n (%), or median [25th to 75th percentile]. [a]Severe CKD and moderate CKD were defined as hemodialysis or eGFR <30 mL/min/1.73 m^2 and eGFR ≥30 and <60 mL/min/1.73 m^2, respectively.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARC-HBR = Academic Research Consortium for High Bleeding Risk; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CTO = chronic total occlusion; DAPT = dual antiplatelet therapy; DES = drug-eluting stents; DOAC = direct oral anticoagulant agent; eGFR = estimated glomerular filtration rate; G1 = first-generation; G2 = second-generation; IVUS = intravascular ultrasound; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; NSTEACS = non-ST-segment elevation acute coronary syndrome; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction; VD = vessel disease.

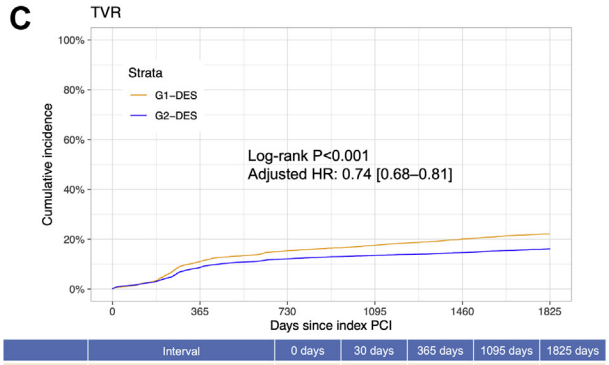
FIGURE 2 Kaplan-Meier Curves for 5-Year Outcomes and 1-Year Landmark Analysis: G1-DES vs G2-DES



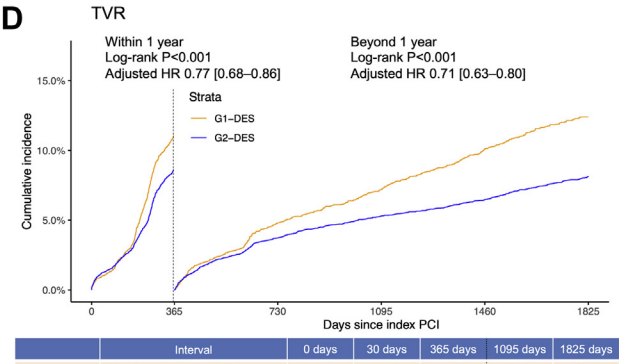
	Interval	0 days	30 days	365 days	1095 days	1825 days
G1-DES	Number of patients at risk	5382	5310	5117	4700	2911
	Number of patients with event		15	22	46	68
	Cumulative incidence		0.3%	0.4%	0.9%	1.4%
G2-DES	Number of patients at risk	9627	9406	8936	8183	6355
	Number of patients with event		31	38	48	62
	Cumulative incidence		0.3%	0.4%	0.5%	0.7%



	Interval	0 days	30 days	365 days	1095 days	1825 days
G1-DES	Number of patients at risk	5382	5310	5117	4700	2911
	Number of patients with event		15	22	24	46
	Cumulative incidence		0.3%	0.4%	0.5%	1.0%
G2-DES	Number of patients at risk	9627	9406	8936	8183	6355
	Number of patients with event		31	38	10	24
	Cumulative incidence		0.3%	0.4%	0.1%	0.3%



	Interval	0 days	30 days	365 days	1095 days	1825 days
G1-DES	Number of patients at risk	5382	5280	4566	3914	2324
	Number of patients with event		46	579	899	1097
	Cumulative incidence		0.9%	11.1%	17.5%	22.1%
G2-DES	Number of patients at risk	9627	9343	8196	7094	5380
	Number of patients with event		98	800	1221	1418
	Cumulative incidence		1.0%	8.7%	13.5%	16.2%



	Interval	0 days	30 days	365 days	1095 days	1825 days
G1-DES	Number of patients at risk	5382	5280	4566	3914	2324
	Number of patients with event		46	579	320	518
	Cumulative incidence		0.9%	11.1%	7.2%	12.4%
G2-DES	Number of patients at risk	9627	9343	8196	7094	5380
	Number of patients with event		98	800	421	618
	Cumulative incidence		1.0%	8.7%	5.3%	8.2%

(A) Definite stent thrombosis over 5 years. **(B)** Definite stent thrombosis, 1-year landmark analysis. **(C)** Target vessel revascularization (TVR) over 5 years. **(D)** Target vessel revascularization, 1-year landmark analysis. Abbreviations as in **Figure 1**.

G2-DES group within 1 year, whereas beyond 1 year, it was more frequent in the G2-DES group than in the G1-DES group (33.5% vs 24.8% at 1 year and 58.8% vs 72.1% at 5 years) (Supplemental Figure 4). In both G1-DES and G2-DES strata, patients with on-DAPT status at 1 year as compared with patients with off-DAPT status at 1 year had more often undergone complex PCI procedures such as for multivessel disease, ≥3 treated lesions, target of chronic total occlusion, and bifurcation lesions (Supplemental Table 4). In the G1-DES stratum, the cumulative 5-year incidence of very late definite ST was significantly higher in the off-DAPT group than in the on-DAPT group (1.6% vs 0.7%; $P = 0.002$), whereas in the G2-DES stratum, it was not significantly different between the off-DAPT and on-DAPT groups (0.3% vs 0.3%; $P = 0.81$) (**Central Illustration**). After adjusting for the confounders, in the G1-DES stratum, the lower risk of on-DAPT relative to off-DAPT status remained significant for definite ST beyond 1 year (adjusted HR: 0.42; 95% CI: 0.24-0.76; $P = 0.004$), whereas in the G2-DES stratum, the lower risk of on-DAPT relative to off-DAPT status was insignificant (adjusted HR: 0.66; 95% CI: 0.26-1.68; $P = 0.38$) ($P_{interaction} = 0.14$) (**Central Illustration**). The cumulative 5-year incidence of TVR was significantly lower in the off-DAPT group than in the on-DAPT group in both DES strata (10.6% vs 13.3%; $P <$

TABLE 2 Clinical Outcomes Through 5 Years: G1-DES vs G2-DES

	Patients With Event (Cumulative 5-y Incidence)				
	G1-DES (n = 5,382)	G2-DES (n = 9,627)	Clinical Outcome Measures	Adjusted HR (95% CI)	*P* Value
Definite stent thrombosis	68 (1.4)	62 (0.7)	0.51 (0.36-0.72)	0.53 (0.37-0.76)	<0.001
Definite or probable stent thrombosis	96 (2.0)	69 (0.8)	0.40 (0.30-0.55)	0.39 (0.28-0.55)	<0.001
TVR	1,097 (22.1)	1,418 (16.2)	0.71 (0.66-0.77)	0.74 (0.68-0.81)	<0.001
Clinically driven TVR	558 (11.6)	711 (8.3)	0.72 (0.64-0.80)	0.76 (0.67-0.85)	<0.001
Any coronary revascularization	1,530 (30.7)	2,229 (25.3)	0.81 (0.76-0.86)	0.84 (0.78-0.90)	<0.001
Myocardial infarction	202 (4.2)	419 (4.8)	1.18 (0.99-1.39)	1.19 (0.99-1.43)	0.06
All-cause death	782 (15.3)	1,506 (16.4)	1.09 (0.999-1.19)	1.01 (0.92-1.12)	0.78
Cardiac death	332 (6.6)	670 (7.5)	1.14 (1.00-1.30)	1.13 (0.97-1.32)	0.11
Noncardiac death	450 (9.3)	836 (9.6)	1.05 (0.94-1.18)	0.93 (0.82-1.06)	0.29
Stroke	323 (6.7)	526 (6.1)	0.92 (0.80-1.06)	0.84 (0.72-0.98)	0.03
Ischemic	241 (5.0)	402 (4.7)	0.94 (0.80-1.11)	0.86 (0.62-1.18)	0.08
Hemorrhagic	90 (1.9)	140 (1.7)	0.88 (0.67-1.14)	0.85 (0.71-1.02)	0.34
GUSTO moderate or severe bleeding	505 (10.2)	1,195 (13.4)	1.36 (1.22-1.51)	1.21 (1.08-1.35)	<0.001
GUSTO severe bleeding	240 (5.0)	592 (6.8)	1.40 (1.21-1.63)	1.32 (1.12-1.55)	<0.001

Values are n (%) or HR (95% CI). We adjusted for baseline characteristics and medications (listed in Supplemental Table 1) with IPTW. We calculated the propensity scores for IPTW with multivariable logistic regression models. We estimated HR of the G2-DES group relative to the G1-DES group for each outcome measure with crude Cox proportional hazards models and Cox proportional hazards models with IPTW as analytic weights, and we presented HR and their 95% CI.

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; IPTW = inverse probability of treatment weights; TVR = target vessel revascularization; other abbreviations as in Table 1.

0.001 in the G1-DES stratum; and 7.1% vs 8.5%; $P < 0.001$ in the G2-DES stratum) (Figure 3). After adjusting for the confounders, the higher risk of on-DAPT relative to off-DAPT status for TVR beyond 1 year was no longer significant in the G2-DES stratum (adjusted HR: 1.06; 95% CI: 0.87-1.29; $P = 0.58$), whereas in the G1-DES stratum, it remained significant (adjusted HR: 1.22; 95% CI: 1.01-1.48; P=0.04) ($P_{\text{interaction}} = 0.64$) (Figure 3). The sensitivity analysis using Cox proportional hazards models with DAPT status as a time-updated covariate showed consistent results (Supplemental Table 5).

DISCUSSION

The main findings in the present study were the followings: first, G2-DES compared with G1-DES was associated with a significantly lower adjusted risk for stent-related adverse events such as definite ST and TVR; second, on-DAPT status compared with off-DAPT status at 1 year was associated with a lower risk for very late ST beyond 1 year in the G1-DES group, but not in the G2-DES group.

In the present study, G2-DES were associated with a substantially lower risk for ST as compared with G1-DES, which was mainly driven by the lower risk beyond 1 year. The majority of DES used in the present study was SES in the G1-DES group and EES in the G2-DES. Among the 4 randomized trials comparing EES with SES, significant reduction in ST with G2-DES compared with G1-DES was demonstrated in the SORT-OUT IV trial (Scandinavian Organization for Randomized Trials with Clinical Outcome IV Trial; NCT00552877), but it was not in the ISAR TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents; NCT00598676) or RESET (Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting Stent Trial; NCT01035450) (8-10). In the RESET trial, the cumulative 7-year incidence of definite ST was 0.9% in the EES group and 1.0% in the SES group (29). The discrepancy between the RESET trial and the present study, although both were conducted in Japan, could be derived from the enrollment of selected lower-risk patients and the lack of adequate power in the RESET trial as compared with enrollment of a large number of real-world consecutive patients in the current observational study. This may be 1 of the reasons that G2-DES compared with G1-DES were associated with a substantially lower risk for very late ST in the present study, which enrolled exclusively Japanese patients, who are known to have a relatively low ST risk (5,30). However, it may be important to note that despite substantial reduction in ST, the lower mortality risk of G2-DES relative to G1-DES was not demonstrated in the present study. This may be explained by the small absolute reduction in the rate of ST (0.7% in 5 years) in the present study.

TABLE 3 Clinical Outcomes Within 1 Year and Landmark Analysis of 1 to 5 Years: G1-DES vs G2-DES

	G1-DES (n = 5,382)	G2-DES (n = 9,627)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P* Value
~1 y					
Definite stent thrombosis	22 (0.4)	38 (0.4)	0.97 (0.57-1.64)	0.84 (0.48-1.49)	0.55
Definite or probable stent thrombosis	37 (0.7)	44 (0.5)	0.67 (0.43-1.04)	0.57 (0.35-0.91)	0.02
TVR	579 (11.1)	800 (8.7)	0.77 (0.70-0.86)	0.77 (0.68-0.86)	<0.001
Clinically driven TVR	186 (3.6)	314 (3.4)	0.96 (0.80-1.15)	0.93 (0.77-1.13)	0.48
Any coronary revascularization	844 (16.2)	1285 (14.0)	0.85 (0.78-0.93)	0.86 (0.78-0.94)	0.002
1-5 y					
Definite stent thrombosis	46 (1.0)	24 (0.3)	0.29 (0.18-0.48)	0.34 (0.20-0.57)	<0.001
Definite or probable stent thrombosis	59 (1.3)	25 (0.3)	0.24 (0.15-0.38)	0.26 (0.16-0.42)	<0.001
TVR	518 (12.4)	618 (8.2)	0.65 (0.58-0.73)	0.71 (0.63-0.80)	<0.001
Clinically driven TVR	372 (8.4)	397 (5.0)	0.60 (0.52-0.69)	0.66 (0.57-0.77)	<0.001
Any coronary revascularization	686 (17.4)	944 (13.2)	0.75 (0.68-0.83)	0.80 (0.72-0.89)	<0.001

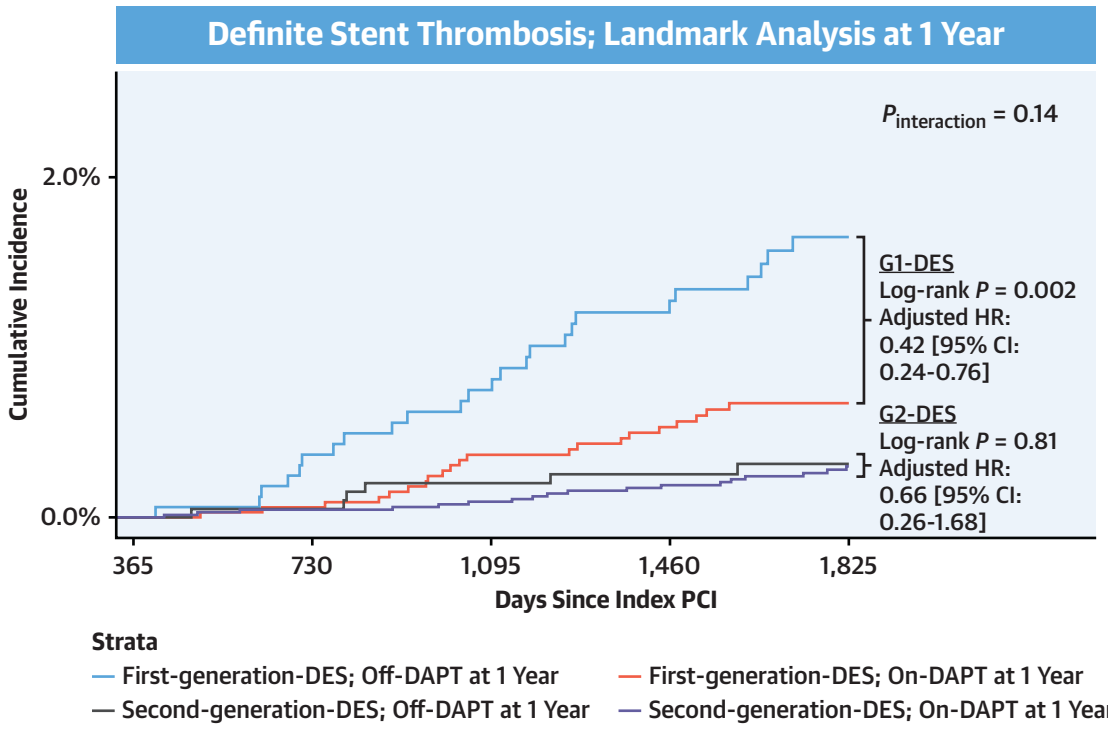
Values are n (%) or HR [95% CI].
Abbreviations as in Tables 1 and 2.

Among the 4 randomized trials comparing EES with SES, G2-DES compared with G1-DES were not associated with a lower TVR risk or target lesion revascularization, which may be regarded as surrogates for restenosis (8-10). However, in the present study, G2-DES compared with G1-DES were associated with a significantly lower TVR risk both within and beyond 1 year. The discordance between the earlier randomized trials and the present study may also be explained by the enrollment of selected lower-risk patients and the lack of adequate power in the randomized trials as compared with the large observational study enrolling consecutive patients in real clinical practice. Indeed, the cumulative 3-year incidence of TVR was much higher in the present study than in the RESET trial (EES, 13.5% vs 10.4%; and SES, 17.5% vs 11.1%) (8).

The importance of DAPT has been underscored by the previous studies that found ST was often preceded by early discontinuation of clopidogrel therapy (31). Along with inappropriately early discontinuation of DAPT, several patient-, lesion-, and procedure-related factors have been reported as high-risk features for ST, and G1-DES have been suggested as important factors to predict very late ST. For instance, in the DAPT trial, where prolonged DAPT was compared with aspirin monotherapy beyond 12 months, PES had a higher thrombotic risk and were included in a clinical score as a thrombotic factor (26). Further, PROTECT (Patient Related OuTcomes With Endeavor Versus Cypher Stenting Trial; NCT00476957) observed a strong interaction between DES types and the influence of DAPT status in the incidence of ST (19). Nevertheless, there is a paucity of data on the relationship between DAPT duration and the risk of ST stratified by the types of DES. In the DAPT trial, DAPT beyond 1 year after placement of a DES as compared with aspirin monotherapy significantly reduced the risk of ST at 30 months (21). In the subgroup analysis that was based on the types of DES, the favorable effect of prolonged DAPT on ST was consistent across the 4 types of DES, such as SES, PES, ZES, and EES, without interaction. However, the numbers of patients with ST were too small for SES, ZES, and EES to allow the investigators to make any meaningful interpretation of the subgroup analysis.

In the present study, on-DAPT status compared with off-DAPT status at 1 year was associated with significantly lower risk for very late definite ST in patients who had received G1-DES, but it was not in patients who had received G2-DES. This finding suggests that prolonged DAPT was protective for preventing very late definite ST in G1-DES but not in G2-DES. Despite possible differences in risk-to-benefit trade-off of antithrombotic treatment between East Asian and European or North American patients (22), the result of this study enrolling exclusively Japanese patients was consistent with the previous meta-analysis that showed a significant interaction between DES generations and DAPT durations (32). More recently, several clinical trials have demonstrated the safety and efficacy of very short (1- to 3-month) DAPT after G2-DES implantation followed by P2Y12 receptor blocker monotherapy up to 12- to 15-month follow-up (33-36). However, given the limited follow-up duration of these trials, it is still unclear whether P2Y12 receptor blocker monotherapy is enough to prevent very late ST of G2-DES. The findings of the present study reassure us about

CENTRAL ILLUSTRATION **Kaplan-Meier Curves for Definite Stent Thrombosis in First- and Second-Generation DES Stratified by Dual Antiplatelet Therapy Status at 1 Year**



		365 Days	730 Days	1,095 Days	1,460 Days	1,825 Days
G1-DES; Off-Dual antiplatelet therapy at 1 Year	No. of patients at risk	1,660	1,607	1,538	1,457	1,104
	No. of patients with event		6	12	20	25
	Cumulative incidence		0.4%	0.7%	1.3%	1.6%
G1-DES; On-Dual antiplatelet therapy at 1 Year	No. of patients at risk	3,457	3,317	3,162	3,013	1,807
	No. of patients with event		2	12	17	21
	Cumulative incidence		0.1%	0.4%	0.5%	0.7%
G2-DES; Off-Dual antiplatelet therapy at 1 Year	No. of patients at risk	2,109	1,990	1,889	1,765	1,375
	No. of patients with event		1	4	5	6
	Cumulative incidence		0.0%	0.2%	0.3%	0.3%
G2-DES; On-Dual antiplatelet therapy at 1 Year	No. of patients at risk	6,827	6,576	6,294	5,954	4,980
	No. of patients with event		3	6	12	18
	Cumulative incidence		0.0%	0.1%	0.2%	0.3%

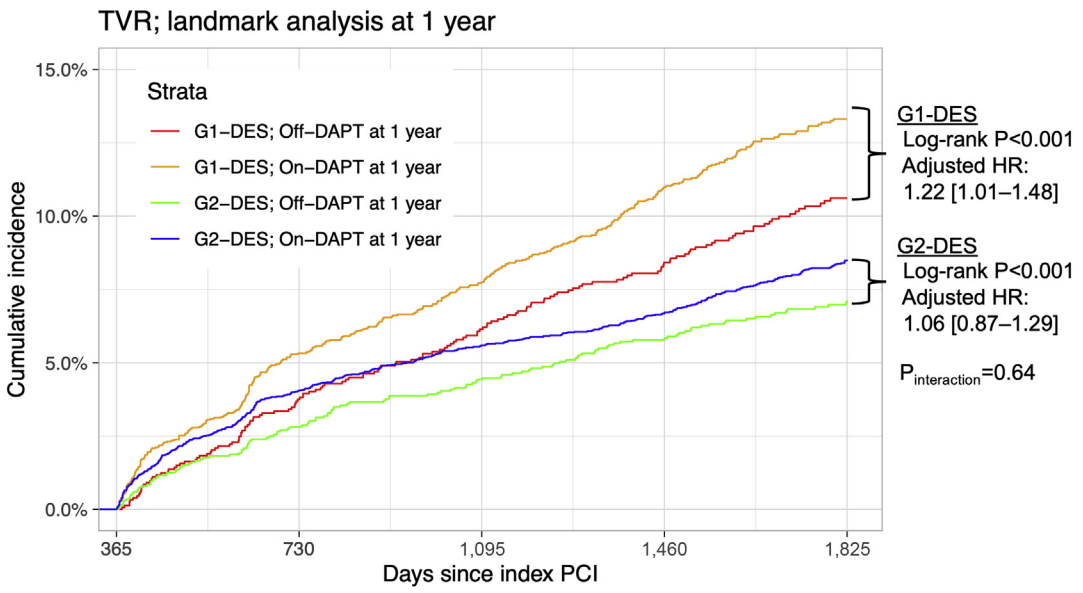
Yoshikawa, Y. et al. JACC: Asia. 2021;1(3):345-356.

DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

implementation of long-term antiplatelet monotherapy after G2-DES implantation.

STUDY LIMITATIONS. The present study has strengths in that the study group consisted of a series of large-scale cohorts with 5-year follow-up, conducted by the same investigators with the identical study methodologies (Supplemental Table 6). Nevertheless, this study has limitations. First, this study

FIGURE 3 Kaplan-Meier Curves for TVR in G1-DES and G2-DES Stratified by DAPT Status at 1 Year



		365 days	730 days	1095 days	1460 days	1825 days
G1-DES; Off-DAPT at 1 year	N of patients at risk	1,537	1,438	1,349	1,252	932
	N of patients with event		57	92	124	151
	Cumulative incidence		3.8%	6.1%	8.4%	10.6%
G1-DES; On-DAPT at 1 year	N of patients at risk	3,029	2,751	2,565	2,361	1,392
	N of patients with event		159	228	316	367
	Cumulative incidence		5.3%	7.8%	11.0%	13.3%
G2-DES; Off-DAPT at 1 year	N of patients at risk	2,009	1,843	1,726	1,593	1,233
	N of patients with event		55	85	110	130
	Cumulative incidence		2.8%	4.4%	5.8%	7.1%
G2-DES; On-DAPT at 1 year	N of patients at risk	6,186	5,712	5,368	5,021	4,147
	N of patients with event		247	337	399	489
	Cumulative incidence		4.1%	5.6%	6.7%	8.5%

DAPT = dual antiplatelet therapy; other abbreviations as in Figures 1 and 2.

has an observational study design with historical comparison, and the choice of DES was totally dependent on the period-specific availability. Each DES group consisted of heterogeneous DES types. The indications for PCI using DES were different between the 2 cohorts, and hence patient- and lesion-related characteristics were substantially different. Despite the extensive statistical adjustment, there should have inevitably been residual confounding and selection bias. However, the additional analysis restricting the study population to the main DES in each group (SES and EES) showed consistent results. Second, the CREDO-Kyoto PCI/CABG Registries did not randomize DAPT duration, and thus the result of the exploratory analysis of DAPT duration should be regarded as hypothesis generating. The general consensus regarding the duration of DAPT after PCI with DES in real clinical practice was different between the G1-DES and G2-DES groups because of their different enrollment periods. Moreover, in the present study, on-DAPT status compared with off-DAPT status was associated with a trend toward a higher risk for TVR in both G1-DES and G2-DES strata that could be related to bias in favor of prolonged DAPT in patients with complex coronary anatomy. Third, the stent generation was not specific to the type of DES. Fourth, medical management of patients after PCI was also different between the 2 registries. For instance, the class of thienopyridine was different. Fifth, coronary angiography was not assessed in a

core laboratory, and hence lesion-specific information was not obtained. Sixth, there was the 12% difference in follow-up at 5 years between the groups. However, that mainly reflected a difference in time spans from the inclusion periods to the times of data collection between the 2 registries. Therefore, we believe that it had a minimal impact on the interpretation of the study results. Seventh, some of the information on DAPT status during follow-up was collected by contact with patients, and thus there may have been recall bias and measurement errors on the status of antiplatelet therapy. Finally, the less widespread use of troponin measurement in Cohort-2 compared with Cohort-3 may have underestimated the incidence of myocardial infarction during follow-up in Cohort-2.

CONCLUSIONS

In this historical comparison of a series of large Japanese registries, G2-DES compared with G1-DES were associated with a significantly lower risk for stent-related adverse events, including definite ST and TVR. DAPT beyond 1 year was associated with a significantly lower risk for very late definite ST of G1-DES but not for that of G2-DES.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There are limited data on the long-term stent-related adverse events as related to the duration of DAPT in G2-DES compared with G1-DES. This pooled cohort consisting of CREDO-Kyoto PCI/CABG Registry Cohort-2 and Cohort-3 showed that G2-DES compared with G1-DES were associated with a lower risk for stent-related adverse outcomes, ST, and TVR. Further, prolonged DAPT was associated with reduced risk for ST in G1-DES but not in G2-DES. This study has shown that G2-DES are superior to G1-DES even in East Asian populations with a very low thrombotic risk.

TRANSLATIONAL OUTLOOK: Several recent clinical trials have demonstrated the safety and efficacy of very short (1- to 3-month) DAPT after newer-generation DES implantation followed by P2Y12 receptor blocker monotherapy up to 12- to 15-month follow-up. The findings of the present study are reassuring about implementation of very long-term antiplatelet monotherapy after stent implantation in the era of a newer generation of DES.

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KEY WORDS drug-eluting stent, dual antiplatelet therapy, stent thrombosis

APPENDIX For lists of participating centers, investigators, research coordinators, and committee members, an expanded definition of outcomes, and supplemental tables and figures, please see the online version of this paper.