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ORIGINAL RESEARCH

Five-Year Impacts of Antithrombotic Therapy Based on 10-Year Clinical Outcomes of Cypher™ Stent Implantation

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ABSTRACT

Introduction: Few researchers have investigated the optimal long-term antithrombotic therapy regimen, especially after first-generation drug-eluting stent (DES) use. This study aimed to evaluate the impact of mid-term antithrombotic therapy on long-term outcomes in patients treated with the first sirolimus-eluting coronary stent (Cypher™).

Methods: Between 2004 and 2009, 1021 patients underwent Cypher™ implantation at our institute; among them, 567 patients had available data on antithrombotic therapy at year 5. We assessed patients' antithrombotic therapy at year 5 post Cypher™ implantation and examined their association with adverse events from year 5 to year 10 post Cypher™ implantation.

Results: Patients with dual-antiplatelet therapy (DAPT) at year 5 had significantly lower risk of stent thrombosis (ST) than those with single-antiplatelet therapy (SAPT) (hazard ratio [HR] 0.24, $p = 0.034$). The HR of major bleeding in

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DAPT, compared to SAPT, was high, but the difference was not significant (HR 1.72, $p = 0.26$). Risk of major bleeding was significantly higher in patients on oral anticoagulants (OAC) than in those in other groups (OAC/SAPT; HR 5.31, $p = 0.0048$, OAC/DAPT; HR 3.08, $p = 0.022$), without significant reduction in the risk of cardiovascular events.

Conclusions: The incidence of ST after Cypher™ implantation in patients with DAPT at year 5 was significantly lower than that in SAPT. However, the risk of bleeding was higher with DAPT than with SAPT. Moreover, the risk of major bleeding was significantly higher in patients on anticoagulant therapy than in other patients. New options for the use of antithrombotic drugs after percutaneous coronary intervention warrant further studies on the optimal antithrombotic therapy for first-generation DES.

Keywords: Bleeding; Coronary artery disease; Sirolimus-eluting stent; Stent thrombosis

Key Summary Points
Why carry out this study?
It is unclear whether dual antiplatelet agent therapy (DAPT) should be continued for patients after first-generation coronary drug-eluting stent (DES) implantation.
This study roughly approximates the effect of continued DAPT after first-generation DES implantation.
What was learned from the study?
Long-term DAPT use significantly reduced the risk of stent thrombosis but increased the risk of major bleeding.
The decision to continue DAPT should be made on a patient-by-patient basis.
There was no marked difference between the number of benefits from reduced stent thrombosis and the number of risks from major bleeding.

INTRODUCTION

Coronary artery drug-eluting stents (DES) were introduced into clinical use more than 15 years ago. Several patients have benefited from this cornerstone therapy for ischemic heart disease (IHD). However, after stent implantation, dual antiplatelet agent therapy (DAPT) is required, in principle, to prevent stent thrombosis (ST), [1] but the resulting increase in bleeding events is a crucial problem. Therefore, the new-generation DES attempt to shorten the DAPT period, and the optimal DAPT period has been set to be shorter than before, depending on the balance between ST and bleeding events [2, 3]. However, while there have been many studies on the DAPT duration of new-generation DES, there are few studies on first-generation DES. The risk of ST is considered to be higher with first-generation DES than with second-generation stents [4]. In addition, the mechanism of stent failure is considered to change with time post-implantation because of the long-term effects of stents on local vessels [5–9]. Therefore, the optimal antithrombotic therapy for the first-generation DES may be different from that of the new-generation DES due to two factors: differences in stents and differences in time post-implantation. Cypher™ is a benchmark first-generation DES. A good understanding of the impact of the mid-term management of patients with these stents on long-term prognoses would be of high clinical value. In this study, we aimed to examine the mid-term status of antithrombotic agents after Cypher™ placement to assess their effects on long-term prognoses.

METHODS

Study Design and Patients

This study is a retrospective, single-center, observational cohort study in Japan. We collected data from patients who received initial Cypher™ stents for IHD at Ome Municipal General Hospital between April 2004 and December 2009. Patients who died or those who

could not be followed up for at least 5 years after the procedure were excluded. We assessed antithrombotic use at year 5 post percutaneous coronary intervention (PCI), and patients were divided into three groups, based on antithrombotic therapy type, as follows: single antiplatelet therapy (SAPT) group, DAPT group, and a group of patients using oral anticoagulants regardless of antiplatelet drug status (OAC). Patients who were not using any antithrombotic drugs were excluded. The association between groups divided by antithrombotic therapy and adverse events between year 5 and year 10 post-PCI were statistically examined.

Our study was approved by the Ethics Committee of Ome Municipal General Hospital (April 30, 2019, reference number 3) and performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and details and other matters related to the study were published based on the recommendations of the Ministry of Health, Labor and Welfare. Informed consent was written and provided by all patients. The primary endpoints of the study were ST and major bleeding incidence from year 5 to year 10 post-PCI. Secondary endpoints examined were all-cause death, cardiac death, non-fatal acute myocardial infarction (AMI), and target lesion revascularization (TLR).

Definitions

The data on baseline clinical characteristics were obtained from hospital charts. The combination of aspirin and P2Y-12 inhibitors was defined as DAPT, and single use of aspirin or P2Y-12 inhibitors was defined as SAPT. ST was defined according to the Academic Research Consortium definition [10]. Since unexplained deaths are more common long term, this study only analyzed definite and probable ST and excluded possible ST. Major bleeding was defined as Bleeding Academic Research Consortium type 3a or higher [11]. All-cause death was regarded as cardiac-related death unless unequivocal non-cardiac causes could be identified. AMI was defined as the presence of ischemic symptoms, followed by a typical increase in troponin concentration above the 99th percentile upper reference limit, or creatine kinase or creatine kinase-MB concentrations to more than twice the normal values. TLR was defined as either PCI or coronary artery bypass grafting for stenosis or thrombosis, within a stent or within the 5-mm border adjacent to the stent.

Statistical Analysis

Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables were compared using Student's t test. All reported p values were two-sided. Normally distributed, continuous variables are expressed as mean ± standard deviation. Variables with non-normal distribution are expressed as median (interquartile range [IQR]). The cumulative incidence of clinical events was estimated using the Kaplan–Meier method, and clinical endpoints were tested using the log-rank test. Multivariable hazard ratios (HR) were evaluated with Cox proportional hazards models. A p value < 0.05 was considered statistically significant. Time in therapeutic range (TTR) was calculated using the fraction of international normalized ratios per the range method with the target prothrombin time-international normalized ratio (PT-INR) set as 1.60–2.59, a commonly used value in Japan. Follow-up was censored at the last known date. When Cypher™ implantation was performed more than twice in the same patient, the first record was used. The incidence of ST, major bleeding, all-cause death, cardiac-related death, non-fatal AMI, and TLR were analyzed. When ST, major bleeding, non-fatal AMI, or TLR occurred within the first 5 years, they were excluded from each parameter. All analyses were conducted by a physician (Ken Kurihara) using JMP®12 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Figure 1 demonstrates the flow chart of the study. A total of 1021 patients received their first Cypher™ stents at our hospital between April 2004 and December 2009. Of these, 686 patients were confirmed to be alive at year 5.

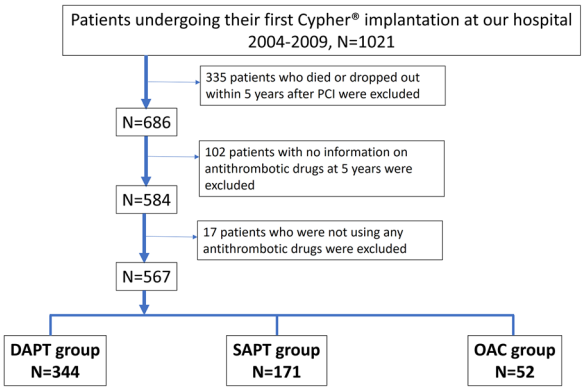


Fig. 1 Flow chart showing patient selection

Further, 584 patients had available data on antithrombotic therapy at year 5. After excluding patients who were not using any antithrombotic drugs, 567 patients were divided into SAPT, DAPT, and OAC groups. Table 1 shows a detailed breakdown of each group of antithrombotic drugs. TTR was also calculated to determine whether warfarin control was adequate. The mean TTR across all patients was 61.6%, which is considered relatively good, and 61.2% of patients had a TTR greater than 60%. Table 2 describes the clinical backgrounds of the entire cohort and of patients divided by their antithrombotic therapy group. Significant differences in age were observed between the patients of each group, without significant differences in other factors. Figure 2 shows the result of Kaplan–Meier analysis of the incidence of ST divided by the antithrombotic therapy groups, which demonstrates a significant difference in the results among the three groups. Figure 3 shows the Kaplan–Meier assessment of major bleeding, showing a significant difference among the three groups as well. Figures 4, 5, 6, and 7 show the Kaplan–Meier analysis of secondary endpoints. Among the events of all-cause death, cardiac death, non-fatal MI, and TLR, there was no significant difference among the three groups. Table 3 shows the incidence of cardiac events by antithrombotic therapy. Table 4 shows the results of Cox proportional hazards analysis for probable and definite ST and major bleeding events. The HR of ST in DAPT to SAPT was 0.24, which was statistically significant ($p = 0.034$). On the other hand, the HR of major bleeding in DAPT to SAPT was also high, but the difference was not significant (HR 1.72, $p = 0.26$). The HR of major bleeding in OAC was significantly higher than that in other groups (OAC/SAPT: HR 5.31, $p = 0.0048$, OAC/DAPT: HR 3.08, $p = 0.022$).

Table 5 outlines ST and bleeding risk based on antithrombotic status corrected for age, which was the patient characteristic that differed significantly. Consistently, the risk of ST

Table 1 Breakdown of antithrombotic drugs groups

All patients	567		
DAPT	344	OAC	52
clopidogrel	131	OAC + DAPT	13
ticlopidine	213	OAC + SAPT	34
SAPT	171	OAC only	5
aspirine	148	Warfarin	47
clopidogrel	17	DOAC	5
		Mean TTR of warfarin use (PT-INR 1.60–2.59)	61.6%
		Patients with TTR ≧ 60%	61.2%

DAPT dual antiplatelet therapy, *SAPT* single antiplatelet therapy, *OAC* oral anticoagulant therapy, *DOAC* direct oral anticoagulants, *TTR* time in therapeutic range

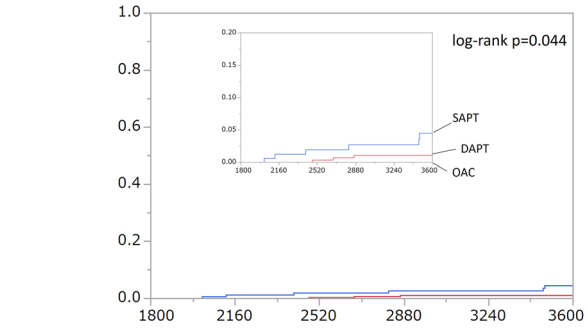
Table 2 Antithrombotic therapy at 5 years and baseline characteristics

Baseline characteristics				
	SAPT (*n* = 130)	**DAPT (*n* = 255)**	**OAC (*n* = 46)**	***p***
Age (years)	67.7 ± 9.4	65.6 ± 10.1	70.8 ± 9.2	0.0004
Male	128 (74.9)	269 (78.2)	35 (67.3)	0.22
Diabetes mellitus	57(33.3)	123 (35.8)	19 (36.5)	0.84
Dyslipidemia	77 (45.0)	152 (44.2)	22 (42.3)	0.94
Hypertension	86 (50.3)	157 (45.6)	29 (55.8)	0.3
Current smoker	28 (16.4)	71 (20.6)	6 (11.5)	0.18
Hemodialysis	4 (2.3)	8 (2.3)	3 (5.8)	0.43
History of MI	34 (19.9)	80 (23.3)	14 (26.9)	0.51
Previous PCI	34 (19.9)	72 (20.9)	17 (32.7)	0.15
Post CABG	10 (5.8)	17 (4.9)	5 (9.6)	0.44
Restenosis lesion	10 (5.8)	23 (6.7)	6 (11.5)	0.41
Chronic total occlusion	8 (4.7)	15 (4.4)	5 (9.6)	0.33
Acute coronary syndrome	61 (35.7)	154 (44.8)	19 (36.5)	0.11
Bifurcation lesion	24 (14.0)	58 (16.9)	7 (13.5)	0.63
LMCA	6 (3.5)	15 (4.4)	1 (1.9)	0.63
RCA	40 (23.4)	83 (24.1)	10 (19.2)	0.73
LAD	101 (59.1)	209 (60.8)	33 (63.5)	0.84
LCx	29 (17.0)	56 (16.3)	8 (15.4)	0.96
Bypass	1 (0.6)	3 (0.9)	1 (1.9)	0.71
Multivessel	25 (14.6)	62 (18.0)	8 (15.4)	0.59
Number of stents used	1.42 ± 0.58	1.44 ± 0.64	1.40 ± 0.57	0.88
Stent size (mm)	2.96 ± 0.37	2.98 ± 0.36	2.96 ± 0.38	0.84
Length of stents used (mm)	32.7 ± 15.2	33.0 ± 17.1	30.5 ± 15.7	0.58

Continuous variables are expressed as mean ± SD, *SAPT* single antiplatelet therapy, *DAPT* dual antiplatelet therapy, *OAC* oral anticoagulant therapy, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *LMCA* left main coronary artery, *RCA* right coronary artery, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery

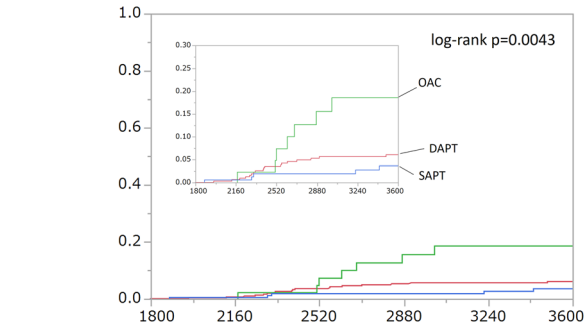
in DAPT was significantly lower than that in SAPT (HR 0.21, $p = 0.024$). The major bleeding risk of OAC was also significantly higher for SAPT and tended to be higher for DAPT after adjustment (OAC/SAPT: HR 4.24, $p = 0.014$, OAC/DAPT: HR 2.29, $p = 0.084$). Because the OAC group comprises subgroups of OAC only, OAC + SAPT, and OAC + DAPT, we further investigated whether there were differences in bleeding events between these three subgroups. However, no significant differences were found (Fig. 8).

For patients with ST and bleeding events, the antithrombotic medications administered



Patients at risk (Definite/Probable ST);						Days
DAPT	339	316	295	273	250	225
SAPT	170	159	137	127	116	102
OAC	52	47	42	37	31	27

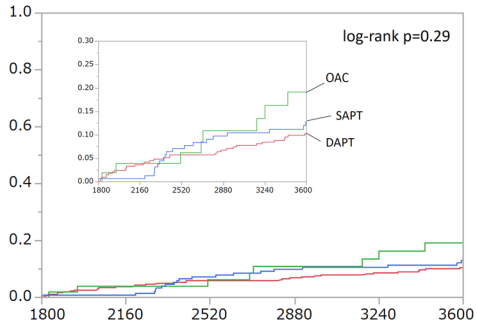
Fig. 2 Kaplan–Meier analysis of the incidence of definite and probable stent thrombosis according to antithrombotic groups



Patients at risk (Major bleeding);						Days
DAPT	337	316	290	266	245	221
SAPT	166	157	137	129	117	103
OAC	51	45	37	30	25	22

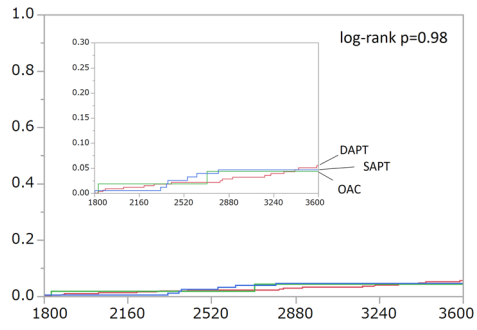
Fig. 3 Kaplan–Meier analysis of the incidence of major bleeding according to antithrombotic groups

immediately prior to the event were also examined (Table 6). Two of the three patients with ST in the DAPT group had been switched to SAPT and OAC + SAPT immediately before the event. In terms of antithrombotic medications administered immediately before the event in patients with major bleeding, although there was a trend toward DAPT being switched to SAPT over time, the percentage of patients who were continued on DAPT remained high than that of patients who had ST events.



Patients at risk (All cause death);						Days
DAPT	344	321	301	280	257	232
SAPT	171	163	141	132	121	108
OAC	52	47	42	37	31	27

Fig. 4 Kaplan–Meier analysis of the incidence of all-cause death according to antithrombotic groups



Patients at risk (Cardiac death);						Days
DAPT	344	321	301	280	257	232
SAPT	171	163	141	132	121	108
OAC	52	47	42	37	31	27

Fig. 5 Kaplan–Meier analysis of the incidence of cardiac death according to antithrombotic groups

DISCUSSION

There have been several reports on the short-term effects of patient characteristics and medical therapy during Cypher™ placement on clinical outcomes [12–14]. Nonetheless, the optimal use of antithrombotic agents at mid-term has not been well investigated. The effects of mid-term medical therapy on clinical outcomes may differ from early term effects. This is important, since more than 15 years have passed since Cypher™ placement treatment strategies were initiated. We examined the status of antithrombotic therapy at 5 years in determining the association between antithrombotic therapy and events at 10 years,

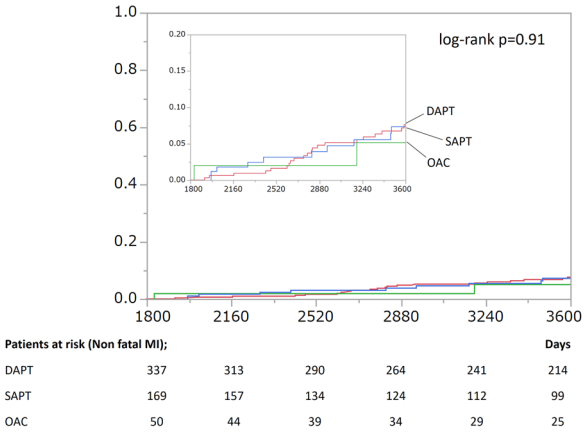


Fig. 6 Kaplan–Meier analysis of the incidence of non-fatal acute myocardial infarction according to antithrombotic groups

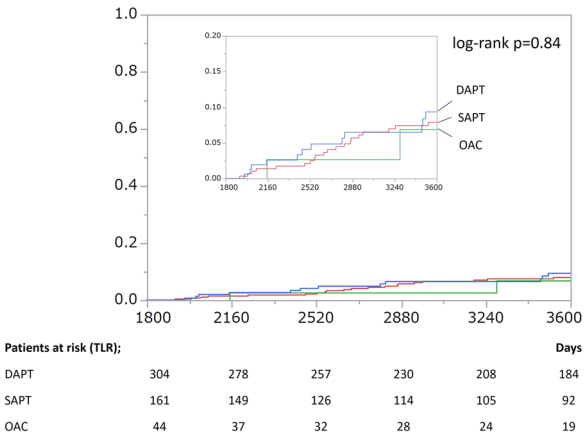


Fig. 7 Kaplan–Meier analysis of the incidence of target lesion revascularization according to antithrombotic groups

based on the fact that 5 years is half of the 10-year observation period and patients who have been on DAPT for 5 years are more likely to remain on DAPT thereafter. This is the first study to assess clinical outcomes based on mid-term antithrombotic therapy.

Clinical Characteristics and ST Incidence

The characteristics of the subjects, their lesions, and the procedures were similar to those reported in large studies conducted in Japan, indicating that the study population closely resembled patients who were treated in daily practice. Furthermore, in other studies investigating the long-term prognosis of Cypher^{TM}, the incidence of ST was 3.7–8.3% [15, 16], which was similar to our results (Fig. 9). Therefore, the results of this study may be applicable in clinical practice.

DAPT vs. SAPT

It is well known that discontinuation of antithrombotic drugs increases the risk of ST in Cypher^{TM} stents [17, 18]. Although there are many studies comparing antithrombotic therapy and cardiac events in the early stage of Cypher^{TM} implantation, there are not many long-term studies. Yano et al. [12] investigated the relationship between antiplatelet drugs and ST up to 5 years after Cypher^{TM} implantation and found that complete discontinuation of antiplatelet drugs increased the risk of ST, but there was no significant difference between DAPT and SAPT. On the other hand, we examined the effect of antithrombotic drugs at 5 years on cardiac events up to 10 years. To our knowledge, this is the longest study to evaluate differences between DAPT and SAPT after Cypher^{TM} implantation. Our research has shown that the incidence of ST was significantly reduced in the DAPT group, and the result was similar after adjusting for confounding factors. Despite the low rate of ST with the DAPT group compared to SAPT, there was a tendency for more bleeding. As antithrombotic therapy was administered based on the opinion of the attending physician, DAPT was likely continued in patients at high risk of ST. The fact that the incidence of ST was lower even though the patients were high risk supports the result that DAPT is more potent than SAPT in reducing ST, even after 5 years of treatment. This may also apply to bleeding events, and therefore, it seems reasonable to select DAPT or SAPT based on risk stratification.

Because antithrombotic medications used at 5 years post-PCI do not necessarily reflect those administered immediately prior to the event, we also examined the occurrence of ST and major bleeding with respect to antithrombotic

Table 3 Antithrombotic therapy and clinical event rate between 5 and 10 years

	Antithrombotic therapy at 5 years			*p*
	SAPT (*n* = 171)	DAPT (*n* = 344)	OAC (*n* = 52)	
Definite/probable ST	4.5%	1.1%	0.0%	0.044
Major bleeding	3.7%	6.0%	18.6%	0.0043
All-cause death	12.8%	10.3%	19.2%	0.29
Cardiac death	4.7%	5.5%	3.1%	0.98
Non-fatal AMI	7.4%	7.6%	3.7%	0.91
TLR	9.4%	7.9%	4.9%	0.84

SAPT single antiplatelet therapy, *DAPT* dual antiplatelet therapy, *OAC* oral anticoagulant therapy, *ST* stent thrombosis, *AMI* acute myocardial infarction, *TLR* target lesion revascularization

Table 4 Antithrombotic therapy and hazard ratio of clinical event

	ST			Major bleeding		
	HR	CI	*p*	HR	CI	*p*
DAPT/SAPT	0.24	0.05–0.89	0.034	1.72	0.69–5.21	0.26
OAC/SAPT	-	0–1.31	0.081	5.31	1.69–17.95	0.0048
OAC/DAPT	-	0–6.58	0.38	3.08	1.20–7.09	0.022

CI confidence interval, *HR* hazard ratio, *ST* stent thrombosis, *SAPT* single antiplatelet therapy, *DAPT* dual antiplatelet therapy, *OAC* oral anticoagulant therapy

Table 5 Antithrombotic therapy and adjusted hazard ratio of clinical event

Adjusted by age						
	ST			Major bleeding		
	HR	CI	*p*	HR	CI	*p*
DAPT/SAPT	0.21	0.04–0.81	0.024	1.85	0.74–5.60	0.20
OAC/SAPT	–	0–1.51	0.10	4.24	1.35–14.38	0.014
OAC/DAPT	–	0–8.77	0.44	2.29	0.88–5.31	0.084

CI confidence interval, *HR* hazard ratio, *ST* = stent thrombosis, *SAPT* single antiplatelet therapy, *DAPT* dual antiplatelet therapy, *OAC* oral anticoagulant therapy

status immediately prior to the event. For ST, two of the three patients originally in the DAPT group had been shifted to other antithrombotic therapy. Given these results, the significance of DAPT for preventing ST does not appear to change, at least not significantly. Although it is expected that the antithrombotic medications of patients who did not have an event would

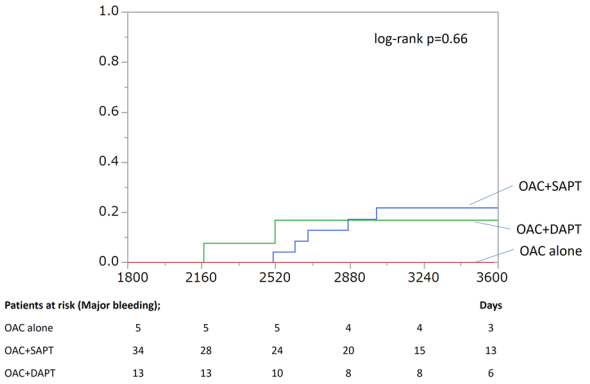


Fig. 8 Kaplan–Meier analysis of the incidence of major bleeding according to anticoagulation subgroups

have been changed between the 5th and 10th years, statistical analysis is difficult to perform because of the paucity of information, as many patients were receiving their medications at other hospitals and the timing of changes in antithrombotic medications varied across patients. This may be a limitation of our retrospective study.

In addition, aspirin was used in most of the patients on SAPT during this period. There is a possibility that SAPT with P2Y12 inhibitor monotherapy may be advantageous over aspirin, and this needs to be investigated further.

Anticoagulant Therapy

Of the patients who received anticoagulants at year 5, none experienced ST between years 5 and 10. In terms of antithrombotic medication administered immediately before the ST event, one patient was on warfarin + SAPT, but the PT-INR of this patient was 1.16, which is inadequate for anticoagulation. It has been reported that anticoagulation in post-acute coronary syndrome patients suppresses subsequent cardiac events, but the benefits do not outweigh the risks because of the increased risk of bleeding [19, 20]. The results of our study are similar, with the advantage of lower ST in patients on anticoagulation being outweighed by the disadvantage of bleeding. In this study, most of the patients on anticoagulation at year 5 were on warfarin. Furthermore, since the majority of patients at 5 years after stenting were receiving antiplatelet therapy before the WOEST trial (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) [2], many patients were using more antiplatelet drug combinations than we currently do. We further analyzed the OAC only, OAC + SAPT, and OAC + DAPT subgroups to examine the breakdown of patients who had bleeding events in the OAC group, but due to the small number of

Table 6 Antithrombotic medications at 5 years and at the time of the clinical event

Stent thrombosis		
Antithrombotic medications at year 5		**At the time of the event**
SAPT 6	⇒	SAPT 6
DAPT 3	⇒	DAPT 1, SAPT 1, OAC + SAPT 1
Major bleeding		
Antithrombotic medications at year 5		**At the time of the event**
SAPT 5	⇒	SAPT 5
DAPT 18	⇒	DAPT 12, SAPT 4, OAC + SAPT 2
OAC + DAPT 2, OAC + SAPT5	⇒	OAC + DAPT 1, OAC + SAPT 4, OAC alone 1, SAPT 1

DAPT dual antiplatelet therapy, *SAPT* single antiplatelet therapy, *OAC* oral anticoagulant therapy

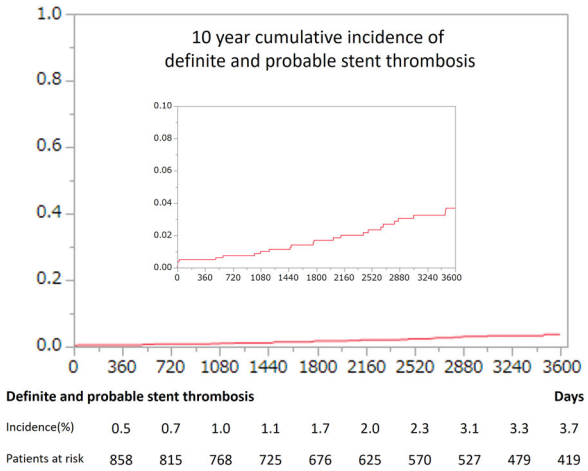


Fig. 9 Ten-year cumulative incidence of definite and probable stent thrombosis

patients who had bleeding events, no statistical differences were evident. The mean PT-INR in patients who had been taking warfarin until immediately before the bleeding event was not particularly high at 2.43 (2.07–3.08). These results indicate that even with a PT-INR relatively close to the therapeutic range, a bleeding event can occur when warfarin is used. By using direct OAC or reducing the dose of antiplatelet agents, bleeding risk could be reduced without increasing the incidence of ST, and this necessitates further study.

Limitations

This single-center, retrospective observational study has several limitations. (A) Some degree of bias was unavoidable because the administration of antithrombotic agents was at the discretion of the attending physician, although there were no significant differences in the characteristics of each group. (B) We used data on antithrombotic agents at year 5 as predictors of clinical outcomes over years 5–10 but did not consider patient status before or after. (C) We did not consider all factors that may affect clinical outcomes, including low-density lipoprotein cholesterol or HbA1c. (D) It is not known if similar trends will be observed with other first-generation DES, since the Cypher™ stent was used in all patients.

Although there are various limitations, it is significant that this study could show that medium-term use of antithrombotic agents affects long-term outcomes.

CONCLUSIONS

There are no clear indications for the use of specific antithrombotic agents with first-generation DES, and in many cases, multiple antithrombotic agents are used due to the fear of ST. The results of this study clearly show the superiority of DAPT over SAPT in preventing ST. However, bleeding events are also common, and the combined risk of ST and bleeding events does not warrant the continued use of DAPT. In the absence of a robust prospective study of the prognostic value of first-generation antithrombotics, it seems reasonable to consider the risk of ST and bleeding when choosing antithrombotic therapy. In addition, incidence of major bleeding in the OAC group was significantly higher than that in other groups. As there are new options for the use of antithrombotic drugs after PCI at present, the optimal antithrombotic therapy for first-generation DES needs to be studied in detail.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339:1665–71. https://doi.org/10.1056/NEJM199812033392303.

2. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381:1107–15. https://doi.org/10.1016/S0140-6736(12)62177-1.

3. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA. 2019;321:2414–27. https://doi.org/10.1001/jama.2019.8145.

4. Waksman R, Barbash IM, Dvir D, et al. Safety and efficacy of the XIENCE V everolimus-eluting stent compared to first-generation drug-eluting stents in contemporary clinical practice. Am J Cardiol. 2012;109:1288–94. https://doi.org/10.1016/j.amjcard.2011.12.019.

5. Niccoli G, Stuteville M, Sudhir K, et al. Incidence, time course and predictors of early vs. late target lesion revascularisation after everolimus-eluting stent implantation: a SPIRIT V substudy. EuroIntervention. 2013;9:353–9. https://doi.org/10.4244/EIJV9I3A57.

6. Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. Circulation. 2016;133:650–60. https://doi.org/10.1161/CIRCULATIONAHA.115.019071.

7. Usui E, Yonetsu T, Kanaji Y, et al. Prevalence of neoatherosclerosis in sirolimus-eluting stents in a very late phase after implantation. EuroIntervention. 2018;14:e1316–23. https://doi.org/10.4244/EIJ-D-18-00486.

8. Torii S, Jinnouchi H, Sakamoto A, et al. Drug-eluting coronary stents: insights from preclinical and pathology studies. Nat Rev Cardiol. 2020;17:37–51. https://doi.org/10.1038/s41569-019-0234-x.

9. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol. 2012;59:2051–7. https://doi.org/10.1016/j.jacc.2011.10.909.

10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344–51. https://doi.org/10.1161/CIRCULATIONAHA.106.685313.

11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736–47. https://doi.org/10.1161/CIRCULATIONAHA.110.009449.

12. Yano M, Natsuaki M, Morimoto T, et al. Antiplatelet therapy discontinuation and stent thrombosis after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Int J Cardiol. 2015;199:296–301. https://doi.org/10.1016/j.ijcard.2015.06.023.

13. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus versus Cypher to Reduce Late Loss After stenting (Excellent) randomized, multicenter study. Circulation. 2012;125:505–13. https://doi.org/10.1161/CIRCULATIONAHA.111.059022.

14. Stefanini GG, Siontis GC, Cao D, Heg D, Jüni P, Windecker S. Short versus long duration of DAPT after des implantation: a meta-analysis. J Am Coll Cardiol. 2014;64:953–4. https://doi.org/10.1016/j.jacc.2014.06.1158.

15. Kufner S, Joner M, Thannheimer A, et al. Ten-year clinical outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease. Circulation. 2019;139:325–33. https://doi.org/10.1161/CIRCULATIONAHA.118.038065.

16. Galløe AM, Kelbæk H, Thuesen L, et al. 10-year clinical outcome after randomization to treatment by sirolimus- or paclitaxel-eluting coronary stents. J Am Coll Cardiol. 2017;69:616–24. https://doi.org/10.1016/j.jacc.2016.11.055.

17. Stabile E, Cheneau E, Kinnaird T, et al. Late thrombosis in Cypher stents after the discontinuation of antiplatelet therapy. Cardiovasc Radiat Med. 2004;5:173–6. https://doi.org/10.1016/j.carrad.2004.11.001.

18. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation. 2004;109:1930–2. https://doi.org/10.1161/01.CIR.0000127105.99982.21.

19. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J. 2006;27:519–26. https://doi.org/10.1093/eurheartj/ehi485.

20. Oldgren J, Wallentin L, Alexander JH, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013;34:1670–80. https://doi.org/10.1093/eurheartj/eht049.