Consideration of Dual Anti-platelet Therapy Duration after Drug-eluting Stent Implantation in a Japanese Population: A Five-year Follow-up after Sirolimus-Eluting Stent Implantation

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Abstract

Objective To investigate the risks and benefits of prolonged dual antiplatelet therapy (DAPT: thienopyridine plus aspirin) following placement of drug-eluting stents (DES). The optimal duration of DAPT is not well established.

Methods We analyzed a prospective registry of 2,050 patients with sirolimus-eluting stents during a 5-year follow-up. We divided 1,691 patients into two groups according to DAPT duration (DAPT ≤12 months (n=749) and DAPT >12 months (n=942)) and compared the clinical outcomes using a landmark analysis.

Results The frequencies of major adverse cardiac events (MACE: 15.6% vs. 18.2%), death (10.0% vs. 11.5%), myocardial infarction (2.3% vs. 2.1%), target lesion revascularization (4.5% vs. 6.3%) and stent thrombosis (0.8% vs. 0.8%) were similar between the two groups. However, the frequency of bleeding was higher in the DAPT >12 months group (1.1% vs. 2.6%, $p=0.030$). The adjusted 12-month landmark analysis showed no differences in the incidence of MACE (hazard ratio (HR) 0.892; 95% confidence interval (CI) 0.689-1.155; $p=0.385$) or a composite of target vessel revascularization, cardiac death and myocardial infarction (target vessel failure: HR 0.922; 95% CI 0.678-1.255; $p=0.606$). There were no differences in the frequency of stent thrombosis between the two groups during years 2 to 5 after stenting; however, with regard to bleeding, an increase in the frequency of hemorrhage events was observed after four years from the index procedures in the DAPT >12 months group.

Conclusion DAPT performed beyond 12 months is associated with increased an frequency of bleeding complications and does not prevent the incidence of MACE, including stent thrombosis, during five years of follow-up after sirolimus-eluting stent implantation. Conducting larger, randomized studies will therefore be needed to confirm this finding.

Key words: follow-up study, stents, hemorrhage

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Introduction

Although the efficacy of drug-eluting stents is widely known, long-term safety concerns remain, especially regarding late stent thrombosis (1-3). Earlier studies have clarified

that early discontinuation of dual antiplatelet therapy (DAPT: clopidogrel/ticlopidine and aspirin) is a risk factor for stent thrombosis in patients with drug-eluting stents (4, 5). However, the optimal duration of DAPT following drug-eluting stent implantation has not yet been well established. Unplanned DAPT continuation may increase the

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Figure 1. Schema of the 12-month landmark analysis. *: There were repetition patients. SES indicates sirolimus eluting stent, MACE: major adverse cardiac death, Non TL-TVR: non target lesion-target vessel revascularization, DAPT: dual antiplatelet therapy

frequency of bleeding without decreasing the incidence of stent thrombosis. Since recent studies have clearly established that hemorrhagic complications from medications may offset the life-prolonging benefits of reduced ischemia, it is therefore important to carefully consider the risk/benefit ratio of prolonged DAPT. To address this issue, we compared differences in the frequencies of death, myocardial infarction (MI), late stent thrombosis and bleeding over five years after stent implantation between patients who received thienopyridine in addition to aspirin for up to one year and those treated for more than one year.

Materials and Methods

Study population

This analysis was conducted using the J-PMS database. J-PMS is a prospective registry for post-marketing 5-year surveillance following index procedures whose creation was mandated by the Japanese government as one of the conditions for regulatory approval. The details of this program have been described previously (6). Briefly, the registry was planned to consecutively enroll a total of 2,053 patients who underwent sirolimus-eluting stent (SES) implantation (there were three delivery failures) between September 2004 and September 2005 at 50 community-based and university hospitals representative of the clinical environment in Japan. The indications for stent implantation were left to the discretion of each cardiologist participating in the registry and thus may have included off-label indications (acute MI, unprotected left main coronary arteries, bifurcation, ostial stenosis, restenotic lesions including in-stent restenosis, bypass grafts, chronic total occlusions, reference diameters less

than 2.5 mm, reference diameters greater than 3.5 mm or lesions greater than 30 mm in length).

Data collection

The patients' baseline characteristics, cardiac histories, risk factors, medications and procedural data were prospectively obtained and recorded by experienced research coordinators. Adjudication was based on the information contained in the case report forms and on the responses to queries addressed to the participating study sites. According to the study design, data were collected continuously for 30 days postprocedure at three, eight and 12 months, then annually from two to five years after the index procedures. The final follow-up ratio of this study was 1,937 out of 2,050 patients (94.5%). Angiographic data for 1,063 of 2,458 lesions obtained at the time of the index procedures were analyzed quantitatively (QCA) by an independent core laboratory (Cardiocre, Tokyo, Japan). The study was approved by the institutional review board at each participating center. The information on DAPT discontinuation was collected via withdrawal reports, surveillance of prescription records or both. Termination of medications for at least 30 days constituted persistent discontinuation.

Group assignments for landmark analysis

A landmark analysis is a form of survival analysis that classifies patients based on some intermediate (non-outcome) event occurring during follow-up. Prognosis is then evaluated from this landmark time point. We defined the landmark time and studied the outcomes in terms of the elapsed time from each patient's index procedure. In this study, the landmark time point was 12 months from the index procedure when thienopyridine was either continued or

Table 1. Patient Characteristics

	DAPT≤12Mo (n=749)	DAPT>12Mo (n=942)	P
Mean age, years	67.0±9.9 (749)	67.2±9.8 (942)	0.643
Age ≥75 years	180 (24.0)	224 (23.8)	0.909
Male	565 (75.4)	716 (76.0)	0.819
LVEF<30% *	19 (2.9)	27 (3.5)	0.653
BMI, kg/m ²	24.0±3.2 (745)	24.1±3.3 (940)	0.299
Type of disease			
Stable ischemia	488 (65.2)	636 (67.5)	0.325
AMI/UAP	145 (19.4)	153 (16.2)	0.095
Previous MI	269 (35.9)	364 (38.6)	0.266
Previous PCI	376 (50.2)	550 (58.4)	<0.001 †
Previous CABG	44 (5.9)	86 (9.1)	0.013 †
Diabetes	306 (40.9)	407 (43.2)	0.346
Treated with insulin	65 (8.7)	94 (10.0)	0.402
Dialysis	17 (2.3)	49 (5.2)	0.002 †
Hypertension	504 (67.3)	674 (71.6)	0.062
Dyslipidemia	446 (59.6)	540 (57.3)	0.372
Peripheral vascular disease	38 (5.1)	69 (7.3)	0.070
Cerebrovascular disease	51 (6.8)	73 (7.8)	0.511
Family history of CAD	56 (7.5)	63 (6.7)	0.566
Current smoker	142 (19.0)	181 (19.2)	0.901
Multi-vessel disease	268 (35.8)	412 (43.7)	0.001 †

DAPT indicates dual antiplatelet therapy, LVEF: left ventricular ejection fraction, BMI: body mass index, AMI: acute myocardial infarction, UAP: unstable angina pectoris, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease

Values are expressed as mean±SD (n) or n (%). The Wilcoxon rank sum test, Chi-square test or Fisher's exact test were used as appropriate.

†: p<0.05 were considered to indicate statistical significance.

*: Excluding unevaluated 263 patients (102 in the DAPT≤12m group and 161 in the DAPT>12m group).

discontinued. Patients who remained event-free (no death, MI or revascularization) at 12 months and completed their first year of follow-up data collection, including questions regarding DAPT, were divided into two groups: thienopyridine discontinuation at or before 12 months and thienopyridine continuation (DAPT) beyond one year (Figure 1). The outcomes for these groups were evaluated up to five years (60 months) after initial percutaneous coronary intervention (PCI). There were 874 lesions in 749 patients who discontinued thienopyridine at 12 months or less (DAPT ≤12 months) and 1,131 lesions in 942 patients who continued DAPT beyond 12 months (DAPT >12 months).

Definition of events

An independent safety and efficacy evaluation committee adjudicated all reported and suspected major adverse cardiac events (MACE) defined as: all-cause death, MI or target lesion revascularization (TLR) by PCI or coronary artery bypass graft surgery (CABG); stent thromboses; and target vessel revascularization (TVR) by PCI or CABG. Deaths were classified as cardiac or noncardiac based on SIRIUS trial protocol definitions; unidentified deaths, i.e., any death in which a cardiac cause could not be excluded, were classified as cardiac in this study. MI was classified as Q wave or non-Q wave according to electrocardiogram (ECG) changes

and/or a rise in creatine kinase enzyme concentrations above twice the normal upper limit. If information for classifying the type of MI was not available, the MI was classified as unidentified. TLR was defined based on the SIRIUS trial protocol definition; all reported re-interventions inside an implanted stent or within 5 mm proximal or distal to a stent were classified as TLR. Repeated PCI in the same vessel but not TLR was recorded as non-target lesion revascularization (non-TL TVR). Target vessel failure (TVF) was defined as the combination of cardiac death, MI and TVR; therefore, this was considered a target vessel-related adverse event. Stent thrombosis was defined according to the Academic Research Consortium (ARC) definition, and both definite and probable cases were classified as stent thrombosis in this study. Because the current study was designed as a landmark analysis at 365 days, stent thrombosis indicated very late stent thrombosis (VLST) (7). Bleeding was defined according to the BARC (Bleeding Academic Research Consortium) definition, and Types 2, 3 and 5 were including in this study (8).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and categorical data are presented as frequencies. For comparisons between groups, the Pearson's Chi-

Table 2. Lesion Characteristics and QCA Analysis

	DAPT≤12Mo	DAPT>12Mo	p
Lesion Characteristics			
N of lesions / stents	874 / 1,148	1,131 / 1,507	-
Target vessel			
RCA	246 (28.2)	363 (32.1)	0.063
LAD	400 (45.8)	482 (42.6)	0.160
LCX	200 (22.9)	238 (21.0)	0.327
LMT	28 (3.2)	48 (4.2)	0.240
ACC/AHA type B2/C *	692 (79.5)	911 (81.0)	0.427
De novo	714 (81.7)	893 (79.0)	0.142
In-stent restenosis	103 (11.8)	170 (15.0)	0.036 †
Concentric ‡	367 (43.1)	502 (45.8)	0.251
Moderate/severe calcification	126 (14.4)	202 (17.9)	0.044 †
Bifurcation	285 (32.6)	370 (32.7)	0.960
Ostial location	128 (14.7)	199 (17.6)	0.078
Total occlusion	91 (10.4)	129 (11.4)	0.517
QCA data			
Lesion length, mm	17.5±10.0 (829)	17.2±10.2 (1,059)	0.411
Ref. diameter, mm	2.56±0.56 (842)	2.58±0.61 (1,084)	0.501
MLD	Pre, mm	0.75±0.49 (870)	0.829
	Post, mm	2.28±0.64 (873)	0.318
%DS	Pre, %	71.2±17.3 (870)	0.926
	Post, %	18.4±13.6 (873)	0.252
Procedural data			
Direct stenting	185 (21.2)	262 (23.2)	0.304
Rotablator usage	26 (3.0)	48 (4.2)	0.152
IVUS usage	569 (76.0)	675 (71.7)	0.052
Maximum pressure, atm	16.0±3.3 (1,148)	15.9±3.7 (1,506)	0.340
Stent diameter, mm	3.02±0.36 (1,148)	2.98±0.36 (1,507)	0.006 †
Total stent length, mm	27.8±13.3 (874)	28.9±14.9 (1,131)	0.139
N of stents per patient	1.52±0.75 (749)	1.59±0.82 (942)	0.188
N of stents per lesion	1.31±0.56 (874)	1.33±0.60 (1,131)	0.681
Post dilatation	400 (45.8)	532 (47.0)	0.588

DAPT indicates dual antiplatelet therapy, RCA: right coronary artery, LAD: left anterior descending, LCX: left circumflex, LMT: left main trunk, ACC/AHA: American College of Cardiology /American Heart Association, QCA: quantitative coronary angiography, MLD: minimal luminal diameter, %DS: percent diameter stenosis, IVUS: intravascular ultrasound

Values are expressed as mean±SD (n) or n (%).The Wilcoxon rank sum test, Chi-square test or Fisher's exact test were used as appropriate.

†: p<0.05 was considered to indicate statistical significance.

*: Excluding unevaluated 10 lesions (4 in the DAPT≤12m group and 6 in the DAPT>12m group).

‡: Excluding unevaluated 57 lesions (23 in the DAPT≤12m group and 34 in the DAPT>12m group).

square test, Fisher's Chi-exact test or the Wilcoxon rank-sum test were used as appropriate. Time-to-event data are presented using Kaplan-Meier estimates. Each event rate during the follow-up period was analyzed using the Kaplan-Meier method. A log-rank test was used for survival rate comparisons. The hazard ratios (HR) with 95 percent confidence intervals (95% CI) were estimated from a Cox proportional hazards model. McNemar's test was used to determine whether there was a statistically significant difference between stent thrombosis and bleeding. Propensity score adjusting was used in the logistic regression models, with DAPT continuation at 12 months used as the dependent variable along with 27 independent variables (listed in the Supplemental tables). Patients with missing values for any

given variable were excluded from the multivariable analysis. The goodness-of-fit of the propensity scores were assessed with the C statistic (C=0.605) and Hosmer-Lemeshow tests (p=0.609). We calculated the adjusted hazard curves of the groups used in the landmark analysis using a Cox proportional hazards model in conjunction with previously described methods (9), adjusting for the propensity scores as a covariance. To additionally assess the adequacy of the propensity score adjustment, a sensitivity analysis using 1-to-many matching based on the propensity score of the final model was also performed and showed results similar to the primary analysis (data not shown). P values were two-sided, with p<0.05 considered statistically significant. The statistical analyses were performed with SAS software,

Figure 2. Crude and propensity score adjusting clinical results at 5-year. MACE indicates major adverse cardiac event, MI: myocardial infarction, CABG: coronary artery bypass graft, TLR: target lesion revascularization, TVR: target vessel revascularization

Figure 3. Adjusted cumulative incidences of major adverse cardiac event (MACE), death, myocardial infarction (MI) and target vessel failure (TVF) using the 12-months landmark analysis.

Figure 4. DAPT duration and incidence of risk (bleeding) and benefit (MACE, death, MI, stent thrombosis). DAPT indicate dual anti-platelet therapy, MACE: major adverse cardiac event, MI: myocardial infarction

Table 3. Incidence of Very Late Stent Thrombosis (VLST) and Bleeding Events

	DAPT≤12Mo (n=749)	DAPT>12Mo (n=942)	p
VLST (Definite + probable)	6 (0.80)	8 (0.85)	0.913
Definite	5 (0.67)	6 (0.64)	0.938
Probable	1 (0.13)	2 (0.21)	0.698
Bleeding	8 (1.07)	24 (2.55)	0.030 †

VLST indicates very late stent thrombosis.

Values are expressed as n (%). The Chi-square test or Fisher's exact test was used as appropriate.

†: p<0.05 was considered to indicate statistical significance.

version 9.1 (SAS Institute Inc., Cary, NC).

Results

Patient and lesion characteristics

The patient characteristics are summarized in Table 1. There were no differences in patient characteristics, except that the DAPT >12 months group had significantly higher frequencies of past coronary revascularization, multi-vessel disease and current treatment with hemodialysis. Regarding procedural and QCA-related parameters, the rates of in-stent restenosis, the presence of moderate/severe calcification and the stent diameters were different between the two groups (p=0.036, p=0.044 and p=0.012), while other parameters were similar (Table 2). The frequency of “off-label” use in patients in the DAPT ≤12 months and DAPT >12 months

groups was also similar (632/749 patients, 84.4%; and 808/942 patients, 85.8%; p=0.449).

Compliance with thienopyridine treatment

Compliance with thienopyridine treatment in the DAPT >12 months group was obviously 100% at the 1-year follow-up. However, a steady decrease in compliance was observed thereafter, down to 84.6% at two years, 77.2% at three years, 70.0% at four years and 65.8% at five years.

Long-term clinical outcomes and DAPT duration

Fig. 2 shows the impact of thienopyridine administration in addition to aspirin beyond one year postprocedure on clinical outcomes. There were no clinical benefits of DAPT lasting more than 12 months. Rather, there was a marked increase in the frequency of bleeding complications associated with prolonged DAPT administration beyond one year; the crude data were 1.07% for the DAPT ≤12 month group and 2.55% for the DAPT >12 month group (p=0.03), and the adjusted data also showed marked differences between the two groups (HR 0.413, 95% CI 0.185-0.918, p=0.030).

Landmark analysis based on DAPT at one year

There were no differences in the cumulative incidences of MACE, death, MI and TVF from years 2 to 5 between the two groups (Figure 3). Similar results were observed for VLST up to year 5 in both groups; however, during the observation period, the cumulative incidence of bleeding events increased in the group receiving DAPT for more than 12 months (Figure 4).

Details of VLST and bleeding

A total of 14 patients (0.83%) presented with definite/probable stent thrombosis and 32 patients (1.89%) experienced bleeding events between years 2 and 5 (Table 3). Three patients who suffered VLST (21.4%) and 11 patients who suffered bleeding (34.3%) died within one day of the events. Two definite cases of VLST were observed after both antiplatelet medications were discontinued. In the DAPT >12 months group, five of eight cases of VLST (62.5%) occurred under complete DAPT treatment. Regarding bleeding events, 12 patients experienced cerebral hemorrhage, 16 patients experienced gastrointestinal bleeding and four patients experienced hemorrhage from other sources (the lungs, mediastinum, intra-ocular areas or urinary tract). Mortality due to bleeding was 0.40% (3/749) in the DAPT ≤ 12 months group and 0.85% (8/942) in the DAPT >12 months group. The frequencies of both VLST and bleeding increased annually. The yearly slopes of the linear portions of the cumulative incidence curves between years 2 to 5 were 0.18% and 0.20% for VLST and 0.27% and 0.72% for bleeding, respectively.

Discussion

The results observed during our long-term observation period with a high follow-up rate (95%) suggest that DAPT administration prolonged beyond one year increases the risk of bleeding without increasing benefits such as prevention of MACE or reduction of the frequency of VLST. Previous studies that addressed this issue did not conduct adequate assessments in terms of the observation periods or details of bleeding. The benefits of prolonged DAPT were thought to include the prevention of VLST, a specific phenomenon related to drug-eluting stents. However, only a study that compares two cohorts under long-term observation can sufficiently address this issue. Our current study shows that bleeding is also associated with prolonged DAPT administration.

Current ACC/AHA/SCAI recommendations call for one year of thienopyridine use to attenuate the risk of stent thrombosis after coronary artery drug-eluting stent implantation in patients not at high risk for bleeding (10). However, chronic thienopyridine use is costly and associated with an approximate 1% annual risk of major bleeding (11). Interestingly, a previous study showed that the predictors of bleeding are similar to those of stent thrombosis, including low ejection fraction, acute MI at presentation and multi-vessel PCI (12). Therefore, it is very important to explore the risk/benefit ratio of DAPT duration. The results of previous large scale registries suggest that prolonged DAPT administration reduces the frequency of death and MI following DES implantation. This observation is consistent with recent reports from the Duke database (9) and findings in a diabetic population (13) where clopidogrel was discontinued at either six or 12 months. These results have led to uncertainty about

the minimal necessary duration of DAPT after implantation of drug-eluting stents. Regarding the Duke database (9), the study design and analysis methods used in that database are similar to those used in the current study. However, the results of the Duke database suggest that extended use of clopidogrel in patients with DES may be associated with a reduced risk of death or MI.

On the other hand, several observational and randomized studies of patients with drug-eluting stents have shown that continuation of clopidogrel therapy beyond six or 12 months does not reduce the risks of stent thrombosis or late clinical events, suggesting that DAPT can be discontinued approximately six to 12 months after performing index procedures (14-21). Two Korean randomized studies also previously reported lack of benefits of either 12 or 24 months of clopidogrel therapy over six or 12 months of clopidogrel therapy, respectively. These discrepancies may be explained by the following differences between the studies. The first difference is that the Duke database involved paclitaxel-eluting stents (PES), while our database analyzed only SES. Regarding DES, there are several comparable studies showing SES to be superior to PES in terms of significant reductions in the risks of re-intervention (22) and stent thrombosis (23). The risk of death is not significantly different between the two types of DES; however, there is a trend toward a higher risk of MI with PES, especially after the first year following the procedure (14). The second difference is that the Duke database included a shorter follow-up period and lacked any assessment of hemorrhage. Our main finding is that an imbalance between the risks and benefits of DAPT are observed beyond 12 months. As shown in the figures, marked differences appeared starting at three years.

Regarding the follow-up period, the median follow-up terms used in the two Korean randomized studies were only 19.2 months (19) and 12 months (20), which might not have been sufficient to illustrate any trends of increasing risk. The reports that focused on both efficacy and the incidence of bleeding complications revealed that longer DAPT administration is not significantly more effective than 6-month DAPT administration in reducing all cause death, MI or cerebral accidents. Another study also demonstrated a greater risk of hemorrhage associated with 24 months of clopidogrel therapy in addition to aspirin (21). Stone et al. examined the effects of prolonged thienopyridine administration using data from the prospective, double-blind, randomized trials of the TAXUS series (24) and concluded that thienopyridine use beyond one year after drug-eluting stent implantation may reduce stent thrombosis over the subsequent 12-month period, although the rates of death and MI at two and five years are not reduced by extended thienopyridine use after either drug-eluting or bare-metal stenting. Further evaluation of the efficacy versus safety of extended DAPT duration (12 vs. 30 months) is being conducted by the DAPT (Dual AntiPlatelet Therapy) study (25). The optimal duration of DAPT after DES should be decided after taking into full consideration the risks and benefits assessed

in that study.

The mechanisms underlying VLST have been investigated using invasive imaging and from a pathology-based approach (26-30). Previous studies suggest that delayed healing and local inflammation, including hypersensitivity or early atherosclerotic changes, may be responsible for the development of VLST, and some studies suspect a correlation between morphological changes and clinical thrombosis (28-30). A direct correlation between these chronic responses and late stent thrombosis can be easily assumed.

However, this and other studies have not shown the fact that prolonged continuation of DAPT markedly reduces the risk of clinical thrombosis (19, 21, 31).

Limitations

This report is retrospective. The constraints of this study, inherent to any registry, include the lack of randomization, the absence of a control group and a lower level of monitoring than that used in standard randomized clinical trials, especially regarding the details of bleeding events. A serial comparison of laboratory values, *e.g.*, hematocrit and hemoglobin, was not performed, which might have led to an underestimation of the frequency of bleeding complications. Even with adjustment, a landmark analysis is observational in nature and still subject to residual confounding (32). Despite any major differences in the groups at baseline, there may be a number of factors that led to the continuation or discontinuation of DAPT at 12 months. A proportion of the patients who discontinued DAPT after 12 months may have developed other problems prompting the discontinuation of clopidogrel therapy. These factors are in many ways impossible to control in a non-randomized study. A sample size of approximately 2,000 subjects is not sufficient to detect small but clinically meaningful differences in stent thrombosis rates; this would require 8,000-10,000 subjects. Additionally, there was no discrimination between ticlopidine and clopidogrel since the registry was started before clopidogrel was approved in Japan. The DAPT continuation group included patients who switched from ticlopidine to clopidogrel. However, previous studies have established that there are no differences in clinical efficacy between these two drugs (6). In addition, the duration of DAPT depended on each participating institution's practices. Finally, this analysis did not assess the efficacy of the systemic anti-atherosclerotic effects of clopidogrel.

Conclusion

Dual antiplatelet therapy, with the addition of thienopyridine to aspirin, extended beyond a period of 12 months, was thus found to increase the incidence of bleeding complications while not exhibiting any marked preventive effects on cardiovascular events, including stent thrombosis, during a five-year follow-up after sirolimus-eluting stent implantation.

The authors state that they have no Conflict of Interest (COI).

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