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Focus on Antiplatelet Therapy

6-Month Versus 12-Month Dual-Antiplatelet Therapy Following Long Everolimus-Eluting Stent Implantation

The IVUS-XPL Randomized Clinical Trial

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ABSTRACT

OBJECTIVES The aim of this study was to investigate whether a 6-month dual-antiplatelet therapy (DAPT) duration was comparable with a 12-month duration in patients who underwent everolimus-eluting stent implantation.

BACKGROUND Well-designed studies that determine optimal DAPT strategies after everolimus-eluting stent implantation are limited.

METHODS A total of 1,400 patients (implanted mean total stent length >45 mm) were randomly assigned to receive 6-month (n = 699) or 12-month (n = 701) DAPT between October 2010 and July 2014 at 20 centers in Korea. The primary endpoint was the composite of cardiac death, myocardial infarction, stroke, or TIMI (Thrombolysis in Myocardial Infarction) major bleeding at 1 year, analyzed using an intention-to-treat approach.

RESULTS The primary endpoint occurred in 15 patients (2.2%) in the 6-month DAPT group and 14 patients (2.1%) in the 12-month DAPT group (hazard ratio [HR]: 1.07; p = 0.854). Definite or probable stent thrombosis occurred in 2 patients (0.3%) in the 6-month DAPT group and in 2 patients (0.3%) in the 12-month DAPT group (HR: 1.00; p = 0.999). There were no significant between-group differences in the primary endpoint in 686 patients with acute coronary syndrome (2.4% in both groups; HR: 1.00; p = 0.994) and in 506 patients with diabetes mellitus (2.2% [6-month] vs. 3.3% [12-month]; HR: 0.64; p = 0.428).

CONCLUSIONS Compared with 12-month DAPT, 6-month DAPT did not increase the composite events of cardiac death, myocardial infarction, stroke, or TIMI major bleeding at 1 year in patients who underwent everolimus-eluting stent implantation. (Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions [IVUS-XPL Study]; NCT01308281) (J Am Coll Cardiol Intv 2016;9:1438–46) © 2016 by the American College of Cardiology Foundation.

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To prevent stent thrombosis after drug-eluting stent (DES) implantation, the American College of Cardiology and American Heart Association guidelines recommend that dual-antiplatelet therapy (DAPT) be administered for ≥12 months after DES implantation (1). Previous randomized clinical trial results suggested that after new-generation DES implantation, the clinical outcomes of 3 to 6 months of DAPT were comparable with those of ≥12 months of therapy (2–8). Meta-analysis results also indicated that the use of new-generation DES decreased the risk for death, myocardial infarction, and stent thrombosis compared with bare-metal stents and first-generation DES (9–12). The European Society of Cardiology guidelines permit 6-month DAPT for new-generation DES-treated patients for stable coronary disease treatment (13). However, a recent randomized

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study with a larger number of patients revealed that compared with aspirin therapy alone, DAPT beyond 1 year after DES implantation significantly reduced the risks for stent thrombosis and major adverse cardiovascular events but was associated with an increased risk for bleeding (14). These findings suggest that even in the era of new-generation DES, optimal DAPT strategies are not clearly established. The everolimus-eluting stent (XIENCE, Abbott Vascular, Santa Clara, California) is the representative new-generation DES and is currently positioned as the benchmark stent for the development of improved new-generation DES (15,16). However, well-designed studies that determine optimal DAPT strategies after everolimus-eluting stent implantation are limited (3).

A Swedish registry analysis indicated the evolution of percutaneous coronary intervention; implanted total stent length per patient has increased over the past 20 years in daily clinical practice (17). Long stent implantation for diffuse long lesions has a high risk for stent thrombosis, myocardial infarction, and target lesion failure, even with the use of new-generation DES (18–21). Stent thrombosis that occurs after clopidogrel is discontinued at 6 months has been of particular concern, especially for patients who undergo long-length everolimus-eluting stent implantation. In this study, we investigated whether a 6-month DAPT duration was comparable with a 12-month duration in patients who underwent long-length everolimus-eluting stent implantation.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

METHODS

STUDY DESIGN AND POPULATION. The IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions) trial, conducted at 20 centers in Korea, was an investigator-initiated, prospective, randomized study of patients who underwent everolimus-eluting stent (XIENCE PRIME) implantation for long coronary lesions. The details of this study have been previously described (22). Patients with typical chest pain or evidence of myocardial ischemia were eligible for enrollment if the implantation of an everolimus-eluting stent for long coronary lesions (implanted stent length ≥28 mm) was indicated by angiographic results. The Institutional Review Board or ethics committee at each participating center approved the study protocol. Each participant provided written informed consent. Study coordination, data management, and site management services were performed at the Cardiovascular Research Center in Seoul, South Korea. The designated trial monitors reviewed the investigational data for accuracy and completeness at appropriate intervals and ensured protocol compliance. Study safety was monitored by a data and safety monitoring board of independent physicians with access to the unblinded data. The funder of this study had no role in study design, collection, analysis and interpretation of data, or writing of this report.

RANDOMIZATION AND STUDY PROCEDURES. Study participants were randomly assigned to treatments using a 2 × 2 factorial design. The factors were DAPT duration (6-month vs. 12-month arms) and intravascular ultrasound use (intravascular ultrasound guidance arm vs. angiographic guidance arm). An interactive Web-based response system was used to randomize participants 1:1 into groups to receive either 6- or 12-month DAPT immediately after preintervention angiography; a block size of 4 was used for the 2 study groups. Concealed randomization was stratified on the basis of enrollment sites, multivessel coronary intervention, and diabetes mellitus (22).

Everolimus-eluting stent implantation was performed using standard techniques and intravascular

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ultrasound or angiographic guidance. Aspirin (100 mg/day) was prescribed for an indefinite period after stent implantation. Clopidogrel (75 mg/day) was administered for at least 6 months. It was discontinued at 6 months for the 6-month DAPT group and maintained up to 12 months for the 12-month DAPT group, as randomized.

STUDY ENDPOINTS AND FOLLOW-UP. The primary endpoint was a composite of cardiac death, myocardial infarction, stroke, or TIMI (Thrombolysis in Myocardial Infarction) major bleeding at 1 year. Clinical events were defined using Academic Research Consortium criteria (22,23). All deaths were considered cardiac deaths unless a definite noncardiac cause could be established. During the 1-year follow-up period after hospital discharge, myocardial infarction was defined as the presence of consistent clinical symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatine kinase myocardial band fraction increase greater than the upper normal limit or an increase in troponin T or troponin I to >99th percentile of the upper normal limit (22–24). Clinically relevant periprocedural myocardial infarction after percutaneous coronary intervention was defined as a peak creatine kinase myocardial band fraction ≥10 times the upper limit measured within 48 h of the procedure or ≥5 times the upper normal limit, with new pathological Q waves in ≥2 contiguous leads, or new persistent left bundle branch block according to the expert consensus document from the Society for Cardiovascular Angiography and Interventions (25). Definite, probable, and possible stent thrombosis was defined using Academic Research Consortium recommendations (23). Stroke, as detected by the occurrence of a new neurological deficit, was confirmed using a neurological examination and imaging studies. The TIMI classification was used to define major bleeding (i.e., intracranial hemorrhage, 5 g/dl decrease in hemoglobin concentration, or 15% absolute decrease in hematocrit) (26). Ischemia-driven repeat revascularization was defined as repeat percutaneous coronary intervention or bypass surgery of the everolimus-eluting stent-implanted lesions with either ischemic symptoms (or positive stress test results) and angiographic diameter stenosis ≥50% detected using quantitative coronary angiographic analysis, or angiographic diameter stenosis ≥70% detected using quantitative coronary angiographic analysis, without ischemic symptoms or positive stress test results (22).

Post-procedural clinical assessments included cardiac symptom evaluation and medication compliance. They were performed in the hospital and at 1-, 3-, 6-, and 12-month physician office visits. A clinical data management center specialist (Cardiovascular Research Center) collected and entered follow-up data into a computer database (22). A blinded independent clinical events committee adjudicated all non-procedural components of adverse clinical events.

STATISTICAL ANALYSIS. Sample size calculation was performed primarily on the basis of testing the superiority of intravascular ultrasound guidance versus angiographic guidance. The secondary objective was to compare the 6- versus 12-month clinical outcomes of the DAPT groups. The analysis in this study was performed using intention-to-treat analysis (i.e., whether 6-month DAPT was comparable with 12-month DAPT with respect to the first primary endpoint occurrence). Cumulative incidence estimates of each endpoint at 1 year were calculated using the Kaplan-Meier method and compared using the log-rank test. Stratified Cox regression and stratified log-rank test were also performed to adjust for the clustering of patients by participating centers as a random effect using a gamma frailty fit. Patients who were lost to follow-up (n = 70 [5.0%]) or withdrew consent (n = 7 [0.5%]) were assessed at the last known event-free time. Patients could experience more than 1 adverse clinical event component, but each patient was assessed only once for the analysis (i.e., during the time until the first event occurrence) (22).

Categorical variables are described as numbers and percentages and were compared using chi-square or Fisher exact tests. Continuous variables are described as mean ± SD or median (interquartile range) and were compared using Student *t* tests or Mann-Whitney *U* tests. The standardized difference was calculated as the difference in means or proportions divided by the SE. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2 sided, and p values <0.05 were considered to indicate statistically significant results.

RESULTS

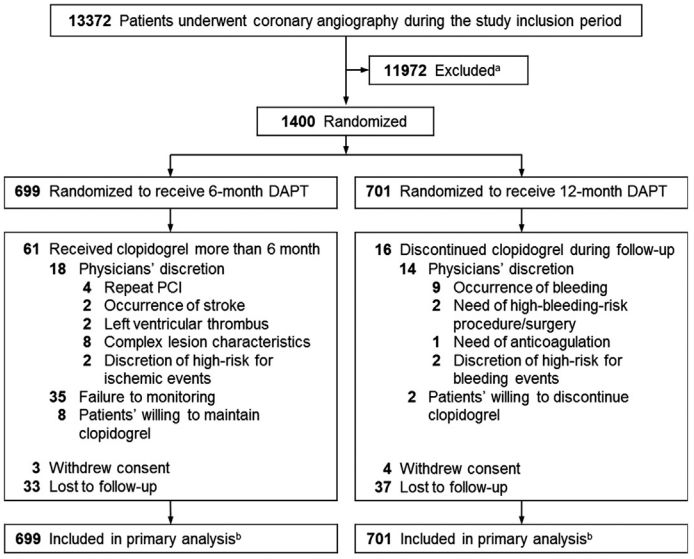
Between October 2010 and July 2014, 1,400 patients were randomly assigned to receive either 6-month (699 patients) or 12-month (701 patients) DAPT. Patient assignment and follow-up numbers are presented in **Figure 1**. Seventy-seven patients withdrew consent or were lost to follow-up. Aspirin and clopidogrel adherence rates at 6 months were 98.9% and 98.9%, respectively, for the 6-month DAPT groups; they were 99.5% and 99.5%, respectively, for the 12-month groups. At 12 months, the rates of aspirin and clopidogrel use were 99.2% and 9.3%, respectively, in the 6-month group and 98.8% and 98.2%,

respectively, in the 12-month group. Baseline clinical, angiographic, and procedural characteristics results were well balanced in both groups (Tables 1 and 2). The mean patient age was 64 ± 9 years; 69% were men. The mean values for implanted stent number per patient, stent length of target long lesions, and total stent length per patient were 1.6 ± 0.8, 39.3 ± 12.7, and 47.3 ± 20.0 mm, respectively; between-group differences were not statistically significant. Periprocedural myocardial infarction was not significantly different between the groups: 12 patients (1.2%) in the 6-month group and 8 patients (0.8%) in the 12-month group (p = 0.378).

The results for 1-year clinical outcomes are presented in Table 3. The primary endpoint of the composite of cardiac death, myocardial infarction, stroke, or TIMI major bleeding occurred in 15 patients (2.2%) in the 6-month and in 14 patients (2.1%) in the 12-month group (hazard ratio [HR]: 1.07; 95% confidence interval [CI]: 0.52 to 2.22; p = 0.854) (Figure 2A). There were no significant between-group differences in the rate for each clinical event, including cardiac death, myocardial infarction, repeat revascularization of stented lesions, stroke, and TIMI major bleeding (Table 3). Also, there were no significant between-group differences in the primary endpoint after adjustment for participating centers (HR: 1.01; 95 CI: 0.88 to 1.12; p = 0.896). There were no significant between-group differences in the primary endpoint in 686 patients with acute coronary syndrome (2.4% [6-month] vs. 2.4% [12-month]; HR: 1.00; 95% CI: 0.37 to 2.66; p = 0.994) and in 506 patients with diabetes mellitus (2.2% [6-month] vs. 3.3% [12-month]; HR: 0.64; 95% CI: 0.21 to 1.95; p = 0.428). Definite or probable stent thrombosis occurred in 2 patients (0.3%) in the 6-month group and in 2 patients (0.3%) in the 12-month group (HR: 1.00; 95% CI: 0.14 to 7.11; p = 0.999). Acute or subacute stent thrombosis occurred in 3 patients with DAPT. Late stent thrombosis occurred at 9 months after everolimus-eluting stent implantation in 1 patient (6-month group) who received aspirin alone after 6 months follow-up.

Six-month landmark primary endpoint analysis results are presented in Figure 2B. There were no significant between-group differences for the primary endpoint after 6 months (HR: 2.00; 95% CI: 0.50 to 7.98; p = 0.319). Post hoc subgroup analyses revealed that there were no statistically significant interactions among subgroups except for the use of intravascular ultrasound (Figure 3). A significant interaction was observed for the use of intravascular ultrasound and the duration of DAPT, suggesting that prolonged DAPT tended to have better clinical outcomes not in patients with intravascular ultrasound

FIGURE 1 Flowchart



[a]Specific reasons for ineligibility were not recorded. [b]All patients were included in the primary time-to-event analysis for their follow-up duration, including patients who withdrew consent or were lost to follow-up. DAPT = dual-antiplatelet therapy; PCI = percutaneous coronary intervention.

TABLE 1 Baseline Clinical Characteristics

	6-Month DAPT (n = 699)	12-Month DAPT (n = 701)	Standardized Difference
Age, yrs	63 ± 9	64 ± 9	−0.06
Male	470 (67)	494 (70)	−0.07
Body mass index, kg/m^2	24.8 ± 3.1	24.6 ± 3.0	0.09
Hypertension	443 (63)	455 (65)	−0.03
Diabetes mellitus	249 (36)	257 (37)	−0.02
Insulin-requiring diabetes	22 (3)	23 (3)	−0.01
Dyslipidemia	473 (68)	456 (65)	0.06
Current smoker	171 (25)	165 (24)	0.02
Prior myocardial infarction	34 (5)	29 (4)	0.04
Prior percutaneous coronary intervention	72 (10)	73 (10)	<−0.01
Prior coronary artery bypass graft	22 (3)	14 (2)	0.07
Left ventricular ejection fraction, %	62.3 ± 10.2	63.1 ± 9.7	−0.08
Clinical presentation			−0.01
Stable angina	356 (51)	358 (51)	
Unstable angina	237 (34)	231 (33)	
Acute myocardial infarction	106 (15)	112 (16)	
Medications at discharge			
Statins	673 (96)	666 (95)	0.06
Beta-blockers	484 (69)	496 (71)	−0.03
ACE inhibitors	194 (28)	185 (26)	0.03
Angiotensin II receptor blockers	242 (35)	240 (34)	0.01
Calcium-channel blockers	235 (34)	236 (34)	<−0.01

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; DAPT = dual-antiplatelet therapy.

TABLE 2 Angiographic and Procedural Characteristics for Target Lesions and All Treated Lesions

	6-Month DAPT (n = 699)	12-Month DAPT (n = 701)	Standardized Difference
Number of diseased vessels			−0.05
1	229 (33)	211 (30)	
2	252 (36)	264 (38)	
3	218 (31)	226 (32)	
Treated lesions per patient	1.4 ± 0.6	1.4 ± 0.6	−0.01
Stents per patients	1.6 ± 0.7	1.6 ± 0.8	−0.07
Total stent length per patient, mm	46.5 ± 19.7	48.2 ± 20.2	−0.09
Stent length of target long lesion, mm	38.6 ± 12.5	39.8 ± 13.0	−0.09
Use of intravascular ultrasound	355 (51)	353 (50)	0.01
Number of all treated lesions	944	950	
Coronary arteries			<0.01
Left anterior descending coronary artery	518 (55)	530 (56)	
Left circumflex coronary artery	187 (20)	175 (18)	
Right coronary artery	239 (25)	245 (26)	
Baseline quantitative coronary angiographic data			
Reference vessel diameter, mm	2.87 ± 0.47	2.88 ± 0.47	−0.02
Minimal luminal diameter, mm	0.84 ± 0.44	0.84 ± 0.43	<0.01
Diameter stenosis, %	70.76 ± 14.50	70.95 ± 13.98	−0.01
Lesion length, mm	31.7 ± 11.7	32.4 ± 11.9	−0.06
Adjunct post-dilation	614 (65)	619 (65)	<−0.01
Final balloon size, mm	3.10 ± 0.48	3.09 ± 0.43	0.02
Maximal inflation pressure, atm	16.11 ± 4.01	16.08 ± 4.18	0.01
Post-intervention quantitative coronary angiographic data			
Total stented length per lesion, mm	34.4 ± 13.5	35.6 ± 14.0	−0.09
Reference vessel diameter, mm	3.00 ± 0.46	3.01 ± 0.45	−0.02
Minimal luminal diameter, mm	2.61 ± 0.44	2.61 ± 0.43	<0.01
Diameter stenosis, %	12.71 ± 8.19	13.19 ± 8.87	−0.06

Values are n (%) or mean ± SD.
Abbreviation as in Table 1.

guidance but in those with angiographic guidance. This finding suggests that intravascular ultrasound guidance with stent optimization might have more favorable outcomes in patients with shorter duration of DAPT, possibly through fewer bleeding episodes and similar ischemic events (Online Table 1). Similarly, a borderline interaction was observed for age and the duration of DAPT, although we did not observe statistically significant interactions for each clinical event (Online Table 2).

DISCUSSION

This randomized, multicenter trial of patients who underwent long-length everolimus-eluting stent implantation (mean total stent length per patient >45 mm) revealed that 6-month DAPT was not associated with a higher risk for the composite outcome of cardiac death, myocardial infarction, stroke, and major TIMI bleeding, compared with 12-month DAPT. These findings were consistent across the subgroups of patients with acute coronary syndrome and with diabetes mellitus.

In the IVUS-XPL trial, participants were randomized to treatments using a 2 × 2 factorial design, intravascular ultrasound use (intravascular ultrasound guidance vs. angiographic guidance), and DAPT duration (6 months vs. 12 months). The effect of intravascular ultrasound use on clinical outcomes was previously reported (22). Intravascular ultrasound-guided stenting compared with angiography-guided stenting resulted in a significantly lower rate of the composite of major adverse cardiac events, including cardiac death, target lesion-related myocardial infarction, or ischemia-driven target lesion revascularization at 1 year (2.9% vs. 5.8%, respectively; HR: 0.48; p = 0.009) (22). In this study, we evaluated the effect of DAPT duration from the IVUS-XPL trial.

Airoldi et al. (18) analyzed 5,389 lesions treated using a first-generation DES (mean stent length 28 mm); stent length was strongly associated with the hazard of stent thrombosis (HR per 10 mm: 2.75; p = 0.001). In their study of 3,145 patients after first-generation DES implantation, Suh et al. (19) found that 31.5 mm was the better cutoff value to predict stent thrombosis at 3 years. In an analysis of a new-generation DES, Naidu et al. (20) found that total stent length was an independent predictor of stent thrombosis hazard (HR per 10 mm: 1.30; p < 0.001; 8,061 everolimus-eluting stent-treated patients). An analysis of 20 years of Swedish registry data of the evolution of percutaneous coronary intervention revealed that per patient implanted, stent length increased from approximately 20 mm from 1996 to 2002 to approximately 29 mm from 2005 to 2010 (17). Three-vessel disease incidence increased from 3.8% in 1990 to 1995, to 17.3% to 19.0% in 2003 to 2010 (17). These results suggest that treated lesions were increasing in complexity and length in daily clinical practice. Therefore, practical issues regarding the optimal duration of DAPT balancing between stent thrombosis prevention and reduction of bleeding risk have emerged, particularly for patients with long-length everolimus-eluting stents. However, long-length DES implantation was not usually included in previous randomized studies; median or mean stent length was usually between 19 and 30 mm (2,4,6–8). It was approximately 38 mm in the ITALIC (Is There a Life for DES After Discontinuation of Clopidogrel) trial (3). Our study included only patients with a 39.3-mm mean stent length of target long lesions and 47.3-mm mean total stented length per patient. This length is the longest among the current randomized trials comparing shorter DAPT duration with a ≥12-month duration after DES implantation.

Comparable clinical outcomes were revealed for patients who received short-duration DAPT after new-generation DES implantation in several randomized clinical trials (2-8). On the contrary, the randomized study with the largest sample size (n = 9,961) revealed that more favorable clinical outcomes occurred in patients who received DAPT beyond 1 year, even after implantation of a new-generation DES (14). Taken together, these results indicate that optimal DAPT strategies after new-generation DES implantation remain to be determined. Optimal DAPT strategies after everolimus-eluting stent implantation are also not clearly established (3), even though this stent is the most extensively evaluated and widely used new-generation DES in daily clinical practice. Various types of DES were used in the previous randomized trials investigating optimal DAPT duration. First- and second-generation DES were used in several randomized studies (2,6-8). Although second-generation DES alone were used in 1 randomized trial, different types of second-generation DES were used (4). A single type of second-generation DES was used in another randomized trial (everolimus-eluting stent) (3), but this trial was terminated early because of recruitment problems.

Similar to our study, the ITALIC trial (3), which used only everolimus-eluting stents (XIENCE V), revealed a very low rate of thrombotic events in the 6-month compared with the 12-month DAPT group. This result could be attributed to the improved vascular healing and reendothelialization properties related to improved stent performance (27,28). One optical coherence tomographic study revealed that the everolimus-eluting stent had more favorable strut coverage than the first-generation DES (28). A meta-analysis revealed that among different DES types,

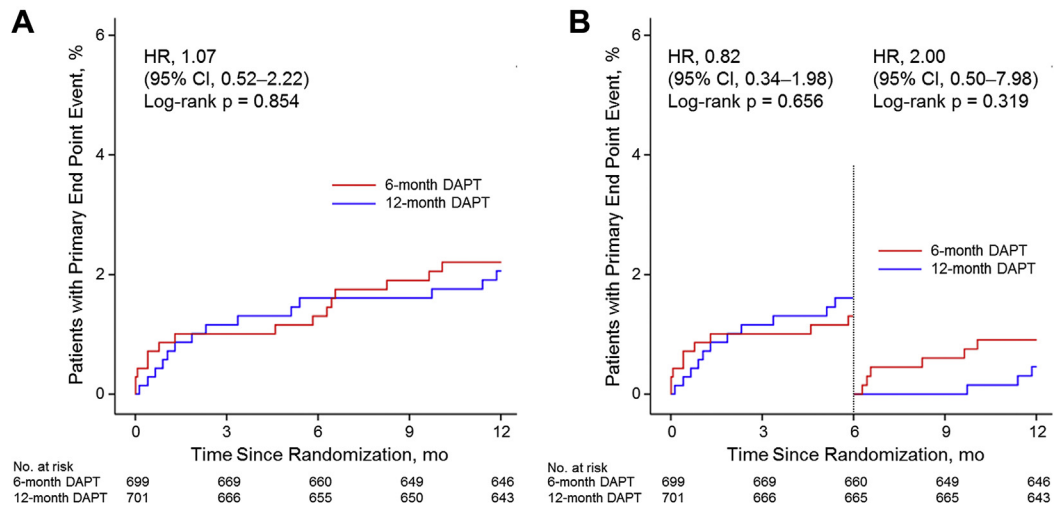
TABLE 3 Clinical Outcomes at 1 Year

	6-Month DAPT (n = 699)	12-Month DAPT (n = 701)	Hazard Ratio (95% CI)	p Value by Log-Rank Test
Primary endpoint*				
Composite of cardiac death, MI, stroke, or TIMI major bleeding	15 (2.2%)	14 (2.1%)	1.07 (0.52–2.22)	0.854
Clinical events*				
Death of any cause	5 (0.7%)	10 (1.5%)	0.50 (0.17–1.45)	0.193
Cardiac death	3 (0.4%)	5 (0.7%)	0.60 (0.14–2.50)	0.474
MI	1 (0.1%)	0	–	0.318
Repeat revascularization of stented lesions	31 (4.7%)	21 (3.1%)	1.49 (0.86–2.59)	0.157
Repeat revascularization of target long lesions	29 (4.4%)	21 (3.1%)	1.39 (0.73–2.44)	0.247
Composite of cardiac death, MI, or repeat revascularization of stented lesions	35 (5.2%)	25 (3.8%)	1.40 (0.84–2.35)	0.193
Composite of cardiac death, target long lesion–related MI, or target long lesion revascularization	33 (4.9%)	25 (3.8%)	1.32 (0.79–2.22)	0.290
Definite or probable stent thrombosis	2 (0.3%)	2 (0.3%)	1.00 (0.14–7.11)	0.999
Acute	1 (0.1%)	1 (0.1%)	–	–
Subacute	0 (0%)	1 (0.1%)	–	–
Late	1 (0.1%)	0	–	–
Stroke	6 (0.9%)	3 (0.4%)	2.00 (0.50–7.99)	0.318
TIMI major bleeding	5 (0.7%)	7 (1.0%)	0.71 (0.23–2.25)	0.563

*Event rates are cumulative 1-year Kaplan-Meier event rates.

CI = confidence interval; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; other abbreviation as in Table 1.

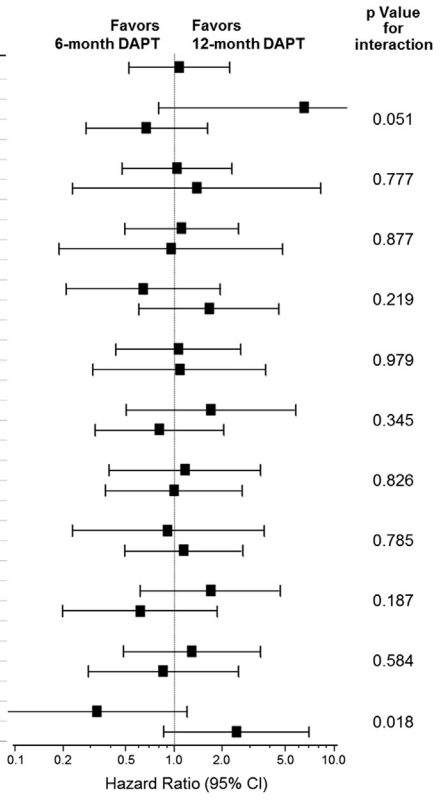
FIGURE 2 Kaplan-Meier Curves



Primary endpoint **(A)** and 6-month landmark analysis for the primary endpoint **(B)**. CI = confidence interval; HR = hazard ratio; other abbreviation as in Figure 1.

FIGURE 3 Subgroup Analysis of the Primary Endpoint

Subgroup	6-month DAPT No. of events	6-month DAPT No. of patients	12-month DAPT No. of events	12-month DAPT No. of patients	Hazard Ratio (95% CI)	p Value for interaction
All patients	15	699	14	701	1.07 (0.52 – 2.22)	
Age, y						
≤65	7	392	1	358	6.50 (0.80 – 52.81)	0.051
>65	8	307	13	343	0.67 (0.28 – 1.62)	
Sex						
Male	12	470	12	494	1.04 (0.47 – 2.31)	0.777
Female	3	229	2	207	1.38 (0.23 – 8.23)	
Hypertension						
Yes	12	443	11	455	1.11 (0.49 – 2.52)	0.877
No	3	256	3	246	0.96 (0.19 – 4.77)	
Diabetes mellitus						
Yes	5	249	8	257	0.64 (0.21 – 1.95)	0.219
No	10	450	6	444	1.65 (0.60 – 4.53)	
Dyslipidemia						
Yes	10	473	9	456	1.06 (0.43 – 2.62)	0.979
No	5	226	5	245	1.08 (0.31 – 3.74)	
Current smoker						
Yes	7	171	4	165	1.69 (0.50 – 5.78)	0.345
No	8	528	10	536	0.81 (0.32 – 2.04)	
Clinical presentation						
Stable angina	7	356	6	358	1.17 (0.39 – 3.49)	0.826
Acute coronary syndrome	8	343	8	343	1.00 (0.37 – 2.66)	
No. of diseased vessels						
One	4	229	4	211	0.91 (0.23 – 3.65)	0.785
Two or three	11	470	10	480	1.15 (0.49 – 2.70)	
Coronary arteries						
LAD	10	432	6	442	1.69 (0.61 – 4.64)	0.187
LCX or RCA	5	267	8	259	0.61 (0.20 – 1.87)	
Reference vessel diameter, mm						
<3.00	9	433	7	435	1.29 (0.48 – 3.46)	0.584
≥3.00	6	266	7	266	0.85 (0.29 – 2.54)	
Use of intravascular ultrasound						
Yes	3	355	9	353	0.33 (0.09 – 1.21)	0.018
No	12	344	5	348	2.45 (0.86 – 6.96)	



LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; other abbreviations as in Figures 1 and 2.

the lowest stent thrombosis rate was observed when the everolimus-eluting stent was used (12). Even though short-duration DAPT had, overall, lower rates of bleeding yet higher rates of stent thrombosis compared with long-duration DAPT in DES-treated patients, the latter effect was significantly attenuated when a second-generation DES was used (29). Therefore, optimal DAPT duration might depend on DES type (5,8,30). In addition, the significant interaction between DES type and DAPT duration for major adverse cardiovascular and cerebrovascular events was also observed in the DAPT (Dual Antiplatelet Therapy) trial comparing 30 versus 12 months of DAPT following DES implantation ($p = 0.048$) (14).

STUDY LIMITATIONS. First, the sample size estimation was not performed on the basis of testing the different DAPT durations. Because clinical events occurred at low rates, our study was underpowered to verify any differences in each event rate. Second, the study was open label and not placebo controlled in the 6-month arm. However, we minimized the risk for potential bias by using an endpoint analysis with precisely defined criteria, blinded the adjudication by event adjudication committee members, and analyzed the data using intention-to-treat measures. Third, each event rate, such as stent thrombosis, was low, and extrapolating our findings should be done with caution, because the issue of stent thrombosis after long DES implantation is very important.

CONCLUSIONS

Among patients requiring long-length everolimus-eluting stent implantation, 6- versus 12-month DAPT did not increase the composite of cardiac death, myocardial infarction, stroke, or TIMI major bleeding at 1 year post-procedure.

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PERSPECTIVES

WHAT IS KNOWN? Long stent implantation for diffuse long lesions has a high risk for stent thrombosis, myocardial infarction, and target lesion failure, even with the use of new-generation DES. Well-designed studies that determine optimal DAPT strategies, particularly after long-length everolimus-eluting stent implantation, are limited.

WHAT IS NEW? Our study showed that 6-month DAPT compared with 12-month DAPT did not increase the composite events of cardiac death, myocardial infarction, stroke, or major bleeding at 1 year in the patients who underwent everolimus-eluting stent implantation.

WHAT IS NEXT? Further randomized studies with larger number of patients and longer term (>1 year) follow-up are needed to confirm these findings.

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KEY WORDS coronary artery disease, drug-eluting stent(s), dual-antiplatelet therapy

APPENDIX For supplemental tables, please see the online version of this article.