Three-Month Dual Antiplatelet Therapy After Implantation of Zotarolimus-Eluting Stents
– The DATE (Duration of Dual Antiplatelet Therapy After Implantation of Endeavor Stent) Registry –

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Background: The optimal duration of dual antiplatelet therapy remains controversial.

Methods and Results: Between December 2006 and March 2008, 823 patients were enrolled in a prospective multicenter registry for 3-month dual antiplatelet therapy (aspirin 100–200 mg+clopidogrel 75 mg daily) followed by aspirin mono-therapy after zotarolimus-eluting stents (ZES). Major exclusion criteria were: cardiogenic shock, stent thrombosis (ST)-segment elevation myocardial infarction (MI) within 48 h, previous drug-eluting stent implantation, severe left ventricular dysfunction, bifurcation lesions requiring 2-stenting, left main and graft lesions. The primary outcome was a composite of cardiac death, MI, or ST at 1 year. The median duration of dual antiplatelet therapy was 95 days (interquartile range 90–101). At 1 year, 3 patients (0.4%) had cardiac deaths, 3 patients (0.4%) had MI, and 4 patients (0.5%) had definite or probable ST, leading to the primary outcome in 5 patients (0.6%). Death, MI, or any revascularization occurred in 68 patients (8.3%). Among patients who were event-free at 3 months (n=812), clopidogrel was discontinued at 3 months in 661 patients and was continued for longer than 3 months in 151 patients. Discontinuation of clopidogrel at 3 months did not increase the primary outcome (HR 0.90; 95%CI, 0.09–9.02), death, MI, or any revascularization (HR 0.89; 95%CI, 0.48–1.67) after adjustment for the propensity score.

Conclusions: Three-month dual antiplatelet therapy seems to be feasible after ZES implantation in relatively low-risk patients. (*Circ J* 2010; **74:** 2314–2321)

Key Words: Antiplatelets; Drug-eluting stents

Although drug-eluting stents (DES) reduce angiographic restenosis and target lesion revascularization (TLR) compared with bare-metal stents (BMS),[1–3] concerns about the safety of DES have been raised because of late stent thrombosis (ST).[4,5] Currently, prolonged dual antiplatelet therapy of at least 12 months of clopidogrel is recommended after percutaneous coronary intervention (PCI) with DES.[6] However, there is a paucity and controversy of evidence regarding the optimal duration of dual antiplatelet therapy.[7,8] Dual antiplatelet therapy increases bleeding risk[9,10] and cost compared with aspirin alone. Endoscopic, dental, and surgical procedures are often delayed due to prolonged dual antiplatelet therapy, which might affect the patient's quality of life.[11] Moreover, it is also unclear whether the optimal duration of dual antiplatelet therapy is similar for all DES types.

Zotarolimus-eluting stents (ZES) (Endeavor, Medtronic Vascular, Inc, Santa Rosa, CA, USA) have a favorable long-term safety profile and carry a lower risk of myocardial infarction (MI) and ST after 1 year compared with paclitaxel-eluting stent (PES).[12] Several animal and human studies support the safety of ZES.[13–17] Theoretically, the duration of dual antiplatelet therapy can be shorter with ZES than with other stents. This study aims to determine the feasibility of 3-month dual antiplatelet therapy after ZES implantation in relatively low-risk patients with coronary artery disease.

Methods

Study Population
The DATE (Duration of dual Antiplatelet Therapy after implantation of Endeavor stent) registry was a prospective multicenter cohort study to evaluate the safety of 3 months of dual antiplatelet therapy after successful implantation of ZES conducted at 17 major centers in Korea. Patients were eligible for participation based on the following inclusion criteria: (1) clinically significant coronary stenosis (diameter stenosis >70% or diameter stenosis >50% with typical angina and/or objective evidence of myocardial ischemia); (2) de novo coronary lesions; and (3) exclusive treatment with ZES. The exclusion criteria were as follows: (1) clinical characteristics including cardiogenic shock, ST-segment elevation MI within 48 h of onset, previous implantation of DES, and severe left ventricular dysfunction (left ventricular ejection fraction <25%) or congestive heart failure; (2) lesion characteristics including total stent length >60 mm, bifurcation lesions requiring side branch stenting, left main lesions, and graft lesions; and (3) patient's characteristics including clopidogrel use for reasons other than PCI, use of warfarin or antiplatelet therapy other than aspirin and clopidogrel, hypersensitivity to aspirin or clopidogrel, expected survival less than 1 year, child-bearing age in women, bleeding diathesis, major bleeding within 3 months, and renal dysfunction (serum creatinine >2.0 mg/dl). The study protocol was approved by the institutional review board at each participating institution and all subjects gave informed consent to participation.

PCI and Antiplatelet Therapy
All procedures were performed with standard interventional techniques. All patients were administered loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) unless they had previously received antiplatelet medications. Anti-coagulation during PCI was performed according to the routine practices of each hospital. Predilation, post-stent adjunctive balloon inflation, use of intravascular ultrasound, and administration of glycoprotein IIb/IIIa receptor antagonists were all at the operator's discretion. After the procedure, aspirin (100–200 mg once daily) was continued indefinitely. Discontinuation of clopidogrel (75 mg once daily) was planned at 3 months (window period: ±2 weeks).

Data Collection and Follow up
This study was coordinated by the Clinical Trial Center of Samsung Medical Center. Demographic, clinical, laboratory, angiographic, procedural, and outcome data were collected by a dedicated web-based case report form. Additional information was obtained by further inquiry into medical records or telephone contact, if necessary. Quantitative angiographic analysis (QCA) was performed at the angiographic core laboratory of the Cardiac and Vascular Center, Samsung Medical Center. All outcome data were confirmed by source documentation collected from each participating center and were reviewed by an independent clinical event adjudication committee. Clinical follow up was scheduled at 1, 3, 6, and 12 months after the index procedure. At each visit, drug compliance was evaluated by interview. Drug compliance was defined as 100×pills taken/pills prescribed. Serious adverse events were reported within 24 h to the steering committee.

Definitions and Study Endpoints
Clinical events were defined based on the recommendations of the Academic Research Consortium (ARC).[18] All deaths were considered cardiac unless a definite non-cardiac cause could be established. MI was defined as the presence of clinical signs of MI combined with a creatine kinase MB fraction or troponin-T/troponin-I increase higher than the upper normal limit. TLR was defined as either a repeat PCI of the lesion within 5 mm of the deployed stent or bypass graft surgery of the target vessel. Target vessel revascularization (TVR) was defined as repeat revascularization of the target vessel by PCI or bypass graft surgery. Definite, probable and possible ST was defined according to the ARC recommendations.[18] The timing of ST was classified as early, late, or very late if it occurred within 1 month, 1 month to 1 year, and greater than 1 year post index procedure, respectively.

The primary outcome of this study was a composite of cardiac death, MI, or definite/probable ST at 1 year. Among patients who were event-free at 3 months, the primary outcome and patient-oriented composite endpoint by the ARC recommendation (all-cause death, any MI, or any repeat revascularization including all target and non-target vessels) at 1 year were compared between patients taking clopidogrel for 3 months only and those taking clopidogrel for more than 3 months.

Statistical Analysis
Continuous variables were analyzed using the Student's t-test or the Mann-Whitney U test, and categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Cumulative event rates were estimated using the Kaplan-Meier methods and were compared by the log-rank test. Adjusted hazard rates were compared with multivariable Cox proportional-hazards regression that incorporated propensity score, to reduce the effect of selection bias regarding the duration of clopidogrel and potential confounding in this observational study.[19] The propensity score was the estimated probability of discontinuation of clopidogrel at 3 months after the index procedure rather than continuation of clopidogrel for longer than 3 months. This propensity score was derived from a separate logistic regression model that predicted discontinuation of clopidogrel at 3 months. Factors significantly associated with death, MI, or repeat revascularization in univariate analysis and potential confounders such as demographic factors, coronary risk factors, medical history, angiographic and procedural variables were included in this logistic regression model for the propensity score. Included variables were as follows: age, gender, clinical presentation, current smoker, diabetes mellitus, hypertension, dyslipidemia, prior MI, prior PCI, prior cerebrovascular disease, disease extent, left anterior descending artery disease, number of treated lesions, reference diameter, lesion length, type B2/C lesion, lesion eccentricity, number of stents used, stent diameter, and total stent length. In addition to the propensity score, history of PCI was incorporated into the Cox model to adjust for differences between patients taking clopidogrel for 3 months and those taking clopidogrel for more than
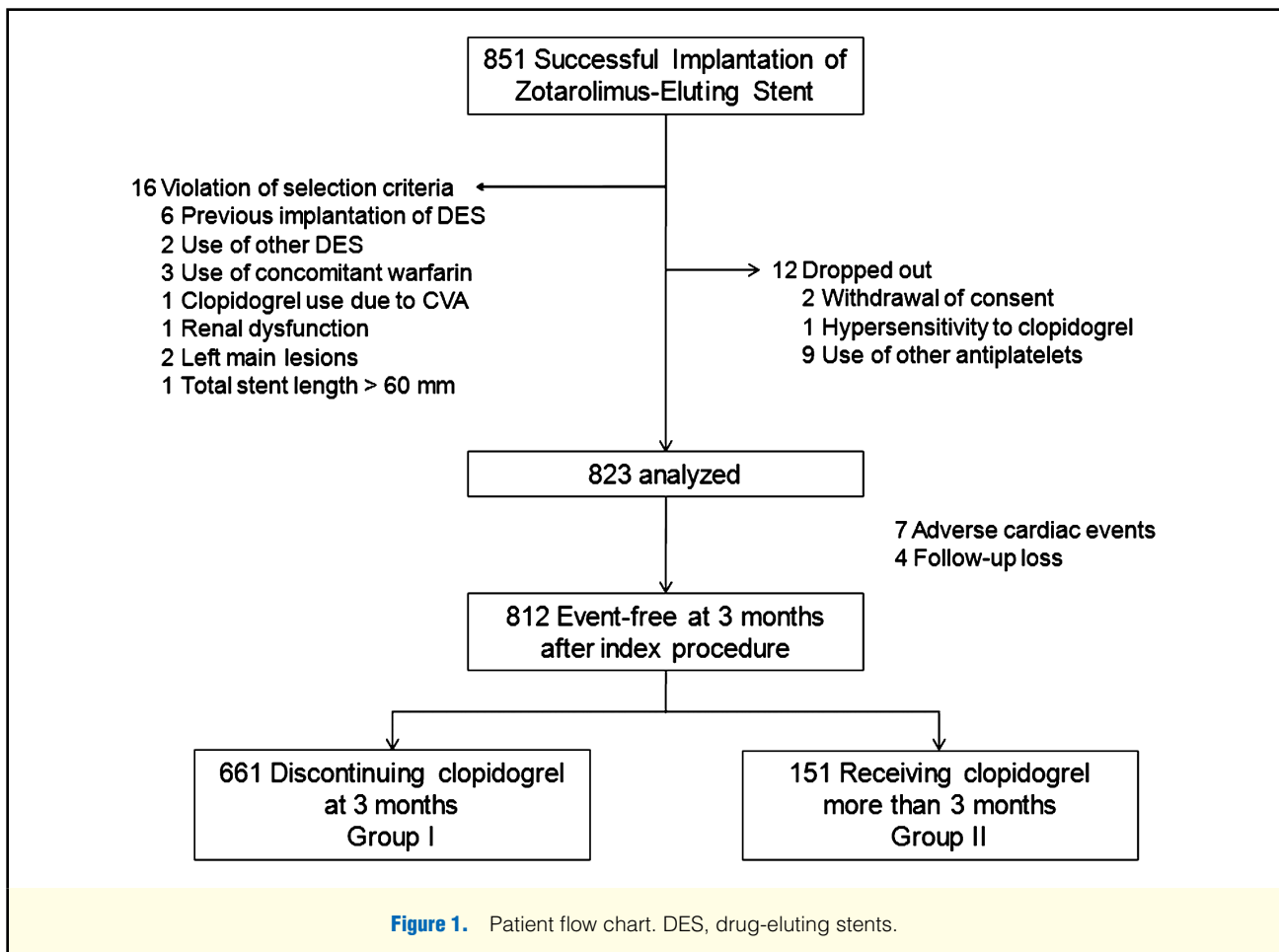
851 Successful Implantation of
Zotarolimus-Eluting Stent

16 Violation of selection criteria
  6 Previous implantation of DES
  2 Use of other DES
  3 Use of concomitant warfarin
  1 Clopidogrel use due to CVA
  1 Renal dysfunction
  2 Left main lesions
  1 Total stent length > 60 mm

12 Dropped out
  2 Withdrawal of consent
  1 Hypersensitivity to clopidogrel
  9 Use of other antiplatelets

823 analyzed

7 Adverse cardiac events
4 Follow-up loss

812 Event-free at 3 months
after index procedure

661 Discontinuing clopidogrel
at 3 months
Group I

151 Receiving clopidogrel
more than 3 months
Group II

Figure 1. Patient flow chart. DES, drug-eluting stents.

Table 1. Baseline Clinical Characteristics

Characteristic	Overall (n=823)	Group I* Clopidogrel for 3 months (n=661)	Group II* Clopidogrel >3 months (n=151)	P value
Age, years, median (interquartile range)	63 (54–70)	64 (53–70)	62 (56–70)	0.75
Men	588 (71)	474 (72)	105 (70)	0.59
Diabetes mellitus	259 (32)	207 (31)	47 (31)	0.96
Hypertension	473 (58)	378 (57)	90 (60)	0.59
Dyslipidemia	211 (26)	167 (25)	41 (27)	0.63
Current smoking	259 (32)	206 (31)	50 (33)	0.64
Peripheral arterial occlusive disease	5 (1)	3 (1)	1 (1)	0.56
Prior MI	19 (2)	12 (2)	6 (4)	0.12
Prior PCI	24 (3)	14 (2)	10 (7)	0.007
Prior CABG	5 (1)	5 (1)	0 (0)	0.59
Prior cerebrovascular disease	28 (3)	19 (3)	9 (6)	0.08
Clinical presentation				0.24
Stable angina	423 (51)	346 (52)	71 (47)	
Acute coronary syndrome	400 (49)	315 (48)	80 (53)	
LVEF†, %, median (interquartile range)	62 (56–68)	62 (56–68)	62 (56–67)	0.88

Data are expressed as number of patients (%) unless otherwise indicated.
*Among patients who were event-free at 3 months.
†Available in 671 of all patients, in 534 patients of group I, and in 127 patients of group II, respectively.
MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction.

Table 2. Angiographic and Procedural Characteristics

Characteristic	Overall (n=823)	Group I* Clopidogrel for 3 months (n=661)	Group II* Clopidogrel >3 months (n=151)	P value
Diseased vessels				0.14
1	713 (87)	571 (86)	132 (87)	
2	100 (12)	84 (13)	15 (10)	
3	10 (1)	6 (1)	4 (3)	
Left anterior descending artery disease	373 (45)	299 (45)	67 (44)	0.85
Treated lesions per patient				0.16
1	705 (86)	567 (86)	130 (86)	
2	108 (13)	88 (13)	17 (11)	
3 or more	10 (1)	6 (1)	4 (3)	
Stent per patient				0.42
1	637 (77)	515 (78)	115 (76)	
2	157 (19)	125 (19)	28 (19)	
3 or more	29 (4)	21 (3)	8 (5)	
Stent diameter†, mm	3.1 (0.5)	3.1 (0.5)	3.1 (0.5)	0.79
Stent total length, mm	26.7 (13.0)	26.3 (12.5)	27.8 (14.8)	0.22
Lesions, no.	951	760	178	
Target-lesion coronary artery				0.73
Left anterior descending	414 (44)	333 (44)	79 (43)	
Left circumflex	257 (27)	202 (27)	53 (29)	
Right	280 (29)	225 (29)	52 (28)	
Lesion characteristics				
ACC-AHA lesion class B2/C	484 (51)	380 (51)	101 (58)	0.09
Bifurcation	179 (19)	144 (19)	33 (19)	0.93
Calcification (moderate to severe)	36 (4)	28 (4)	8 (5)	0.60
Eccentric lesion	275 (29)	233 (31)	40 (23)	0.04
Thrombus present	44 (5)	38 (5)	6 (3)	0.37
Ulceration	34 (4)	27 (4)	7 (4)	0.80
Procedural characteristics				
Stent diameter, mm	3.1 (0.5)	3.1 (0.4)	3.1 (0.5)	0.90
Stent length, mm	23.0 (8.7)	22.9 (8.6)	23.5 (9.5)	0.35
Maximal pressure, atm	13.5 (3.3)	13.5 (3.3)	13.2 (3.2)	0.22
No. of stent per lesion	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.64
Quantitative coronary angiography				
Preintervention				
Reference vessel diameter, mm	3.0 (0.6)	3.0 (0.6)	3.1 (0.6)	0.32
Minimal luminal diameter, mm	0.9 (0.5)	0.9 (0.5)	0.9 (0.5)	0.78
Diameter stenosis, %	70.0 (16.2)	70.0 (16.2)	70.3 (16.1)	0.81
Lesion length, mm	15.7 (7.9)	15.5 (7.9)	16.5 (8.2)	0.12
Postintervention				
Minimal luminal diameter, mm	2.9 (0.5)	2.9 (0.5)	2.9 (0.5)	0.76
Diameter stenosis, %	8.8 (9.5)	8.9 (8.9)	8.4 (11.8)	0.51

Data are expressed as mean (SD) or number of patients (%).
*Among patients who were event-free at 3 months.
†In patients undergoing multiple stenting, the smallest diameter is presented.

3 months. All analyses were performed with Stata software, version 11.0 (Stata Corp, College Station, TX, USA). P<0.05 was considered statistically significant.

Results

Baseline Characteristics and Antiplatelet Therapy
Between December 2006 and March 2008, 851 patients were registered. Of these, 16 patients did not meet the enrollment criteria: use of warfarin in 3 patients; clopidogrel use for neurologic disease in 1 patient; previous implantation of DES in 6 patients; use of other DES in addition to ZES in 2 patients; left main lesions in 2 patients; renal dysfunction in 1 patient; and total stent length >60mm in 1 patient. During follow up, 12 additional patients dropped out; withdrawal of consent for 2 patients; hypersensitivity to clopidogrel in 1 patient; and use of antiplatelets other than aspirin and clopidogrel in 9 patients. Thus, the final analysis included data from 823 patients (**Figure 1**). Among these, 350 patients (42.5%) received clopidogrel prior to the index PCI for at least 1 week and the other patients were administered loading doses of clopidogrel (300–600mg) before PCI. The median

Table 3. Clinical Outcomes

Endpoint	Overall (n=823)	Group I* Clopidogrel for 3 months (n=661)	Group II* Clopidogrel >3 months (n=151)	Unadjusted HR for Group I** (95%CI)	P value	Adjusted HR for Group I** (95%CI)	P value
Death	7 (0.9)	2 (0.3)	3 (2.0)	0.16 (0.03–0.93)	0.04	0.20 (0.03–1.27)	0.09
Cardiac death	3 (0.4)	1 (0.2)	1 (0.7)	0.23 (0.01–3.69)	0.30	0.52 (0.03–9.88)	0.67
MI	3 (0.4)	2 (0.3)	1 (0.7)	0.46 (0.04–5.11)	0.53	0.48 (0.04–5.56)	0.55
ST†	4 (0.5)	2 (0.3)	1 (0.7)	0.45 (0.04–4.98)	0.52	0.44 (0.04–5.08)	0.51
Primary outcome††	5 (0.6)	3 (0.5)	1 (0.7)	0.67 (0.07–6.43)	0.73	0.90 (0.09–9.02)	0.93
TLR	34 (4.1)	27 (4.1)	6 (4.0)	0.99 (0.41–2.39)	0.97	1.04 (0.42–2.55)	0.93
TVR	43 (5.2)	31 (4.7)	8 (5.3)	0.85 (0.39–1.84)	0.67	0.89 (0.41–1.96)	0.77
Any revascularization	62 (7.5)	46 (7.0)	11 (7.3)	0.91 (0.47–1.76)	0.78	0.96 (0.49–1.88)	0.91
MACE‡	68 (8.3)	48 (7.3)	13 (8.6)	0.82 (0.45–1.52)	0.53	0.89 (0.48–1.67)	0.72

Data are expressed as number of patients (%).
*Among patients who were event-free at 3 months.
**Adjusted for propensity score and history of prior PCI.
†Definite/probable ST.
††Composite of cardiac death, MI, or definite/probable ST.
‡Composite of all-cause death, any MI, or any repeat revascularization.
HR, hazard ratio; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiac events. Other abbreviations see in Table 1.

Table 4. Stent Thrombosis and Outcomes

	Case 1	Case 2	Case 3	Case 4*	Case 5†
Classification	Probable, Subacute	Probable, Late	Possible, Late	Definite, Late	Definite, Late
Timing of event, days from index procedure	20	147	179	191	214
Antiplatelet therapy					
Aspirin	Continued	Continued	Continued	Discontinued at day 188	Continued
Clopidogrel	Continued	Continued	Discontinued at day 99	Discontinued at day 84	Discontinued at day 100 and restarted at day 213
Outcomes	Death	Death due to cardiogenic shock	Death	MI	MI

*The patient stopped taking aspirin arbitrarily.
†Stent thrombosis occurred secondary to an intervening TLR with a paclitaxel-eluting stent (day 213).
Abbreviation see in Tables 1,3.

duration of dual antiplatelet therapy was 95 days (interquartile range 90–101). Clopidogrel was discontinued as planned at 3 months (window period: ±2 weeks) in 661 patients (80% of all patients). Patients who were event-free at 3 months (n= 812) were divided into 2 groups according to their duration of clopidogrel use. Patients taking clopidogrel for 3 months were classified as group I (n=661) and those taking clopidogrel for more than 3 months were classified as group II (n= 151). The median duration of dual antiplatelet therapy was 93 days (interquartile range 90–97) in group I and 157 days (interquartile range 115–353) in group II (P<0.001). Drug compliance was very high and similar in both groups (98.6± 4.9% in group I vs 98.7±5.2% in group II, P=0.91 for aspirin and (98.6±6.5% in group I vs 98.2±8.7% in group II, P=0.50 for clopidogrel).
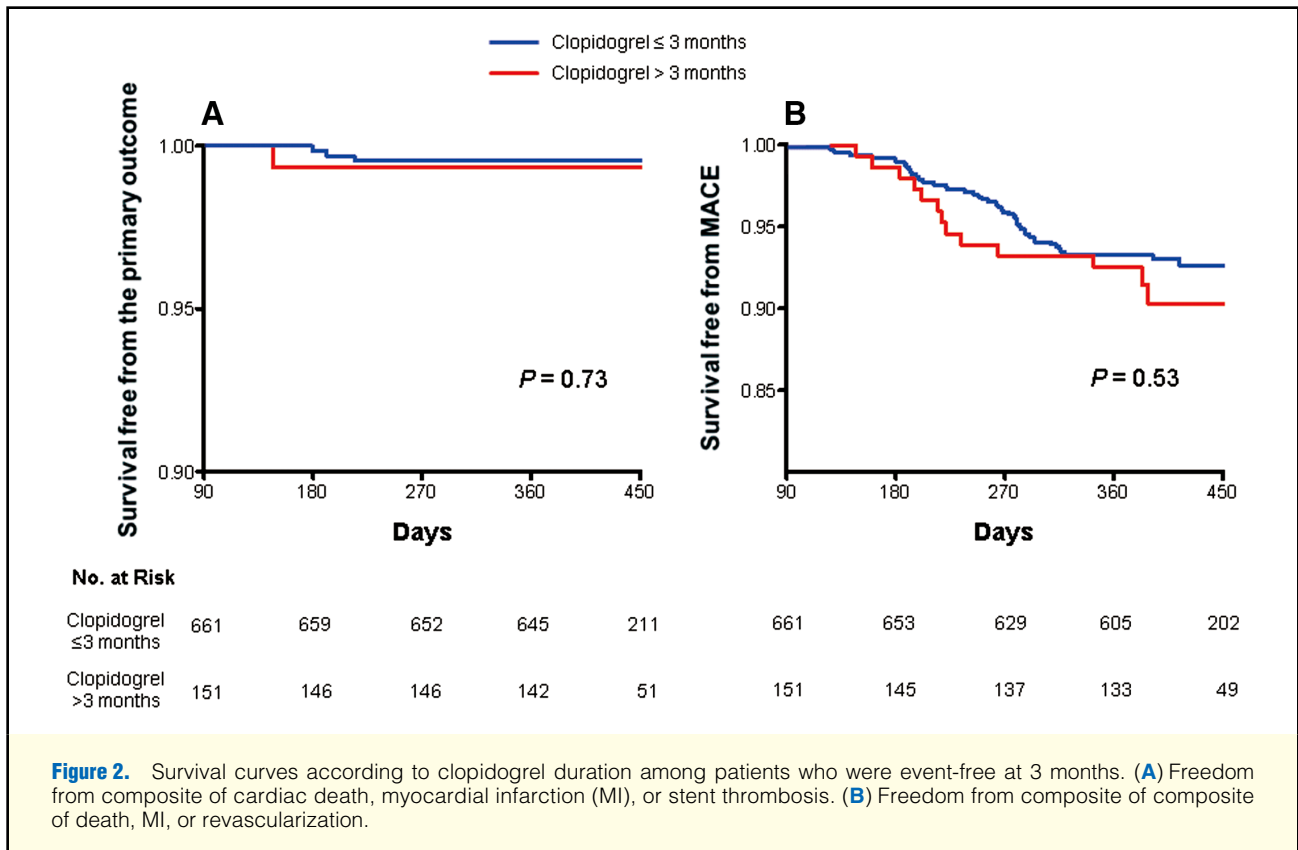
Baseline clinical characteristics are presented in **Table 1**. Male patients were 71% and their median age was 63 years. Approximately half of the patients presented with acute coronary syndrome. Patients with a previous history of PCI were found more frequently in group II than in group I. Otherwise, no significant differences in the baseline clinical characteristics between groups I and II were found.

Angiographic and Procedural Data

Angiographic and procedural data are presented in **Table 2**. The majority of patients had single vessel disease and most patients were treated with 1 stent. No significant differences were found in angiographic and procedural data between groups I and II, with the exception of lesion eccentricity. However, type B2/C lesions were more common in group II compared to group I, with borderline statistical significance.

Clinical Outcomes

Complete clinical follow-up 1-year data were obtained for 808 patients (98.2% of the overall cohort). At 1 year, the primary outcome (cardiac death, MI or definite/probable ST) occurred in 5 patients (0.6%), with cardiac death in 3 patients (0.4%) and MI in 3 patients (0.4%) (**Table 3**). Definite or probable ST was noted in 4 patients (0.5%) and 1 patient had possible ST. The timing of ST, antiplatelet therapy at the time of ST, and the outcome of ST are presented in **Table 4**. TLR, TVR, and any revascularization occurred in 34 patients (4.1%), 43 patients (5.2%), and 62 patients (7.5%), respectively. The composite of all causes of death, MI, or any revascularization occurred in 68 patients (8.3%). Survival free from the primary outcome and survival free from com-

Figure 2. Survival curves according to clopidogrel duration among patients who were event-free at 3 months. (**A**) Freedom from composite of cardiac death, myocardial infarction (MI), or stent thrombosis. (**B**) Freedom from composite of composite of death, MI, or revascularization.

Table 5. Baseline Characteristics of Patients by Clopidogrel Duration Within Tertile of Propensity Score for Discontinuation of Clopidogrel at 3 Months

Characteristic	Lowest tertile		Intermediate tertile		Highest tertile	
	Group I* Clopidogrel for 3 months (n=202)	Group II* Clopidogrel >3 months (n=69)	Group I* Clopidogrel for 3 months (n=223)	Group II* Clopidogrel >3 months (n=48)	Group I* Clopidogrel for 3 months (n=236)	Group II* Clopidogrel >3 months (n=34)
Age, median (interquartile range), years**	65 (56–71)	64 (58–72)	63 (53–69)	63 (53–70)	62 (53–70)	61 (56–69)
Men**	134 (66)	44 (64)	150 (67)	33 (69)	190 (81)	28 (82)
Diabetes mellitus††	66 (33)	21 (30)	57 (26)	13 (27)	84 (36)	13 (38)
Hypertension†	130 (64)	46 (67)	129 (58)	24 (50)	119 (50)	20 (59)
Dyslipidemia††	58 (29)	23 (33)	58 (26)	15 (31)	51 (22)	3 (9)
Current smoking**	83 (41)	24 (35)	72 (32)	16 (33)	51 (22)	10 (29)
Prior MI†	8 (4)	5 (7)	2 (1)	1 (2)	2 (1)	0 (0)
Prior PCI**	14 (7)‡	10 (15)‡	0 (0)	0 (0)	0 (0)	0 (0)
Prior cerebrovascular disease**	18 (9)	8 (12)	1 (0.4)	1 (0)	0 (0)	0 (0)
Acute coronary syndrome**	134 (66)	44 (64)	116 (52)	26 (54)	65 (28)	10 (29)
No. of diseased vessels	1.2 (0.4)	1.2 (0.5)	1.1 (0.4)	1.1 (0.4)	1.2 (0.4)	1.1 (0.4)
Left anterior descending artery disease	80 (40)	32 (46)	100 (45)	20 (42)	119 (50)	15 (44)
Reference diameter**, mm	3.2 (0.6)	3.1 (0.6)	3.0 (0.5)	3.1 (0.5)	2.8 (0.5)	2.8 (0.5)
Lesion length**, mm	23.0 (13.0)	25.2 (15.4)	16.9 (9.7)	16.1 (8.1)	14.5 (7.8)	13.6 (8.3)
Type B2/C lesion**	135 (67)	49 (71)	92 (41)	23 (48)	104 (44)	12 (35)
Lesion eccentricity**	15 (7)	8 (12)	47 (21)	10 (21)	141 (60)	16 (47)
No. of treated lesions per patient**	1.2 (0.4)	1.2 (0.5)	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)	1.2 (0.5)
No. stent per patient†	1.3 (0.6)	1.4 (0.7)	1.2 (0.5)	1.1 (0.4)	1.2 (0.5)	1.1 (0.5)
Stent diameter, mm	3.1 (0.5)	3.0 (0.5)	3.2 (0.5)	3.2 (0.5)	3.1 (0.4)	3.1 (0.4)
Stent total length**, mm	30.0 (15.3)	32.4 (17.8)	25.0 (11.1)	24.5 (8.6)	24.4 (10.1)	22.9 (12.0)

Values are mean±SD or n (%) unless otherwise indicated.
*Among patients who were event-free at 3 months.
**P<0.001 between tertiles. †P<0.01 between tertiles. ††P<0.05 between tertiles. ‡P value for prior PCI in the lowest tertile=0.056.

posite of death, MI, or any revascularization were not significantly different between groups I and II (**Figure 2**). Among patients who were event-free at 3 months, patients in the highest tertile of propensity score for discontinuation of clopidogrel at 3 months were less likely to have risk factors such as hypertension, dyslipidemia, and current smoking, and previous history of MI or revascularization (**Table 5**). Number of stents per patient was highest and total stent length was longest in the lowest tertile. However, no significant differences in baseline characteristics were observed between groups I and II within each tertile, except that patients in group II had a history of prior PCI more frequently than those in group I in the lowest tertile. Propensity score-adjusted analysis showed no significant differences in the primary outcome (hazard ratio for group I, 0.90; 95%CI, 0.09–9.02) and composite of death, MI, or any revascularization (hazard ratio for group I, 0.89; 95%CI, 0.48–1.67) between groups I and II (**Table 3**). Of 3 patients who had the primary outcome in group I, only 1 patient had possible ST within 3 months after discontinuation of clopidogrel. Of 48 cases with composite of death, MI, or any revascularization in group I, 7 cases occurred within 3 months after discontinuation of clopidogrel.

Discussion

In this study, we constructed a prospective multicenter registry to evaluate the safety of 3-month dual antiplatelet therapy after successful implantation of ZES. The primary outcome occurred infrequently. Among patients who were event-free at 3 months, no significant differences were observed in adverse cardiac events between patients taking clopidogrel for only 3 months and those taking clopidogrel for more than 3 months.

Optimal Duration of Dual Antiplatelet Therapy
The optimal duration of dual-antiplatelet therapy has not been well established. Although some studies have reported that extended use of clopidogrel in patients with DES is associated with a reduced risk of death or MI,[8,20] other studies have reported that there is no apparent clinical benefit to dual antiplatelet therapy for greater than 6 months.[7,21] There have been no prospective, randomized trials addressing this issue thus far. Moreover, the optimal duration of dual antiplatelet therapy might be different according to DES types. Therefore, we constructed a prospective multicenter registry to evaluate the safety of 3-month dual antiplatelet therapy after successful implantation of ZES. To the best of our knowledge, this is the first study to evaluate the feasibility of 3-month dual antiplatelet therapy, particularly after implantation of ZES.

Favorable Outcomes With a Short Duration of Dual Antiplatelet Therapy
The main finding of our study is that 3-month dual antiplatelet therapy appears to be safe and efficacious after ZES implantation. The results might be explained by our patient profiles and the relative safety of ZES. Patients enrolled in our registry were considered to be at relatively low risk. Patients with a high risk of ST such as those with renal failure, bifurcation lesions with 2 stents, and lower ejection fractions,[22] or those with expected high fatality after ST such as patients with left main lesions, were excluded. Half of the patients presented with acute coronary syndrome, but patients with cardiogenic shock or ST-segment elevation MI within 48h of onset were excluded. Compared with previous studies of patients receiving ZES,[23,24] the patients in our study had a

lower prevalence of prior MI and revascularization. Although the only exclusion criteria based on lesion complexity were very long stenting and bifurcation lesions with 2 stents, investigators might have been reluctant to enroll patients with complex lesions. As a result, the lesion characteristics were not complex in this study. The reference vessel size was larger and the prevalence of type B2/C lesions and multivessel disease was lower in our study than in previous studies with ZES.[23,24]

There are several possible mechanisms explaining the relative safety of ZES. The phosphorylcholine coating of ZES has been reported to promote rapid healing of the endothelium and to show an excellent biocompatibility with aspirin-only treatment.[13] In a rabbit model, less inflammation was seen with ZES than with sirolimus-eluting stents (SES) or PES, and there were uncovered struts with SES and PES but not with ZES and BMS.[14] Several clinical studies have also supported the safety of ZES. In optical coherence tomography studies, most of the stent struts were covered with neointima at 3 months after ZES implantation,[15] and exposure of stent struts and thrombi was observed less frequently in patients undergoing PCI with ZES than in those undergoing PCI with SES at 9 months follow up.[16] In other OCT studies, uncovered struts were frequently observed in SES at 9–12 months.[25–27] Vasoconstriction to incremental doses of acetylcholine was observed less intensely with ZES compared with SES.[17] Collectively, these findings suggest that ZES might be advantageous for re-endothelialization and preservation of endothelial function. However, head-to-head comparisons are needed to determine whether ZES is safer than other DES of ST.

Outcomes According to Clopidogrel Duration
Among patients who were event-free at 3 months, clopidogrel was not discontinued at 3 months in 19% of patients in this study. To evaluate the safety and efficacy of discontinuation of clopidogrel at 3 months specifically, we compared clinical outcomes between patients taking clopidogrel for only 3 months and those taking clopidogrel for more than 3 months. Baseline clinical, angiographic, and procedural characteristics were mostly similar between the 2 groups. To reduce the effect of selection bias regarding the duration of clopidogrel and potential confounding in this observational study, we calculated a propensity score for the discontinuation of clopidogrel at 3 months and incorporated it into the multivariable Cox proportional-hazard model. After adjustment, no significant differences between the 2 groups were seen for safety and efficacy outcomes. Moreover, most events occurred more than 3 months after the discontinuation of clopidogrel (6 months after the index procedure) in patients taking clopidogrel for only 3 months. However, continuation or discontinuation of clopidogrel at 3 months was not randomly assigned. Physicians might have continued clopidogrel in patients who they felt had high-risk profiles and we cannot discount the possibility of confounding by unmeasured variables. Some previous observational studies reported that discontinuation of thienopyridine therapy was the major determinant of ST within the first 6 months after DES implantation,[7] and the extended use of clopidogrel in patients with DES might be associated with a reduced risk for death or MI.[8] These results seem to be contrary to our study, which might be explained by differences in the baseline characteristics of the study population and used stents. They studied real-world registries without strict exclusion criteria and enrolled patients with SES or PES. To determine the optimal duration of dual antiplatelet therapy, a larger randomized

study is needed.

Study Limitations

There are several limitations to our study. First, the sample size was too small to provide a definite answer regarding low-frequency events such as ST. However, we constructed a high-quality prospective registry with detailed information on antiplatelet therapy and performed thorough follow up, with the goal of challenging prolonged dual antiplatelet therapy after ZES. Second, because we enrolled patients after successful implantation of ZES and the exclusion criteria were strict, patients in our registry had a low-risk profile, limiting generalization of the study results to all patients undergoing PCI with DES. Finally, our findings apply only to ZES. Because safety and efficacy differ according to the DES type, other studies are needed to determine the feasibility of short duration dual antiplatelet therapy after other DES are used.

Conclusions

Three-month dual antiplatelet therapy followed by aspirin alone seems to be feasible after implantation of ZES in relatively low-risk patients with coronary artery disease. These results should be confirmed by a large randomized trial.

Disclosure

None.

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