Six Versus 12 Months of Dual Antiplatelet Therapy After Implantation of Biodegradable Polymer Sirolimus-Eluting Stent

Randomized Substudy of the I-LOVE-IT 2 Trial

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Background—There are no reports on a large-scale randomized trial exploring optimal dual antiplatelet therapy (DAPT) duration after biodegradable polymer sirolimus-eluting stent implantation. We sought to report the outcomes of a randomized substudy of the prospective Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization (I-LOVE-IT 2) trial.

Methods and Results—In the prospective noninferiority randomized I-LOVE-IT 2 trial, 1829 patients allocated to the biodegradable polymer sirolimus-eluting stent group were also randomized to receive either 6-month (n=909) or 12-month DAPT (n=920). The primary end points of this noninferiority substudy were 12-month target lesion failure (composite of cardiac death, target vessel myocardial infarction or clinically indicated target lesion revascularization), and the major secondary end points were 12-month net adverse clinical and cerebral events (composite of all-cause death, all myocardial infarction, stroke, or major bleeding [Bleeding Academic Research Consortium type ≥3]). The 12-month target lesion failure in 6-month DAPT group was comparable with the 12-month DAPT group (6.8% versus 5.9%; difference and 95% confidence interval, 0.87% [−1.37% to 3.11%], *P* for noninferiority=0.0065). Further follow-up at 18 months showed that incidence of target lesion failure and net adverse clinical and cerebral events were similar between the 2 groups (7.5% versus 6.3%, log-rank *P*=0.32; 7.8% versus 7.3%, log-rank *P*=0.60; respectively), as well as their individual end point components.

Conclusions—This study indicated noninferiority in safety and efficacy of 6-month versus 12-month DAPT after implantation of a novel biodegradable polymer sirolimus-eluting stent.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01681381.

(*Circ Cardiovasc Interv*. 2016;9:e003145. DOI: 10.1161/CIRCINTERVENTIONS.115.003145.)

Key Words: clinical trial ■ drug-eluting stents ■ hemorrhage ■ myocardial infarction ■ polymers

Drug-eluting stent (DES) use during percutaneous coronary intervention (PCI) has resulted in improved clinical outcomes compared with bare metal stents.[1,2] However, late stent thrombosis after DES remains a concern.[3,4] Although current guidelines recommend prolonged dual antiplatelet therapy (DAPT) for all patients undergoing implantation of

See Editorial by Piccolo and Windecker

Received July 22, 2015; accepted January 13, 2016.

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The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.115.003145/-/DC1.

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WHAT IS KNOWN

- Many studies do not reveal major advantages of prolonged dual antiplatelet therapy (DAPT) after drug-eluting stent implantation.
- The precise type of drug-eluting stent may affect subsequent stent thrombosis.
- In our prospective noninferiority randomized I-LOVE-IT 2 trial, 1829 patients allocated to the biodegradable polymer sirolimus-eluting stent group were also randomized to receive either 6-month or 12-month DAPT.

WHAT THE STUDY ADDS

- This study indicated noninferiority in safety and efficacy of 6-month versus 12-month DAPT after implantation of a novel biodegradable polymer sirolimus-eluting stent.
- Definite or probable stent thrombosis was rare in both 6-month DAPT group and in 12-month DAPT group during 18-month follow-up.
- Independent predictors of 18-month net adverse clinical and cerebral events included age ≥65 years, diabetes mellitus, emergent percutaneous coronary intervention for acute myocardial infarction, peripheral arterial disease, left ventricular ejection fraction ≤40%, high baseline synergy between PCI with TAXUS and cardiac surgery score, and lesion length ≥20 mm.

DES,[5,6] the optimal duration of DAPT remains uncertain. Recent studies examined different DAPT durations after DES, ranging from 3 to 12 months to 12 to 30 months treatment regimens,[7–16] and while results of most studies did not reveal major advantages of prolonged DAPT, 2 studies showed that extending DAPT beyond 1 year after placement of a DES (in comparison with aspirin monotherapy beyond 1 year post-DES) significantly reduced the risk of stent thrombosis and major adverse cardiovascular events.[13,14] The precise type of DES may affect subsequent stent thrombosis; in this respect, a shorter DAPT duration may indeed suffice after the newer generation thin-strut DES types and particularly those avoiding a durable polymer (DP), which may be implicated in late vascular inflammation.[17] To date, only scarce data have been reported to compare short-term versus long-term DAPT after implantations of DES with biodegradable polymer (BP). Furthermore, possible event rates after DAPT regimen completion have not been well studied.

In this prospective randomized noninferiority substudy in the BP-DES arm of the larger Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization (I-LOVE-IT 2) trial,[18] we sought to investigate the clinical implications of short-term (6 months) versus standard long-term (12 months) DAPT in patients undergoing PCI with the novel BP-DES device.

Methods

This was a prespecified substudy of I-LOVE-IT 2 trial, which was a prospective, multicenter, randomized, assessor-blinded, noninferiority study comparing BP sirolimus-eluting stents (BP-SES, Tivoli, Essen Tech, Beijing, China) with DP-SES (Firebird 2, MicroPort, Shanghai, China). The description of the study stents, overall inclusion/exclusion criteria, methods and results have been presented in detail previously.[18] In brief, both stents are low-profile, thin-strut CoCr alloy stents with similar dosage of antiproliferative drug, sirolimus. Polymer is polylactide-co-glycolide in BP-SES, and styrene-butadiene block copolymer in DP-SES. The study enrolled patients with stable coronary artery disease or acute coronary syndromes (ACSs) undergoing PCI in 32 centers across China; patients were randomly assigned to receive either a BP-SES or a DP-SES in a 2:1 ratio. Procedure details have been reported previously.[18] Patients who were randomized to the BP-SES group, were additionally randomized (1:1 ratio) to follow a 6-month DAPT or 12-month DAPT duration before the index PCI. No mixture of type of stent in a patient was permitted unless the operator was unable to insert the study stent. A loading dose of 300 mg of aspirin and 300 mg of clopidogrel was administered before the PCI. All patients were discharged with a prescription for 100 mg of aspirin indefinitely, and 75 mg of clopidogrel for 6 or 12 months after index procedure. The study complied with the provisions of the Declaration of Helsinki, and the study protocol was approved by the institutional review board at each study center. All patients provided written informed consent.

End Points

In the main study,[18] the primary end point was 12-month target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction [MI], or clinically indicated target lesion revascularization. Secondary end points included TLF components, device/lesion/procedure success rates, definite/probable stent thrombosis, and patient-oriented composite end point(composite of all-cause death, all MI, or any revascularization). Definitions of those end points have been described in previous report.[18]

The primary end points (efficacy end points) of this substudy were also 12-month TLF. Major secondary end point (safety end points) was net adverse clinical and cerebral events (NACCE), a composite of all-cause death, all MI, stroke, and major bleeding (Bleeding Academic Research Consortium type ≥3 bleeding). This report also provided 18-month follow-up outcomes in patients who were treated by BP-SES and randomized to 6-month DAPT or 12-month DAPT. All patients were followed up by telephone or hospital visit at 1, 6, 9, 12, 18, 24 months, and annually to 5 years.

Statistical Analysis

The substudy was designed for noninferiority testing of 1-year rate of TLF. Assuming an expected 1-year event rate of 8.3% in both groups, we applied a noninferiority margin of 3.7%. Allowing for a 2-sided type I error of 0.05, 1754 patients randomized in a 1:1 ratio would yield at least 80% power to declare noninferiority with respect to the above margin. Allowing for ≤5% loss to follow-up, a total of 1848 subjects would need to be enrolled. Noninferiority would be achieved if the upper limit of the 95% confidence interval of the event rate difference <3.7%.

Categorical variables are reported as counts and percentages, and between-group differences were assessed with χ^2 or Fisher exact test. Continuous variables are presented as mean±SD and were compared with a 2-sample t test. The Kaplan–Meier method was used to calculate time to clinical end points, and the log-rank test was used to analyze between-group differences. Six months after the index procedure was selected as the time point for subsequent landmark analyses about all the end points.

We also analyzed the clinical end point at 18 months according to age, sex, body mass index, history of diabetes mellitus, smoking history, clinical presentation, multivessel PCI, number of treated lesion, preprocedural thrombolysis in myocardial infarction flow grade, total occlusion, bifurcation, reverence vessel diameter, and lesion length.

All analyses were accompanied by tests for interaction between DAPT treatment allocation and subgroup.

Unless otherwise specified, a 2-sided P value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using SAS software version 9.1.3 (SAS Institute, Cary, NC).

Results

A total of 1829 patients assigned to BP-SES group in I-LOVE-IT 2 trial were randomized to receive 6 (n=909) or 12 months (n=920) of DAPT and became part of this study population (Figure 1). Most of the patients (98.0%) were treated solely with the Tivoli BP-SES, as assigned. Only 11 patients (0.6%) were lost to follow-up. Review of the actual DAPT use throughout 1 year of follow-up indicated a rather high compliance with the protocol (Table I in the Data Supplement); 59 patients (6.6%) in the 6-month DAPT group continued DAPT until 12 months, whereas 3 patients (0.3%) in the 12-month DAPT group discontinued DAPT at 6 months after BP-SES implantation.

Baseline patient and procedural characteristics were well matched between the 2 groups (Tables 1–3). Transradial approach was used in 93.0% of the patients in 6-month DAPT group and 92.5% of the patients in 12-month DAPT group (P=0.71); total stent length per patient were 41.0±25.1 mm and 41.2±24.6 mm in 6- and 12-month DAPT groups, respectively, (P=0.87).

Difference in 1-year TLF rates between the 6-month DAPT (6.8% [61/902]) and the 12-month DAPT (5.9% [54/916]) groups was 0.87% (95% confidence interval, −1.37% to 3.11%), demonstrating noninferiority of 6-month DAPT to 12-month DAPT with a noninferiority margin of 3.7% (P for noninferiority=0.0065), thus fulfilling the noninferiority clause as set in our statistical methods. Cumulative incidences of adverse events through 1 year and 18 months were shown in Table 4. At 18 months, there was still no difference in TLF between 6- and 12-month DAPT groups (7.5% versus 6.3%, log-rank P=0.32). The 18-month incidence of NACCE were also similar between the 2 groups (7.9% versus 7.3%, log-rank P=0.60; Figure 2).

Definite or probable stent thrombosis ≤6 months occurred in 5 patients (0.6%) in 6-month DAPT group and in 2 patients (0.2%) in 12-month DAPT group (log-rank P=0.25) as shown in Table II in the Data Supplement. However, all stent thrombosis cases occurred within 6 months from index procedure while the patients were taking clopidogrel and 6 of them within 30 days of PCI. There were no more new definite or probable stent thrombosis between 6 and 18 months period of follow-up (Table III in the Data Supplement). All the above results were consistent in the "as treated" analysis.

Results of the subgroup analyses for 18-month NACCE and TLF are shown in Figure 3 and Figure I in the Data Supplement, respectively. There was no statistically significant heterogeneity between duration of DAPT and the occurrence of NACCE among the subgroups. Clinical outcomes in patients with ACS were shown in Table IV in the Data Supplement. Overall, there was no difference between 2 groups in terms of both NACCE and its components through 18 months in either ST-segment–elevation MI or non–ST-segment–elevation ACS.

Multivariable Cox regression analysis showed that independent predictors of 18-month NACCE included age ≥65 years, diabetes mellitus, emergent PCI for acute MI, peripheral arterial disease, left ventricular ejection fraction ≤40%, high baseline synergy between PCI with TAXUS and cardiac surgery (SYNTAX) score, and lesion length ≥20 mm. Independent predictors of 18-month TLF included diabetes mellitus, lesion length ≥20 mm, procedural complications, emergent PCI for acute MI, left main disease, and

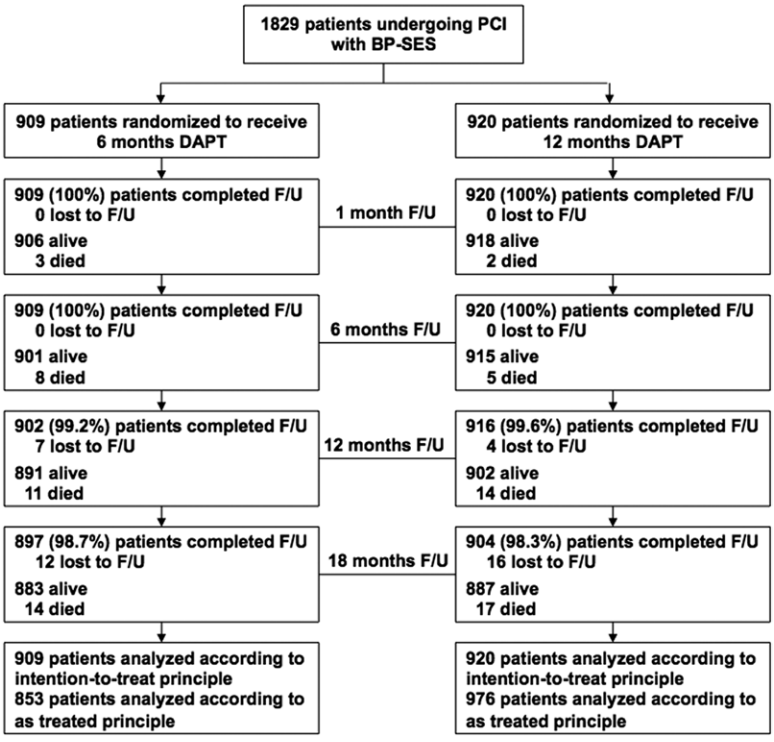

Figure 1. Study patient flow. A total of 1829 patients assigned to biodegradable polymer sirolimus-eluting stent (BP-SES) group in I-LOVE-IT 2 trial were then randomized to receive 6 vs 12 months dual antiplatelet therapy (DAPT). In the "as treated" analysis, 59 patients in the 6-month DAPT group who continued DAPT until 12 months were reallocated to 12-month DAPT group; whereas 3 patients in the 12-month DAPT group were reallocated to 6-month DAPT group because of premature discontinuation of DAPT at 6 months after BP-SES implantation. F/U indicates follow-up.

Table 1. Baseline Patient Characteristics

	6-Mo DAPT Group (n=909)	12-Mo DAPT Group (n=920)	*P* Value
Age, y	60.4±10.2	60.0±10.0	0.41
Male sex	611 (67.2)	632 (68.7)	0.50
Body mass index, kg/m^2	25.1±3.1 (893*)	25.3±3.0 (903*)	0.16
Diabetes mellitus	211 (23.2)	203 (22.1)	0.56
Insulin-requiring diabetes mellitus	88 (9.7)	66 (7.2)	0.05
Hypertension	554 (61.0)	596 (64.8)	0.09
Hyperlipidemia	230 (25.3)	215 (23.4)	0.34
Family history of CAD	57 (6.3)	47 (5.1)	0.28
Smoking history			
Current smoker	333 (36.6)	352 (38.3)	0.77
Ex-smoker	107 (11.8)	106 (11.5)	
None	469 (51.6)	462 (50.2)	
Previous myocardial infarction	156 (17.2)	145 (15.8)	0.42
Previous stroke	84 (9.2)	87 (9.5)	0.87
Peripheral arterial disease†	13 (1.4)	10 (1.1)	0.51
Previous PCI	77 (8.5)	60 (6.5)	0.11
Previous CABG	4 (0.4)	4 (0.4)	1.00
STEMI	122 (13.4)	126 (13.7)	0.86
NSTEMI	103 (11.3)	98 (10.7)	0.64
Unstable angina	527 (58.0)	520 (56.5)	0.53
Stable angina	130 (14.3)	139 (15.1)	0.63
Asymptomatic myocardial ischemia	27 (3.0)	37 (4.0)	0.22
LVEF, %	60.8±8.4 (825*)	60.3±8.2 (848*)	0.29

Values are mean±SD or n (%). CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*The number of patients for whom the continuous variables were calculated.

†Peripheral arterial disease includes lower extremity peripheral artery disease, abdominal aortic aneurysm, renal and mesenteric artery disease, and extracranial carotid artery disease.

Table 2. Baseline Angiographic Characteristics

	6-Mo DAPT Group (Patient, n=909; Lesion, n=1240)	12-Mo DAPT Group (Patient, n=920; Lesion, n=1255)	*P* Value
Target vessel disease extent			
1-vessel	666 (73.3)	690 (75.0)	0.83
2-vessel	202 (22.2)	194 (21.1)	
3-vessel	18 (2.0)	15 (1.6)	
Left main disease	23 (2.5)	21 (2.3)	
Baseline SYNTAX score	11.6±8.1	11.7±8.2	0.68
No. of target lesions per patient			
1	622 (68.4)	635 (69.0)	0.79
2	253 (27.8)	251 (27.3)	
3	31 (3.4)	32 (3.5)	
4	3 (0.3)	2 (0.2)	
No. of target lesions per patient	1.36±0.56	1.35±0.56	0.79
Target vessel location			
Left main artery	23 (1.9)	21 (1.7)	0.88
Left anterior descending artery	569 (45.9)	569 (45.3)	
Left circumflex artery	284 (22.9)	279 (22.2)	
Right coronary artery	364 (29.4)	386 (30.8)	
ACC/AHA lesion classification B2+C	1037 (83.6)	1046 (83.4)	0.85
Complex lesions	533 (43.0)	576 (45.9)	0.14
Bifurcation lesion	382 (30.8)	415 (33.1)	0.23
Ostial lesion	10 (0.8)	15 (1.2)	0.33
Total occlusion	148 (11.9)	158 (12.6)	0.62
Severely tortuous or angulated lesion	27 (2.2)	30 (2.4)	0.72
Moderate to heavy calcification	32 (2.6)	34 (2.7)	0.84
Preprocedural TIMI flow			
0	150 (12.1)	157 (12.5)	0.77
1	20 (1.6)	24 (1.9)	
2	71 (5.7)	62 (4.9)	
3	999 (80.6)	1012 (80.6)	
Preprocedural QCA			
Reference vessel diameter, mm	2.78±0.46	2.79±0.47	0.78
Lesion length, mm	20.5±12.0	20.6±12.6	0.64
Minimal lumen diameter, mm	0.81±0.52	0.80±0.50	0.66
Diameter stenosis, %	71.4±17.0	71.7±16.8	0.74

Values are mean±SD or n (%). Complex lesions were defined by the presence of at least 1 of the following lesion characteristics: unprotected left main coronary artery; bifurcation, ostial lesion; total occlusion; severely tortuous or angulated lesion; and moderate to heavy calcification. ACC/AHA indicates American College of Cardiology/American Heart Association; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TIMI, thrombolysis in myocardial infarction; and SYNTAX, synergy between PCI with TAXUS and cardiac surgery.

previous stroke. Independent predictors of major bleeding included emergent PCI for acute MI (Table V in the Data Supplement).

Discussion

This prospective, multicenter, randomized trial of DAPT duration after PCI with implantation of a novel BP-SES indicated that a 6-month DAPT duration post-PCI was noninferior to a 12-month DAPT course with respect to the prespecified composite clinical end points.

The safety and efficacy of short- versus long-term DAPT have been well demonstrated in patients treated with first or second generation DES. The Duration of Clopidogrel Therapy After Drug-Eluting Stent (DES-LATE) trial showed that among patients who were on 12-month DAPT without complications, an additional 24 months of DAPT versus aspirin alone did not reduce the risk of the composite end point of death from cardiac causes, MI, or stroke.[19] Similarly, a recent study suggests no apparent benefit but instead possible harm with extension of DAPT beyond 1 year after stenting with DES when no event has occurred within the first year after stenting.[20] Moreover, the Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting (EXCELLENT) trial reported the noninferiority of 6- versus 12-month DAPT

Table 3. Procedural Characteristics and Results

	6-Mo DAPT Group (Patient, n=909; Lesion, n=1240)	12-Mo DAPT Group (Patient, n=920; Lesion, n=1255)	*P* Value
Transradial approach	845 (93.0)	851 (92.5)	0.71
Use of IVUS and OCT	29 (3.2)	31 (3.4)	0.83
Balloon predilation	986 (79.5)	993 (79.1)	0.83
Stents per patient	1.70±0.87	1.71±0.85	0.68
Stents per lesion	1.25±0.49	1.27±0.51	0.34
≥3 stents implanted per patient	143 (15.7)	144 (15.7)	0.43
Stent diameter, mm	3.06±0.44	3.05±0.44	0.76
Total stent length per patient, mm	41.0±25.1	41.2±24.6	0.87
Total stent length per lesion, mm	30.2±15.6	30.5±16.0	0.63
Postdilation	642 (51.8)	640 (51.0)	0.68
Postprocedural TIMI flow grade 3	1235 (99.6)	1247 (99.4)	0.42
Postprocedural QCA			
Minimum lumen diameter, mm			
In-stent	2.54±0.42	2.54±0.42	0.81
In-segment	2.37±0.46	2.38±0.46	0.65
Diameter stenosis, %			
In-stent	8.51±5.26	8.21±5.07	0.14
In-segment	11.7±7.3	11.6±7.2	0.80
Residual SYNTAX score	3.20±4.74	3.41±5.35	0.38
Device success	1541 (99.7)	1575 (99.4)	0.21
Lesion success	1234 (99.5)	1244 (99.1)	0.23
Procedure success	870 (95.7)	882 (95.9)	0.86

Values are mean±SD or n (%). DAPT indicates dual antiplatelet therapy; IVUS, intravascular ultrasound; OCT, optical coherence tomography; QCA, quantitative coronary angiography; SYNTAX, synergy between PCI with TAXUS and cardiac surgery; and TIMI, thrombolysis in myocardial infarction.

Table 4. Kaplan–Meier Cumulative Events Through 18 Months

	6-Mo DAPT Group, n=909	12-Mo DAPT Group, n=920	Log-Rank *P* Value
12-month follow-up			
NACCE	66 (7.2)	60 (6.4)	0.53
Target lesion failure	61 (6.5)	54 (5.8)	0.45
All-cause death	11 (1.1)	14 (1.4)	0.57
Cardiac death	6 (0.6)	7 (0.8)	0.80
All MI	41 (4.4)	36 (3.9)	0.53
Q-wave MI	9 (0.9)	5 (0.5)	0.27
TVMI	36 (3.9)	30 (3.3)	0.42
Stroke	11 (1.2)	13 (1.4)	0.71
Any revascularization	49 (5.1)	43 (4.3)	0.47
TVR	31 (3.3)	27 (2.7)	0.55
TLR	27 (2.9)	21 (2.2)	0.35
CI-TLR	27 (2.9)	21 (2.2)	0.35
All bleeding	50 (5.5)	52 (5.7)	0.90
Major bleeding	11 (1.2)	6 (0.7)	0.21
Stent thrombosis	11 (1.1)	7 (0.8)	0.33
Definite	2 (0.2)	1 (0.1)	0.56
Probable	3 (0.3)	1 (0.1)	0.31
Definite/probable	5 (0.6)	2 (0.2)	0.25
18-month follow-up			
NACCE	72 (7.8)	67 (7.3)	0.60
Target lesion failure	68 (7.5)	58 (6.3)	0.32
All-cause death	14 (1.5)	17 (1.9)	0.61
Cardiac death	7 (0.8)	8 (0.9)	0.82
All MI	42 (4.6)	37 (4.0)	0.53
Q-wave MI	9 (1.0)	6 (0.7)	0.42
TVMI	36 (4.0)	30 (3.3)	0.42
Stroke	15 (1.7)	18 (2.0)	0.62
Any revascularization	59 (6.6)	60 (6.5)	0.99
TVR	38 (4.2)	32 (3.5)	0.43
TLR	33 (3.7)	25 (2.7)	0.26
CI-TLR	33 (3.7)	24 (2.6)	0.21
All bleeding	57 (6.1)	60 (6.6)	0.84
Major bleeding	13 (1.3)	7 (0.8)	0.17
Stent thrombosis	12 (1.3)	8 (0.9)	0.35
Definite	2 (0.2)	1 (0.1)	0.56
Probable	3 (0.3)	1 (0.1)	0.31
Definite/probable	5 (0.6)	2 (0.2)	0.25
Acute (0–1 d)	2 (0.2)	1 (0.1)	0.56
Subacute (2–30 d)	2 (0.2)	1 (0.1)	0.56
Late (31–365 d)	1 (0.1)	0 (0)	0.31
Very late (>365 d)	0 (0)	0 (0)	N/A

Values are n (%). *P* values were calculated with the use of the log-rank test on the basis of all available follow-up data. Net adverse clinical and cerebral events were defined as a composite of all-cause death, all MI, stroke, or major bleeding (BARC type ≥3 bleeding); target lesion failure was defined as a composite of cardiac death, TVMI, or clinical indicated TLR. BARC indicates bleeding academic research consortium; CI-TLR, clinical indicated target lesion revascularization; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NACCE, net adverse clinical and cerebral events; TVMI, target vessel myocardial infarction; and TVR, target vessel revascularization.

in preventing major adverse cardiovascular events after everolimus-eluting stent or SES implantation.[11] In addition, the Synergy Between Stent and Drugs to Avoid Ischemic Recurrences After Percutaneous Coronary Intervention (PRODIGY) trial demonstrated the noninferiority of 6 months of DAPT when compared with 24 months in terms of death, stent thrombosis, MI, or cerebrovascular accident in patients who received a balanced mixture of DES or bare-metal stents.[9]

There were 2 notable features of our study that were different from previous DAPT studies. First, the stent used in our study was a new BP-SES with cobalt–chromium platform. We previously demonstrated a satisfactory safety profile of BP-DES with low rates of overall stent thrombosis.[21] Similarly, a pooled analysis of the Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis (ISAR-TEST-3), 3 Limus Agent Eluting Stents With Different Polymer Coating (ISAR-TEST-4), and Limus Eluted From a Durable Versus Erodable Stent Coating (LEADERS) trials showed that BP-DES were associated with a significantly lower rate of very late definite stent thrombosis from 1 to 4 years compared with DP-DES.[22] Our study was designed on the above evolving findings and showed for the first time the

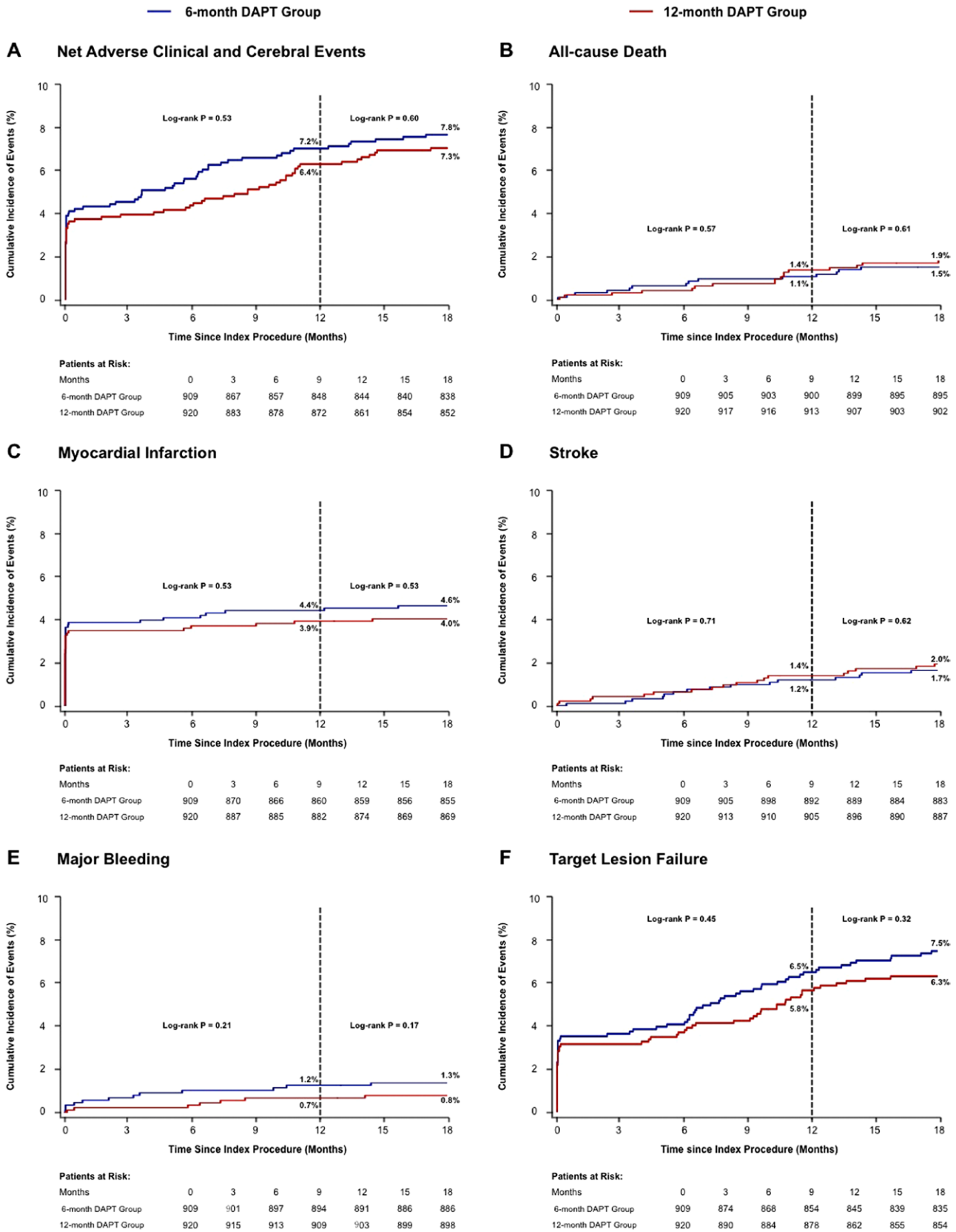

Figure 2. Kaplan–Meier cumulative event curves on an intention-to-treat basis. Cumulative event curves through 18 months of net adverse clinical and cerebral events (**A**), all-cause death (**B**), myocardial infarction (**C**), stroke (**D**), major bleeding (**E**), and target lesion failure (**F**) for patients receiving 6-month dual antiplatelet therapy (DAPT; blue line) or 12-month DAPT (red line) are shown.

safety and efficacy of 6-month DAPT in patients treated by BP-SES. Second, most enrolled patients had a diagnosis of ACS at the time of the index intervention, and 4.7% of them suffered acute MI within 24 hours (including ST-segment–elevation MI and non–ST-segment–elevation MI).

ACS are nearly always caused by a luminal thrombus or a sudden plaque hemorrhage imposed on an atherosclerotic plaque with or without concomitant vasospasm.[23] In ST-segment–elevation MI, the thrombus is mostly occlusive and sustained, whereas in unstable angina and non–ST-segment–elevation MI, the thrombus is usually incomplete and dynamic, or even absent. The current guidelines of American professional societies (American College of Cardiology, American Heart Association, and Society for Coronary Angiography and Intervention) for PCI recommend DAPT for at least 12 months after PCI for ACS.[6] Continuation of DAPT beyond 12 months may be considered. The European Society of Cardiology, in its most recent guidelines on myocardial revascularization recommends 6-month DAPT in stable coronary artery disease patients undergoing PCI with new-generation DES, and 12 months of DAPT for patients with ACS, regardless of revascularization status or stent used (class I; level of evidence A).[7] However, in our study, we did not observe any superiority of 12-month DAPT over 6-month DAPT in patients with ACS. Therefore, our study suggests that not all ACS patients with BP-DES need 12-month DAPT, and 6-months DAPT may be one option for patients with high risk of bleeding or patients who cannot tolerate >6-month

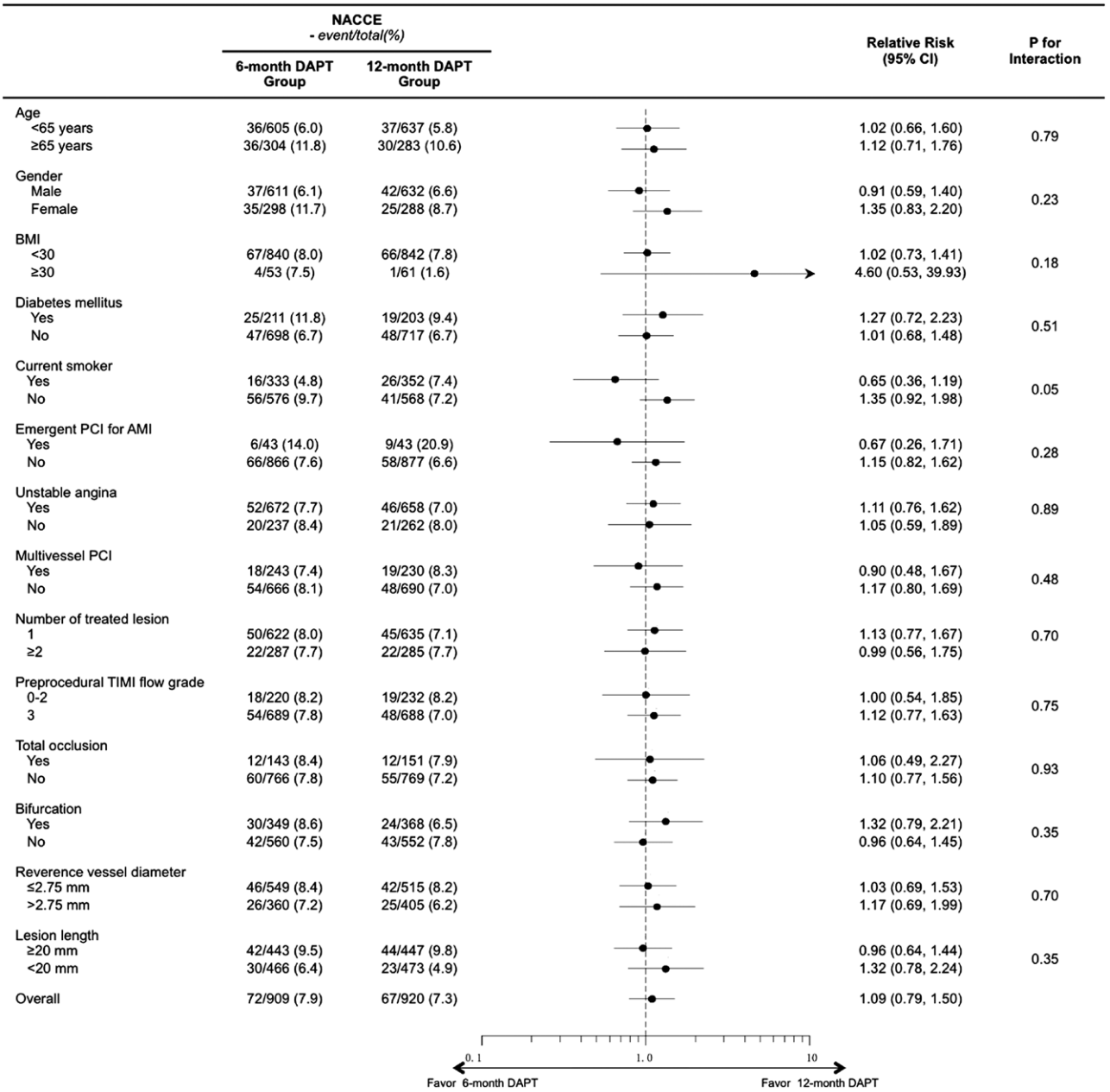

Figure 3. Subgroup analysis of net adverse clinical and cerebral events (NACCE) at 18 months. NACCE, a composite of all-cause death, all myocardial infarction, stroke, and major bleeding (Bleeding Academic Research Consortium type ≥3 bleeding). CI indicates confidence interval; DAPT, dual antiplatelet therapy; and PCI, percutaneous coronary intervention.

DAPT. Of course, those hypothesis need to be confirmed in future large trials.

Results from a recent meta analysis showing long-term DAPT is associated with increased mortality because of an increased risk of noncardiovascular mortality.[24] The mechanistic underpinnings of the greater risk of noncardiac mortality with extended DAPT remain unclear. In our study, there were numerically more bleeding events in the 12-month DAPT group than that in the 6-month DAPT group, which is consistent with results from a recent large study showing increased rate of moderate or severe bleeding with prolonged DAPT.[13] The lower rates of major bleeding with shorter DAPT compared with longer DAPT in the recent meta-analysis might partly explain the reduction in noncardiac mortality.[25,26] Finally, DES type has been shown to affect the benefit derived from prolonging DAPT[26]; this study extends this clinical impression to the modern BP-DES types.

This study has some limitations. Because of the relatively low event rates observed and small sample size, our study might not have been powered to detect small differences in bleeding events after 6 months, and the sensitivity analysis was not powered for any subgroup. Second, we randomized patients at the time of the index procedure and not 6 months later. Approximately 4% of NACCE and TLF events occurred during the periprocedural period. However, this is a debatable limitation because randomizing only event-free patients at 6-month post-PCI may, in turn, bias selection toward patients at lower risk for late adverse events. Third, new generation of antiplatelet drugs, such as ticagrelor or prasugrel, were not used in our trial. Fourth, lack of placebo-controlled group resulted in DAPT protocol deviation of 3.4% patients; however, this is a rather low rate and the per-protocol analysis regrouping these patients with "as treated" principle were concordant to the results of the intention-to-treat analysis. Fifth, the evidence supporting the use of the Tivoli stent is limited to 1 study and, therefore, the results of the study cannot be extrapolated to other biodegradable polymer DES. Finally, current socioeconomic reasons underlie the preference of most Chinese patients with stable coronary artery disease to receive medical over invasive therapy, which was the main reason for low rate of inclusion (14.7%) of patients who had stable coronary disease in this study.

Conclusions

The present dedicated I-LOVE-IT 2 DAPT duration randomized substudy demonstrated that 6-month DAPT seemed noninferior to 12-month DAPT in patients who underwent PCI with a new-generation BP-SES implantation.

Sources of Funding

The study was sponsored by Essen Technology (Beijing, China), and it was also supported by National Key Technology R&D Program in the 12th Five-Year Plan of China (2011BAI11B07) and Key Project of National 12th Five-Year Research Program of China (2012ZX093016–002).

Disclosures

None.

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