Efficacy and safety of a biodegradable polymer sirolimus-eluting stent in primary percutaneous coronary intervention: a randomized controlled trial

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Abstract

Introduction: With long-term follow-up, whether biodegradable polymer drug-eluting stents (DES) is efficient and safe in primary percutaneous coronary intervention (PCI) remains a controversial issue. This study aims to assess the long-term efficacy and safety of DES in PCI for ST-segment elevation myocardial infarction (STEMI).

Material and methods: A prospective, randomized single-blind study with 3-year follow-up was performed to compare biodegradable polymer DES with durable polymer DES in 332 STEMI patients treated with primary PCI. The primary end point was major adverse cardiac events (MACE) at 3 years after the procedure, defined as the composite of cardiac death, recurrent infarction, and target vessel revascularization. The secondary end points included in-segment late luminal loss (LLL) and binary restenosis at 9 months and cumulative stent thrombosis (ST) event rates up to 3 years.

Results: The rate of the primary end points and the secondary end points including major adverse cardiac events, in-segment late luminal loss, binary restenosis, and cumulative thrombotic event rates were comparable between biodegradable polymer DES and durable polymer DES in these 332 STEMI patients treated with primary PCI at 3 years.

Conclusions: Biodegradable polymer DES has similar efficacy and safety profiles at 3 years compared with durable polymer DES in STEMI patients treated with primary PCI.

Key words: biodegradable polymer drug-eluting stents, percutaneous coronary intervention.

Introduction

Drug-eluting stents (DES) have been proven to be effective in primary percutaneous coronary intervention (PCI) in the treatment of patients with ST-segment elevation myocardial infarction (STEMI) by several randomized trials with mid-term follow-up [1–3]. The major safety concern about DES is the infrequent but catastrophic complications such as acute thrombosis hours or days after myocardial infarction, late stent thrombosis (LST) and very late stent thrombosis (VLST) [4]. Furthermore, events of LST are more frequently reported after primary stenting than after elective stenting [5]. However, with long-term follow-up, whether DES is efficient and safe in PCI remains a controversial issue [6–8].

The durable polymer surface coatings used in the first generation of DES potentially contribute to persistent inflammation and impaired endothelialization, and thereby lead to LST [9]. The new generation of DES coated with biodegradable polymer, with only a bare-metal platform remaining after drug delivery and subsequent complete polymer degradation, might theoretically help reduce the risk of LST. Efficacy of biodegradable polymer DES has been reported [10, 11].

This study aims to evaluate the long-term efficacy and safety of the biodegradable polymer DES (Excel, JW Medical System, Weihai, China) in primary PCI for treatment of STEMI patients, based on a 3-year clinical follow-up, compared with the durable polymer DES (Cypher Select, Cordis Corporation, Miami Lakes, Fla).

Material and methods

This study was approved by the Local Human Research Ethics Board in Beijing, China, and all participants gave written informed consent before being enrolled in the study.

Study design

This is a single-center, open-labeled, randomized prospective study. This study aims to evaluate the clinical and angiographic results in STEMI patients undergoing primary PCI with biodegradable polymer coated DES. Primary PCI was performed by 6 experienced operators during May 2007 to Dec 2008.

Study population and randomization

Consecutive patients were included if they were > 18 years of age, had symptoms of acute MI for ≥ 30 min but ≤ 12 h, and had the electrocardiogram showing ST-segment elevation (at least 1 mm in two or more standard leads or at least 2 mm in two or more contiguous precordial leads) or left bundle-branch block. Exclusion criteria were: 1) cardiogenic shock (systolic blood pressure < 80 mm Hg for > 30 min or need for intravenous pressors or intra-aortic balloon counterpulsation); 2) left main coronary artery or graft disease; 3) previous PCI or coronary artery bypass grafting of the infarct-related artery; 4) thrombolytic therapy for the index infarction; 5) target vessel reference diameter < 2.5 mm or > 3.5 mm; 6) a history of bleeding diathesis, leukopenia, thrombocytopenia, or severe hepatic or renal dysfunction; 7) contraindication to the use of aspirin, clopidogrel, heparin, or tirofiban; 8) participation in another study; or 9) life expectancy < 12 months.

Once blood flow was established (spontaneously or by balloon inflation), the operator determined whether the patient qualified for randomization. Using the Statistics Analysis System (SAS) software, a randomization table was generated with a block randomization procedure provided by an independent statistician who was unaware of the study subjects. Each subject received a number within a concealed envelope indicating the randomization assignment. The study employed a two-group design, including a biodegradable polymer DES group and a durable polymer DES group. According to the sample size equation $n = (\sigma/\Delta)^2 \times (Z_{\alpha/2} + Z_{\beta})^2$, $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$, $\beta = 0.1$, $Z_{\beta} = 1.65$, the sample size was determined considering the primary endpoint in this study. Combined with our previous drop-out rate, 338 individuals were equally assigned to the biodegradable polymer DES group and the durable polymer DES group. The statistical power level was set to 0.80, and the statistical significance level was set at 0.05.

Device description

The Excel stent is a sirolimus-eluting stent (SES) coated with a biodegradable polylactic acid (PLA) polymer and its feature has been described elsewhere [12]. The PLA polymer resorption is complete in the porcine model by 6 to 9 months, thus leaving only the bare-metal platform in perpetuity. Its sustained efficacy and safety have been documented [13].

Catheterization and study procedure

Before the procedure, all patients received 300 mg of aspirin and 300 to 600 mg of clopidogrel. Administration of both aspirin and clopidogrel was started in the same phase in all patients in the catheterization lab. The procedure was performed through the femoral or radial artery at the operator's discretion using standard techniques. Lesions were treated according to current interventional practice and stent size and length selection was based on visual estimation. If more than 1 stent was required, the same type of stent was used. Direct stenting was allowed and dilatation after stent placement was at the operator's discretion. Heparin was administered throughout the procedure in order to maintain an activated clotting time of 250 s or longer. Administration of platelet glycoprotein IIb/IIIa-receptor inhibitors was left to the investigator's discretion.

Follow-up

Clinical follow-up was performed at 30 days, 3 months, 6 months, and then every 6 months for a total of 3 years after the procedure. Aspirin (75 to 100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for at least 12 months. The duration of treatment of both drugs was comparable in two study groups. Patients were treated with

β-blocking agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin II blockers according to the judgment of the patient's physician. Follow-up angiography at 9 months was recommended to all patients.

Quantitative coronary angiography (QCA) analysis

Technicians unaware of treatment assignment analyzed all angiographic images using an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems). Late luminal loss (LLL) was calculated as the difference between the minimum luminal diameter immediately after the procedure and at 9-month angiographic follow-up. Binary restenosis was defined as ≥ 50% reduction of the initial lumen diameter in the target lesion inside or at the proximal and distal 5 mm of the stent at 9 months. Flow in the infarct-related vessel was graded according to the Thrombolysis in Myocardial Infarction (TIMI) trial classification.

End points

The primary end point of this study was major adverse cardiac events (MACE), defined as the composite of cardiac death, recurrent infarction, and target vessel revascularization at 3 years. The clinical events committee whose members were blinded to the assigned stent type reviewed and adjudicated all serious clinical events, including stent thrombosis. Target-vessel revascularization was defined as repeated PCI or bypass grafting of the target vessel, driven by anginal symptoms and/or functional ischemia with ≥ 50% stenosis of the reference luminal diameter or ≥ 70% diameter stenosis irrespective of the presence or absence of ischemic signs or symptoms. The definition of cardiac death included death from acute myocardial infarction, cardiac perforation, or pericardial tamponade; an arrhythmia or conduction abnormality; complications of the interventional procedure at baseline; stroke (including bleeding) within 30 days after the procedure or in connection with the procedure; and all deaths that could not be clearly attributed to a non-cardiac cause. Recurrent infarction was defined as the recurrence of clinical symptoms or the occurrence of electrocardiographic changes accompanied by a new elevation in levels of creatine kinase, creatine kinase MB enzyme, or both. The level of creatine kinase required for the diagnosis of reinfarction depended on the interval from the index infarction: the creatine kinase level had to be at least 1.5 times the previous value if new symptoms appeared within 48 h and at least 3 times the upper limit of normal if new symptoms appeared after 48 h [14, 15].

The secondary end points included in-segment late luminal loss and binary restenosis at 9 months angiographic follow-up, and cumulative thrombotic event rates up to 3 years after the index procedure. Stent thrombosis (ST) was classified as definite, probable, or possible according to the Academic Research Consortium (ARC) definition [16], further subdivided into early (0 to 30 days), late (> 30 days to 1 year), and very late (> 1 year) stent thrombosis.

Statistical analysis

All analyses were conducted according to the intention-to-treat principle. Continuous data were expressed as mean ± SD or as median (interquartile range); dichotomous data were presented as numbers and percentages. All continuous variables were compared with Student's *t* test or, in the case of a non-Gaussian distribution, with a nonparametric test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test as appropriate. Event-free survival curves were generated by the Kaplan-Meier method, and survival between groups was compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by the Cox proportional hazards regression model. A 2-sided p value < 0.05 was considered significant for all tests. All analyses were conducted using SPSS version 16.0 (SPSS, Inc., Chicago, Illinois).

Results

Patients

A total of 338 STEMI patients were enrolled in this study. Five patients were subsequently excluded because the assigned study stent was not available and another one was excluded because of the inability to cross the lesion with an Excel stent (Figure 1). Data of 332 patients (168 assigned to the Cypher group and 164 assigned to the Excel group) were analyzed finally. The 2 groups were well matched (Table I) though a higher percentage of patients in the Excel group had hypercholesterolemia (46.3% vs. 32.7%, $p = 0.013$). In addition, there were more patients with triple-vessel disease (though not significant) in the Cypher group, which might have influenced the results.

Procedural results

Procedural characteristics are summarized in Table II. The rate of procedural success according to angiographic criteria (< 30% residual stenosis, TIMI flow grade 3) was similar between the two groups: 95.1% (Excel) and 94.0% (Cypher) ($p = 0.810$). Total stent length and stent diameter also did not statistically differ between the two groups.

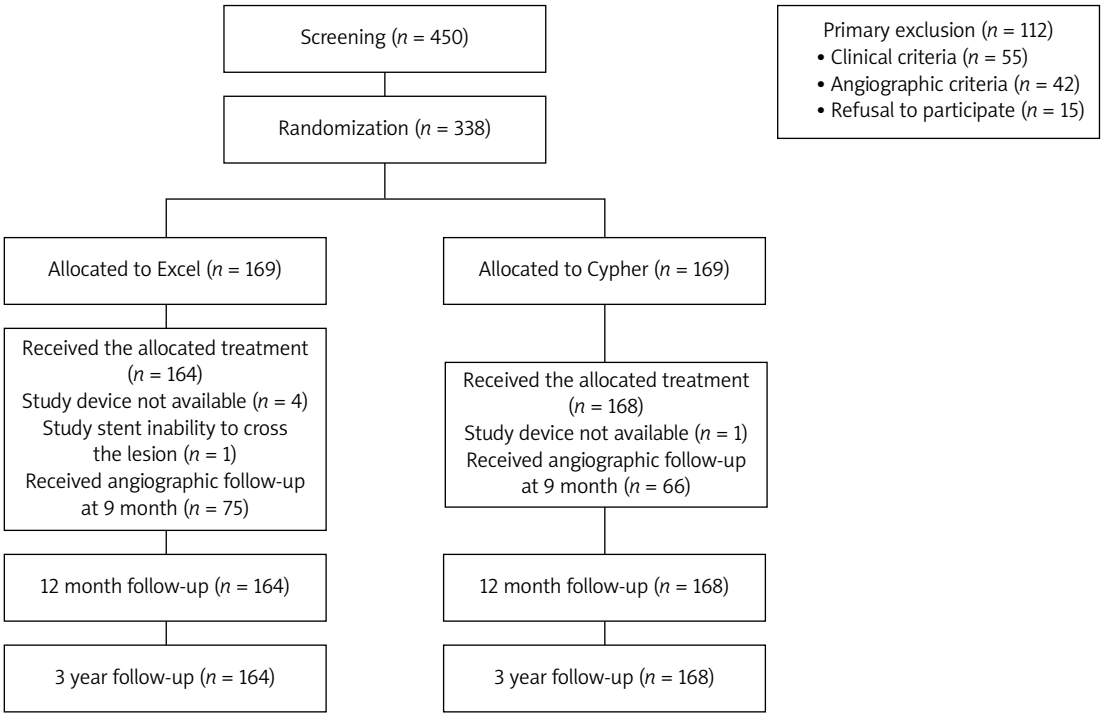

Figure 1. Flow of participants through the trial

Table I. Clinical characteristic of patients

Parameter	Excel (*n* = 164)	Cypher (*n* = 168)	Value of *p*
Age [years]	59.95 ±11.19	59.77 ±11.79	0.892
Male gender	122 (74.4)	130 (77.4)	0.608
Hypertension	95 (57.9)	87 (51.8)	0.272
Hypercholesterolemia	76 (46.3)	55 (32.7)	0.013
Diabetes mellitus	43 (26.2)	55 (32.7)	0.229
Current smoker	108 (65.9)	102 (60.7)	0.363
Family history of CAD	22 (13.4)	26 (15.5)	0.641
Prior myocardial infarction	9 (5.5)	7 (4.2)	0.617
Prior CABG	2 (1.2)	0	0.243
Prior PCI	5 (3.0)	4 (2.4)	0.748
Time from symptom onset to balloon	6.5 ±6.4	6.7 ±6.3	0.425
Killip class			
I	110 (67.1)	122 (72.6)	0.284
II	42 (25.6)	36 (21.4)	0.437
III	12 (7.3)	10 (6.0)	0.664
Extent of coronary disease			0.247
Single-vessel disease	41 (25.0)	33 (19.6)	0.291
Double-vessel disease	53 (32.3)	46 (27.4)	0.339
Triple-vessel disease	70 (42.7)	89 (53.0)	0.063
Infarct-related vessel			
Left anterior descending artery	79 (48.2)	72 (42.9)	0.378
Left circumflex artery	27 (16.5)	25 (14.9)	0.763
Right coronary artery	58 (35.3)	71 (42.2)	0.216
LVEF(%)	46.9 ±7.2	45.5 ±6.9	0.651

Table II. Procedural characteristics

Variable	Excel (n = 164)	Cypher (n = 168)	Value of p
Procedural success per patient	95.1%	94.0%	0.810
No. of lesions treated	167	172	
No. of stents implanted	1.30 ±0.53	1.34 ±0.56	0.571
Stent length [mm]	22.97 ±11.85	24.25 ±10. 21	0.383
Stent diameter [mm]	2.94 ±0.35	3.01 ±0.37	0.456
Quantitative coronary analysis			
Before procedure			
TIMI flow			0.758
Grade 0 or 1	117 (71.3)	120 (71.4)	
Grade 2	29 (17.7)	26 (15.0)	
Grade 3	18 (11.0)	22 (13.4)	
Diameter of reference vessel	2.84 ±0.56	2.93 ±0.54	0.325
Minimal luminal diameter	0.24 ±0.39	0.27 ±0.35	0.614
Stenosis, % of luminal diameter	92.2 ±12.6	91.0 ±12.3	0.702
Immediately after procedure			
TIMI flow			0.638
Grade 0 or 1	2 (1.2)	1 (0.6)	
Grade 2	6 (3.7)	9 (5.4)	
Grade 3	156 (95.1)	158 (94.0)	
Diameter of reference vessel	2.98 ±0.52	3.04 ±0.49	0.479
Minimal luminal diameter	2.68 ±0.38	2.75 ±0.40	0.272
Stenosis, % of luminal diameter	10.2 ±0.67	9.6 ±0.71	0.194
Acute gain	2.45 ±0.51	2.49 ±0.46	0.648

Angiographic results

At 9 months after the procedure, 75 (45.7%) patients in the Excel group and 69 (41.1%) patients in the Cypher group received follow-up angiography. The median time to angiographic follow-up was 265 days (248 to 292 days) in the Excel group and 274 days (261 to 288 days) in the Cypher group (p = 0.562). The rates of restenosis in in-stent (4.0% vs. 2.9%, respectively; p = 0.671) and in in-segment (6.7% vs. 5.8%, respectively; p = 0.738) were comparable between the Excel group and Cypher group. There were no significant differences in LLL both in in-stent (0.16 ±0.40 mm vs. 0.14 ±0.37 mm, respectively; p = 0.483) and in in-segment (0.19 ±0.44 mm vs. 0.18 ±0.39 mm, respectively; p = 0.519) between the two groups (Table III).

Clinical events

In-hospital adverse events were infrequent, with no significant difference between groups (Table IV). In-hospital death occurred in 1 Excel patient and 3 Cypher patients (0.6% vs. 1.8%, respectively; p = 0.623). One patient (0.6%) in the Cypher group had a reinfarction due to angiographically documented

Table III. Angiographic results at 9-month follow-up

Variable	Excel (n = 75)	Cypher (n = 69)	Value of p
Late luminal loss, mean ±SD [mm]			
In stent	0.16 ±0.40	0.14 ±0.37	0.483
In segment	0.19 ±0.44	0.18 ±0.39	0.519
Angiographic restenosis, n (%)			
In stent	3 (4.0)	2 (2.9)	0.671
In segment	5 (6.7)	4 (5.8)	0.738

Table IV. Clinical outcomes at 1-year and 3-year follow-up

Outcomes	Excel (n = 164)	Cypher (n = 168)	Value of p
At hospital discharge			
Death	1 (0.6)	3 (1.8)	0.623
Cardiac	1 (0.6)	2 (1.2)	1.000
Noncardiac	0	1 (0.6)	1.000
Reinfarction	1 (0.6)	1 (0.6)	1.000
TLR	1 (0.6)	1 (0.6)	1.000
TVR	1 (0.6)	1 (0.6)	1.000
MACEs	2 (1.2)	3 (2.4)	1.000
At 1 year			
Death	3 (1.8)	5 (3.0)	0.723
Cardiac	3 (1.8)	4 (2.4)	1.000
Noncardiac	0	1 (0.6)	1.000
Reinfarction	3 (1.8)	4 (2.4)	1.000
TLR	4 (2.4)	6 (3.6)	0.750
TVR	6 (3.7)	7 (4.2)	1.000
MACEs	10 (6.1)	12 (7.1)	0.826
At 3 year			
Death	6 (3.7)	8 (4.8)	0.786
Cardiac	4 (2.4)	6 (3.6)	0.750
Noncardiac	2 (1.2)	2 (1.2)	1.000
Reinfarction	6 (3.7)	9 (5.4)	0.599
TLR	8 (4.9)	10 (0.6)	0.810
TVR	10 (6.1)	11 (6.5)	1.000
MACEs	17 (10.4)	20 (11.9)	0.728
Stent thrombosis	5 (3.0)	8 (4.8)	0.574
Definite	2 (1.2)	4 (1.8)	0.685
Probable	2 (1.2)	2 (1.8)	1.000
Possible	1 (0.6)	2 (1.2)	1.000
Early	2 (1.2)	3 (1.8)	1.000
Late	2 (1.2)	1 (0.6)	0.619
Very Late	1 (0.6)	4 (2.4)	0.371

stent thrombosis. Clinical follow-up was complete for all patients over 3-year duration. There was no significant difference between the Excel group and the Cypher group in the rate of death, recurrent myocardial infarction, target vessel revascularization (TVR), MACE and ST (6.1% vs. 6.5%, respectively; p = 1.000) at 3-year follow-up (Table IV, Figure 2). The survival rate free from MACE was 89.6% and 88.1% in Excel and Cypher groups at 3 years (p = 0.728, HR 0.772, 95% CI: 0.458–1.337). The 3-year cumulative incidence of ST was 3.0% and 4.8% in Excel and Cypher groups (p = 0.574, HR 0.485, 95% CI: 0.374–0.962) and was also similar at different time intervals (early, late, and very late) between 2 groups (Table IV).

Discussion

The catastrophic event of LST occurs steadily at an annual rate of 0.4% to 0.6% for at least up to 4 years after DES implantation [4]. Although the mechanisms of LST are multifactorial and have not yet been clarified, the durable polymers used in first-generation DES, associated with persistent localized vascular inflammation, delayed endothelialization, and thrombogenic reactions, seem to play an important role. Therefore, there is growing interest in developing new generation DES with biodegradable polymers, which may overcome this potential shortcoming of durable polymer DES.

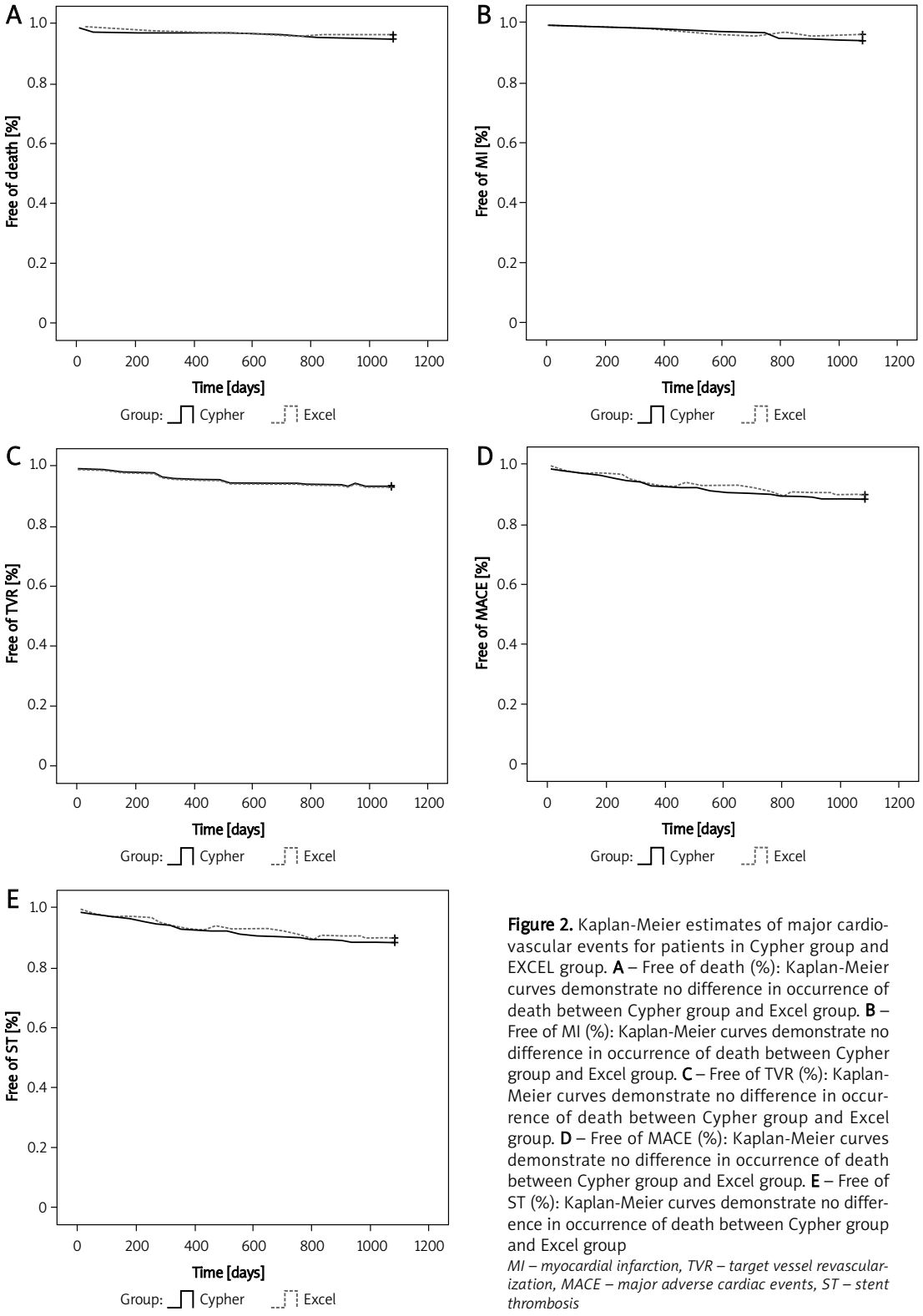

Figure 2. Kaplan-Meier estimates of major cardiovascular events for patients in Cypher group and EXCEL group. **A** – Free of death (%): Kaplan-Meier curves demonstrate no difference in occurrence of death between Cypher group and Excel group. **B** – Free of MI (%): Kaplan-Meier curves demonstrate no difference in occurrence of death between Cypher group and Excel group. **C** – Free of TVR (%): Kaplan-Meier curves demonstrate no difference in occurrence of death between Cypher group and Excel group. **D** – Free of MACE (%): Kaplan-Meier curves demonstrate no difference in occurrence of death between Cypher group and Excel group. **E** – Free of ST (%): Kaplan-Meier curves demonstrate no difference in occurrence of death between Cypher group and Excel group

MI – myocardial infarction, TVR – target vessel revascularization, MACE – major adverse cardiac events, ST – stent thrombosis

To the best of our knowledge, this is the first randomized prospective study evaluating the efficacy and safety of the biodegradable polymer SES in STEMI patients undergoing primary angioplasty with a long-term follow-up (3 years). The Excel stent in the study is a new generation SES coated with a biodegradable polymer (PLA). In this single-center study for STEMI patients treated with primary PCI, Excel showed competitive effectiveness in clinical events in 3 years and showed similar angiographic LLL and restenosis rate at 9 months compared with Cypher Select.

A bioabsorbable polymer paclitaxel-eluting stent (PES) was demonstrated to have promising clinical efficacy and safety at 6 months in the STELLIUM I study [17], while in the COSTAR II study, another absorbable polymer PES showed higher risk of binary stenosis and TVR [18]. Long-term follow-up of ISAR-TEST-3 and ISAR-TEST-4 trials showed non-inferiority of biodegradable polymer SES in efficacy compared with durable polymer SES [10, 11]. Angiographic outcomes of the ISAR-TEST-4 trial at 6–8 months showed similar LLL and restenosis between the two types [11]. In a multicentre study, Biolimus-eluting stent (BES) with biodegradable polymer displayed non-inferiority in overall cardiac event rates compared with durable polymer SES [19]. To date, most studies have shown that biodegradable polymer DES were non-inferior to permanent polymer DES in efficacy [10, 11, 18, 19].

Although biodegradable polymer DES might theoretically act as a bare metal stent (BMS) after drug delivery and polymer degradation and potentially decrease the occurrence of LST, current studies have not yet confirmed the superiority of biodegradable polymer over durable polymer DES in ST events, even with long-term follow-up. Biodegradable polymer and permanent polymer SES were associated with similar rates of ST at 2 years in the ISAR-TEST 3 trial and at 3 years in the ISAR-TEST 4 trial [10, 11]. During 4-year follow-up of the LEADERS trial [20], biodegradable polymer BES showed a comparable overall ST rate to durable polymer SES. However, in the LEADERS trial during 1–4 years after stent implantation, biodegradable polymer BES showed a significantly lower risk of very late definite and very late definite/probable ST compared with durable polymer SES, with the rate of very late definite ST as 0.12% per year vs. 0.6% per year respectively [21]. A recent pooled analysis of the ISAR-TEST 3, ISAR-TEST 4 and LEADERS trials demonstrated that biodegradable polymer DES reduced the risk of ST at 4 years, driven by lower risk of VLST [22]. A systematic review and meta-analysis of 13 randomized trials with 7,352 patients and 18 registry studies with 26,521 patients has demonstrated that the use of first generation DES in STEMI patients appears safe and efficacious, without an increase in ST within 2 years compared to BMS [23]. In the present study, the Excel group displayed a similar rate of ST compared to Cypher. This might be due to the low rate of ST and the small sample size of the present study.

Another appealing advantage of biodegradable polymer DES is the potential for shortening dual antiplatelet therapy (DAPT) duration. Current guidelines recommend that DAPT should be given for at least 12 months following DES placement unless patients are at high risk for bleeding. Focusing on the DAPT regime after new generation DES placement, some studies have shown that 6-month DAPT would be safe in patients treated with zotarolimus-eluting or everolimus-eluting stents [24, 25]. The CREAT registry reported that with 6 months (mean duration 199.8 ±52.7 days) of DAPT, Excel had sustained clinical safety to 3 years. But considering the life-threatening complication of LST, one must cautiously shorten the DAPT period after implantation of DES. According to the recommendation of current guidelines, we advocated 12-month DAPT in this study after STEMI in patients receiving either biodegradable polymer DES or permanent polymer DES, with mean duration of DAPT as 389.6 ±67.9 days in Excel patients and 394.8 ±71.4 days in Cypher patients. At 12 months, 83.2% (134/161) of Excel patients and 80.4% (131/163) of Cypher patients discontinued clopidogrel. It will be promising if a biodegradable polymer DES can act safely enough with less dependency on DAPT. As it may be device-specific, optimal duration of DAPT after biodegradable polymer DES placement remains to be further clarified.

Several potential limitations of this study should be highlighted. First, this is a relatively small sample in a single-center study. As the occurrence rate of late and very late in-stent thrombosis is low, the study is largely underpowered to analyze these types of very rare events. A larger, multicenter study is highly needed to clarify this point. Second, an angiographic primary end-point would be better for this number of patients with for example OCT control of endothelialization. However, the angiography rate during the follow-up stage is low. For example, follow-up angiography at 9 months was recommended to all patients. However, less than 50% of patients underwent angiography. Nevertheless, considering the results from this study and also the most recent study, the COMFORTABLE AMI randomized trial, which showed that the use of Biolimus-eluting stents with a biodegradable polymer could result in a lower rate of the composite of major adverse cardiac events at 1 year among patients with STEMI undergoing primary PCI [26], biodegradable polymer DES is recommended for STEMI patients undergoing primary PCI.

In conclusion, biodegradable polymer DES has similar efficacy and safety profiles at 3 years compared with durable polymer DES in STEMI patients treated with primary PCI.

Acknowledgments

Qiang Li and Zichuan Tong contributed equally to this work.

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