Comparison of the Efficacy and Safety of *Zotarolimus*-, *Sirolimus*-, and *Paclitaxel*-Eluting Stents in Patients With ST-Elevation Myocardial Infarction

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Drug-eluting stents (DESs) are increasingly used for treatment of acute ST-segment elevation myocardial infarction (STEMI), but there are few comparisons of outcomes of various types of DES. We compared the efficacy and safety of zotarolimus-eluting stents (ZESs), sirolimus-eluting stents (SESs), and paclitaxel-eluting stents (PESs) in primary intervention for STEMI. This multicenter, prospectively randomized ZEST-AMI trial included 328 patients at 12 medical centers who were randomly assigned to ZES (n = 108), SES (n = 110), or PES (n = 110) deployment. The primary end point was major adverse cardiac events (death, MI, and ischemia-driven target vessel revascularization) at 12 months. Secondary end points included the individual components of the primary end point, late loss, angiographic restenosis, and stent thrombosis. Baseline clinical and angiographic characteristics were well matched. In-segment late loss (0.28 ± 0.42 vs 0.46 ± 0.48 vs 0.47 ± 0.50 mm, respectively, p = 0.029) and restenosis rate (2.7% vs 15.9% vs 12.3%, respectively, p = 0.027) at 8 months were lowest in the SES group compared to the ZES and PES groups. At 12 months, cumulative incidence rates of primary end points in the ZES, SES, and PES groups were 11.3%, 8.2%, and 8.2%, respectively (p = 0.834). There were 2 acute (in the SES group) and 5 subacute (2 in the SES group and 3 in the PES group) stent thromboses. Incidence of death, recurrent MI, or ischemia-driven target vessel revascularization did not differ among the 3 groups. In conclusion, despite the difference in restenosis rate, the efficacy and safety of the 3 different DESs showed similar, acceptable results in the treatment of STEMI. **(Am J Cardiol 2009;104:1370–1376)**

Primary angioplasty has become the standard of care for acute ST-segment elevation myocardial infarction (STEMI); however, its long-term success is limited by the occurrence of restenosis.[1,2] The introduction of drug-eluting stents (DESs) has greatly alleviated this problem,[3] and their use in coronary intervention has markedly increased. DESs (Cypher and Taxus) are considered more effective and equally safe compared to bare metal stents for on-label use.[4–6] Despite debates over the safety of off-label use,[7–10] the Cypher and Taxus DESs seem to be superior to bare metal stents in improving 1-year event-free survival in patients with STEMI.[11–21] The zotarolimus-eluting stent (ZES; Endeavor) is a second-generation DES with an excellent safety and efficacy profile; these stents contain zotarolimus, a low-profile cobalt alloy stent, and a biocompatible phosphorylcholine polymer. The Endeavor stent has been shown to decrease the need for repeat revascularization compared to bare metal stents, but there were no differences in the incidence of death or MI between these 2 stent types.[22–25] Although new DESs are increasingly used for the treatment of patients with STEMI, there have been few direct comparisons of outcomes among the currently approved DESs in these patients.[26] We therefore compared the efficacy and safety of ZESs, sirolimus-eluting stents (SESs), and paclitaxel-eluting stents (PESs) as primary coronary intervention for STEMI.

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Table 1
Clinical characteristics

Characteristics	ZES (n = 108)	SES (n = 110)	PES (n = 110)	p Value
Age (years)	61.9 ± 11.0	57.8 ± 11.3	59.3 ± 11.2	0.025
Men/women	84 (77.8%)	95 (86.4%)	91 (82.7%)	0.249
Current smoker	56 (51.9%)	62 (56.4%)	68 (61.8%)	0.331
Diabetes mellitus	30 (27.8%)	29 (26.4%)	26 (23.6%)	0.777
Hypertension	52 (48.1%)	42 (38.2%)	51 (53.6%)	0.066
Total cholesterol (>200 mg/dl)	52 (48.1%)	45 (40.9%)	51 (46.4%)	0.534
Ejection fraction (%)	50.9 ± 10.3	51.9 ± 10.3	49.7 ± 10.3	0.39
Pain to admission (h)	3.48 ± 3.48	3.27 ± 2.93	3.14 ± 2.79	0.726
Admission to angioplasty (h)	1.51 ± 1.37	1.45 ± 1.32	1.28 ± 0.98	0.361
Pain to angioplasty (h)	5.04 ± 3.99	4.80 ± 3.32	4.42 ± 3.02	0.427
Anterior wall myocardial infarction	52 (48.1%)	50 (45.5%)	50 (45.5%)	0.900
Previous coronary angioplasty	7 (6.5%)	1 (0.9%)	2 (1.8%)	0.063
Glycoprotein IIb/IIIa inhibitor use	20 (18.5%)	23 (20.9%)	22 (20.0%)	0.905
Medications at discharge				
Angiotensin-converting enzyme inhibitor	87 (80.6%)	87 (79.1)	74 (67.3%)	0.043
β blocker	79 (73.1%)	86 (78.2%)	79 (72.5%)	0.570
Calcium antagonists	17 (15.7%)	21 (19.1%)	28 (25.7%)	0.178
Statin	92 (85.2%)	97 (88.2%)	93 (85.3%)	0.768

Methods

This prospective single-blind, randomized multicenter trial—the Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent versus Paclitaxel-Eluting Stent for Acute Myocardial Infarction Patients (ZEST-AMI) trial—was performed at 12 centers in Korea (http://ClinicalTrials.gov, NCT00422565). Patients were eligible for the trial if they had chest pain >30 minutes, presentation within 12 hours after onset of symptoms, and ST-segment elevation (>1 mm in ≥2 standard leads or >2 mm in ≥2 contiguous precordial leads). Exclusion criteria included previous administration of fibrinolytic agents, previously documented left ventricular ejection fraction <30%, concomitant left main coronary artery disease, previous MI, cardiogenic shock, and an estimated life expectancy <12 months. The trial protocol was approved by the ethics committee or institutional review board at each local site, and all participants provided written informed consent.

Patients meeting all eligibility criteria were randomly assigned to the 3 groups in a 1:1:1 ratio immediately after coronary angiography, if the target lesion was suitable for angioplasty. Randomization was stratified according to participating site and concealed using a central interactive Web response service. Patients, but not investigators, were unaware of the treatment assignment.

Stent implantation with Endeavor stents (Medtronic, Minneapolis, Minnesota), Cypher stents (Cordis Corporation, Miami Lakes, Florida), or Taxus Liberte stents (Boston Scientific Corporation, Natick, Massachusetts) was performed according to standard techniques. Patients were pretreated with aspirin (300 mg) and clopidogrel (600 mg). During the procedure, patients received a bolus of heparin 100 U/kg, with a repeat bolus of 2,000 U to maintain an activated clotting time ≥300 seconds. Patients were discharged when clinically stable as per local practice.

Aspirin (100 to 200 mg/day) was given indefinitely and clopidogrel (75 mg/day) for ≥12 months. Patients were evaluated at time of hospital discharge and at clinic visits at 1, 4, 9, and 12 months. Routine angiographic follow-up was recommended at 8 months. All demographic, clinical, and procedural characteristics were prospectively entered into the Web-based database, and all adverse cardiac events, including death, recurrent MI, repeat revascularization, and stent thrombosis, were recorded.

Coronary angiograms were sent to the core laboratory at the Cardiovascular Research Foundation (Seoul, Korea) and were independently analyzed by experienced angiographers unaware of treatment assignment and study goal. Percent diameter stenosis, minimal lumen diameter, and reference diameter using an on-line quantitative angiographic analysis system (CASS 2.0, Pie Medical Imaging, Maastricht, The Netherlands) were measured before dilation, after the stenting procedure, and at follow-up. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using a guiding catheter to calibrate magnification. Single matched views with the worst diameter stenosis were compared.

The primary end point was the occurrence of major adverse cardiac events defined as the composite of death (all-cause), recurrent MI, and ischemia-driven target vessel revascularization at 12 months. Secondary end points included individual components of the composite primary end point, late luminal loss, angiographic restenosis, and stent thrombosis. Deaths that could not be classified were considered cardiac. Recurrent MI was defined as recurrence of clinical symptoms or occurrence of electrocardiographic changes accompanied by a new increase of creatine kinase-MB to >3 times the upper limit of normal. For patients who maintained increased levels of cardiac enzymes, the creatine kinase-MB level had to be ≥1.5 times the previous measurement. Ischemia-driven target vessel revascularization was defined as diameter stenosis ≥70% by quantitative coronary angiography or 50% to approximately 70% diameter stenosis in the presence of ischemic symp-

Table 2
Angiographic and procedural characteristics

Variables	ZES (n = 108)	SES (n = 110)	PES (n = 110)	p Value
Infarct-related coronary artery				0.059
Left anterior descending	52 (48.1%)	50 (45.5%)	50 (45.5%)	
Left circumflex	5 (4.6%)	14 (12.7%)	19 (17.3%)	
Right	51 (47.2%)	46 (41.8%)	41 (37.3%)	
Coronary ostial narrowing	14 (13.0%)	5 (4.5%)	10 (9.1%)	0.091
Bifurcation lesions	10 (9.4%)	13 (11.9%)	17 (15.7%)	0.369
No. of narrowed coronary arteries				0.055
1-vessel disease	63 (58.3%)	61 (55.5%)	56 (50.9%)	
2-vessel disease	21 (19.4%)	25 (22.7%)	39 (35.5%)	
3-vessel disease	24 (22.2%)	24 (21.8%)	15 (13.6%)	
Calcified lesion				0.873
None or mild	98 (95.1%)	102 (94.4%)	98 (92.5%)	
Moderate	2 (1.9%)	3 (2.8%)	5 (4.7%)	
Severe	3 (2.9%)	3 (2.8%)	3 (2.8%)	
Thrombus present	45 (41.7%)	38 (34.5%)	38 (34.5%)	0.454
Initial TIMI grade flow				0.730
0	65 (60.2%)	62 (56.4%)	65 (59.1%)	
1	8 (7.4%)	12 (10.9%)	13 (11.8%)	
2	14 (13.0%)	19 (17.3%)	18 (16.4%)	
3	21 (19.4%)	17 (15.5%)	14 (12.7%)	
Final TIMI grade flow after intervention				0.498
0	1 (1.0%)	0 (0%)	0 (0%)	
1	1 (1.0%)	0 (0%)	1 (0.9%)	
2	7 (6.7%)	14 (13.1%)	12 (11.2%)	
3	95 (91.3%)	93 (86.9%)	94 (87.9%)	
Angiographic collaterals (grade ≥2)	25 (24.3%)	81 (24.3%)	85 (20.6%)	0.758
Multivessel coronary intervention	19 (17.6%)	18 (16.4%)	22 (19.8%)	0.775
No. of treated coronary lesions per patients	1.20 ± 0.46	1.21 ± 0.54	1.23 ± 0.50	0.893
Stent size (mm)	3.26 ± 0.43	3.23 ± 0.32	3.27 ± 0.43	0.760
No. of stents per culprit lesion	1.33 ± 0.54	1.16 ± 0.39	1.22 ± 0.48	0.031
Total stent length (mm)	33.7 ± 15.7	30.0 ± 12.4	31.1 ± 13.7	0.130
Thrombectomy before PCI	5 (4.9%)	6 (5.7%)	5 (4.8%)	0.954
Direct stenting	6 (5.6%)	4 (3.6%)	6 (5.5%)	0.759
Maximal inflation pressure (atm)	14.39 ± 3.71	16.53 ± 3.44	14.76 ± 4.33	<0.001
Maximal device size (mm)	3.56 ± 0.47	3.63 ± 0.41	3.64 ± 0.45	0.466
Procedural success*	88 (81.5%)	89 (80.9%)	91 (82.7%)	0.938
Maximum creatine kinase-MB (U/L)	207.4 ± 190.9	221.2 ± 187.9	213.6 ± 165.9	0.870

PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.
* Defined as residual diameter stenosis <30% and final TIMI grade 3 flow.

toms or signs documented by functional stress testing. Stent thrombosis was classified by the Academic Research Consortium definition as definite (presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion), probable (unexplained deaths within 30 days after the procedure or acute MI involving the target vessel territory without angiographic confirmation), acute (<24 hours after procedure), subacute (1 day to 30 days after procedure), or late (>30 days after procedure). Procedural success was defined as residual diameter stenosis <30% and a final Thrombolysis In Myocardial Infarction grade 3 flow.

The clinical event committee independently reviewed and adjudicated all major clinical events without information on the treatment assignment of individual patients.

To calculate the sample size, we assumed anticipated major adverse cardiac event rates of 8.5% in the SES and PES groups, based on results of the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION)[11] and the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON)[12] trials, and 15.0% in the ZES group. We calculated 1,482 patients (494 patients in each group) using 80% statistical power and corrected alpha level of 0.025 (for primary comparison of SES vs ZES and PES vs ZES). Recruitment rate, however, was much slower than expected, and the planned enrollment of 1,482 patients was not feasible. Consequently, recruitment was closed for operational reasons before the required sample size was achieved.

All analyses were performed according to the intention-to-treat principle. Continuous variables were compared using analysis of variance or nonparametric Kruskal-Wallis test, as appropriate. Categorical variables were compared using chi-square test or Fisher's exact test. Cumulative incidence rates of the primary and secondary end points

Table 3
Quantitative coronary angiographic measurements

Variable	ZES (n = 108)	SES (n = 110)	PES (n = 110)	p Value
Patients at follow-up angiography	69 (63.9%)	73 (66.4%)	73 (66.4%)	0.906
Reference diameter (mm)	3.00 ± 0.45	2.98 ± 0.41	2.91 ± 0.43	0.373
Lesion length (mm)	29.88 ± 13.35	24.47 ± 11.41	26.99 ± 12.22	0.034
Stented length (mm)	33.55 ± 15.59	29.73 ± 12.28	30.79 ± 13.60	0.115
Minimal lumen diameter (mm)				
In-segment				
Before procedure	0.28 ± 0.44	0.25 ± 0.39	0.29 ± 0.43	0.724
After procedure	2.26 ± 0.51	2.36 ± 0.48	2.36 ± 0.47	0.210
At follow-up	1.79 ± 0.57	2.15 ± 0.47	1.91 ± 0.66	0.001
In-stent				
After procedure	2.58 ± 0.44	2.61 ± 0.38	2.62 ± 0.42	0.747
At follow-up	1.84 ± 0.61	2.42 ± 0.42	2.11 ± 0.63	<0.001
Diameter stenosis				
In-segment				
Before procedure	90.71 ± 14.33	91.73 ± 12.70	90.03 ± 14.33	0.665
After procedure	18.95 ± 9.94	17.18 ± 9.34	17.04 ± 9.84	0.287
At follow-up	37.64 ± 18.03	26.35 ± 13.48	33.44 ± 19.96	0.001
In-stent				
After procedure	10.39 ± 9.08	12.25 ± 7.49	11.96 ± 10.18	0.274
At follow-up	36.21 ± 19.74	19.51 ± 11.90	28.59 ± 19.31	<0.001
Acute gain (mm)				
In-segment	1.97 ± 0.65	2.12 ± 0.61	2.06 ± 0.61	0.240
In-stent	2.29 ± 0.61	2.37 ± 0.53	2.32 ± 0.59	0.648
Late loss (mm)				
In-segment	0.46 ± 0.48	0.28 ± 0.42	0.47 ± 0.50	0.029
In-stent	0.73 ± 0.53	0.25 ± 0.37	0.52 ± 0.57	<0.001
Proximal edge	0.23 ± 0.33	0.29 ± 0.40	0.40 ± 0.41	0.064
Distal edge	0.16 ± 0.28	0.16 ± 0.31	0.25 ± 0.38	0.172
Restenosis				
In-segment	11 (15.9%)	2 (2.7%)	9 (12.3%)	0.027
In-stent	11 (15.9%)	1 (1.4%)	7 (9.6%)	0.009
Proximal edge	2 (2.9%)	1 (1.4%)	2 (2.7%)	0.870
Distal edge	1 (1.4%)	0 (0%)	2 (2.7%)	0.540
Pattern of restenosis				
Focal/diffuse	8/3	1/1	6/3	>0.999

were estimated with the Kaplan-Meier method and compared among groups using log-rank tests. A 2-sided p value <0.05 was required for statistical significance.

Results

From September 2006 to September 2007, 328 patients with STEMI were enrolled and randomized to the ZES (n = 108), SES (n = 110), and PES (n = 110) groups. Baseline patient characteristics were well matched among the 3 groups except age, use of angiotensin-converting enzyme inhibitors, number of stents per lesion, or maximum inflation pressure (Tables 1 and 2). Mean patient age was 59.6 ± 11.2 years; 82.3% of patients were men, and 25.9% had diabetes mellitus. Mean time from onset of symptoms to first balloon inflation was 4.8 ± 3.5 hours, and mean interval from arrival at the hospital to inflation of the balloon catheter was 85.0 ± 74.3 minutes. Sizes of infarcts, estimated by peak value of creatine kinase-MB, were similar among the 3 groups. Mean stented length was 31.5 ± 14.0 mm, and mean number of stents implanted per lesion was 1.2 ± 0.5. Procedural success rate was 81.7%, and final Thrombolysis In Myocardial Infarction grade 3 flow was achieved in 94.2% of patients.

Quantitative angiographic data are listed in Table 3. Angiographic follow-up at 8 months was obtained for 215 of 314 patients without major clinical events before 8 months (68.5% of those eligible). Reference diameter and minimal luminal diameter at baseline were similar among the 3 groups. At follow-up, however, minimal lumen diameter was significantly larger in the SES group than in the ZES and PES groups (2.15 ± 0.47 vs 1.79 ± 0.57 vs 1.91 ± 0.66, respectively, p = 001). In-segment late loss was lower in the SES group than in the ZES and PES groups (0.28 ± 0.42 vs 0.46 ± 0.48 vs 0.47 ± 0.50, respectively, p = 0.029), as was the rate of angiographic restenosis (2.7% vs 15.9% vs 12.3%, respectively, p = 0.027; Figure 1).

Of the 328 patients, 322 (98.2%) completed 1-year clinical follow-up. At 30 days, cumulative incidences of major adverse cardiac events were 2.8% in the ZES group, 3.6% in the SES group, and 2.7% in the PES group (p = 0.99). There were 2 noncardiac deaths (1 from pneumonia and 1 from respiratory failure) in the ZES group and 2 cardiac deaths in the SES group (1 from fatal recurrent MI and 1

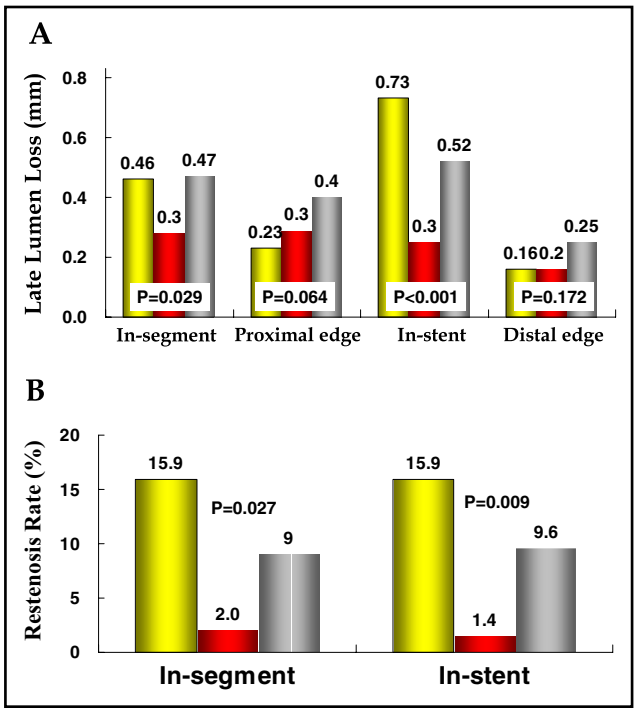

Figure 1. Late lumen loss *(A)* and binary restenosis *(B)* for the ZES *(yellow bars)*, SES *(red bars)*, and PES *(gray bars)* groups.

unexplained sudden cardiac arrest). Acute stent thrombosis occurred in 2 patients (1.8%) in the SES group, and subacute stent thrombosis occurred in 2 patients (1.8%) in the SES group (at 3 and 4 days after stenting) and in 3 patients (2.7%) in the PES group (at 3 and 4 days after stenting). There was no case of stent thrombosis in the ZES group.

At 12 months, cumulative incidences of the primary end point were 11.3% in the ZES group, 8.2% in the SES group, and 8.2% in the PES group ($p = 0.834$; Figure 2). After 30 days, there was 1 noncardiac death (cancer) in the ZES group and 2 (1 stroke and 1 mesenteric infarct) in the SES group. Late stent thrombosis did not occur in any patient. There were also no significant differences among the 3 groups in the incidence of death, recurrent MI, or ischemia-driven target vessel revascularization.

Discussion

The major findings of this study are as follows: (1) there was no difference in the overall rate of major adverse cardiac events at 12 months among the ZES, SES, and PES groups; (2) there was a nonsignificant trend in favor of ZESs in the rate of stent thrombosis; (3) SESs were associated with lower late loss and restenosis rates compared to ZESs or PESs; and (4) the rate of ischemia-driven target vessel revascularization was the same among the 3 DESs. Our results are thus in agreement with those of previous studies comparing different types of DESs in stable coronary artery disease, which found that late loss was significantly higher after ZES compared to SES implantation, but that, below a certain threshold level, this difference did not translate to an increase in repeat revascularization rate.[22–25] It is unclear, however, whether the increased rate of late loss after ZES implantation is beneficial in protecting against stent thrombosis in the setting of STEMI.

Due to its superiority to balloon angioplasty, stent implantation has become the preferred approach for treating STEMI.[1,2] Stent technology has continuously evolved over the years, and many interventionists are currently using DESs for patients with STEMI. However, concern remains over the use of DESs in this indication because patients with STEMI are thought to be at higher risk for stent thrombosis. Two large, randomized, controlled trials, TYPHOON and PASSION,[11,12] therefore investigated the safety and efficacy of DESs in STEMI. In the TYPHOON trial, SESs were associated with a significant decrease in the rate of target vessel revascularization compared to bare metal stents (5.6% vs 13.4%, respectively, $p < 0.001$), with no differences in rates of death or MI.[11] In the PASSION trial, however, there were no differences in 1-year major adverse cardiac event and target lesion revascularization rates (5.3% vs 7.8%, respectively, $p = 0.23$) between the PES and bare metal stent groups.[12] These results suggest that DESs can be used safely in the setting of primary angioplasty and are likely to decrease the need for repeated revascularization. The Global Registry of Acute Coronary Events (GRACE) registry data showed that patients with STEMI who received DESs were at greater than fourfold increased risk of dying compared to patients who received bare metal stents.[10] In contrast, recent meta-analysis and registry data showed that, although the risks of stent thrombosis, death, or recurrent MI were each similar for patients treated with DESs and bare metal stents, the risk of reintervention was significantly lower in those treated with DESs compared to bare metal stents.[17–21] These differences may be related to the limitations of an observational database. Taken together, however, these results indicate that DESs in patients with STEMI can significantly decrease revascularization procedures without additional risks of death or MI at 1 year.

SESs and PESs have been found to decrease the risk of restenosis compared to bare metal stents. Although SESs and PESs are very effective, SESs were found to have a somewhat greater benefit in restenosis rate. In the setting of STEMI, SES implantation resulted in a lower angiographic restenosis rate at 6 months compared to PES implantation, although there were no differences in major adverse cardiac event rates between the 2 stents. The ZES, a new type of DES based on a different type of biostable polymer, may improve arterial healing with less inflammation.[27,28] Several studies have shown that ZESs provide a consistent and sustained decrease in the need for repeat procedures compared to bare metal stents and maintain an excellent safety profile.[22–25] These findings, however, could not be extrapolated to patients with STEMI because of different clinical settings. To date, there have been no direct comparisons of these 3 DESs for this indication. Our study showed that SESs were the most efficacious in late loss and binary restenosis, but there were no differences in repeat revascularization rates among the 3 DESs. This may be due to a curvilinear relation between late loss and target lesion revascularization. Late loss of 0 to 1.0 mm lies on a relatively flat portion of the curve for revascularization, and late loss

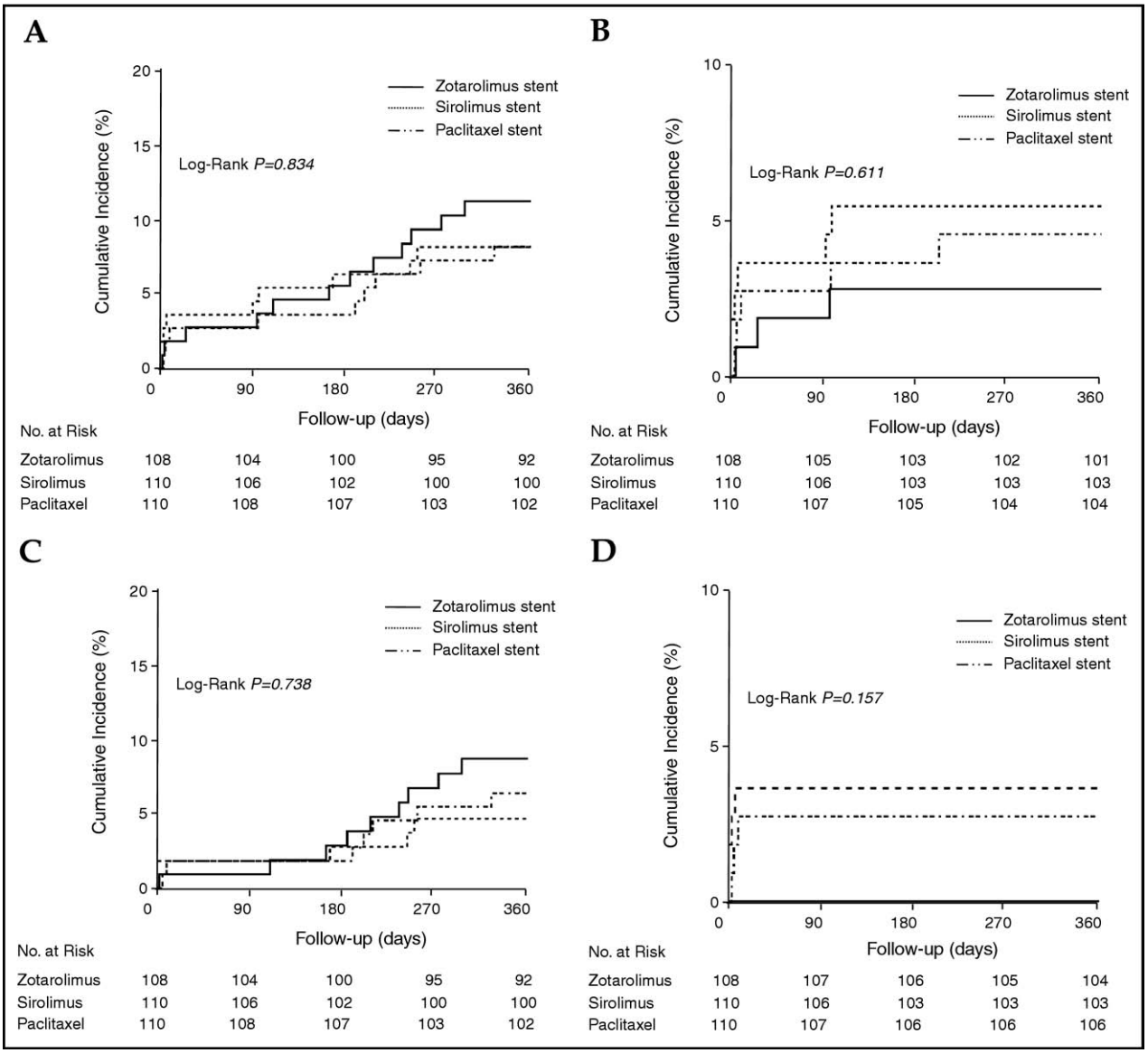

Figure 2. Cumulative incidence of primary end point (death, recurrent MI, and ischemia-driven target vessel revascularization) *(A)*, death or recurrent MI *(B)*, ischemia-driven target vessel revascularization *(C)*, or stent thrombosis *(D)*.

up to 0.75 mm in low-risk populations seem to be acceptable.[29] The ZES showed a nonsignificant trend toward a lower risk of stent thrombosis, suggesting that it may be safer than SESs or bare metal stents in the setting of STEMI. A preclinical study showed that ZESs induced the least inflammation of the 3 DESs, and that all struts of the ZES were covered by neointimal tissue.[28] This may be an advantage in view of current concerns about the safety of DESs in a prothrombogenic environment.[28,30] Additional data, however, are needed to prove this hypothesis.

There are several potential limitations of our study. First, it did not have sufficient statistical power to establish the superiority of 1 DES over the others in patients with STEMI. Second, 12-month follow-up may be too short for conclusive determination of the safety of DESs in the setting of STEMI. A larger and more adequately powered prospective study may be needed to clarify this issue. Third, routine angiographic follow-up may increase the rate of target lesion revascularization due to the oculostenotic reflex. Nevertheless, our results indicate that DESs may be safe and effective in the treatment of STEMI, with no differences in major adverse cardiac events among the 3 DESs.

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