Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

A Pooled Analysis of the REAL-LATE and the ZEST-LATE Trial

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on behalf of the REAL-LATE and the ZEST-LATE trial

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BACKGROUND

- The use of drug-eluting stents (DES) is associated with significant reductions in restenosis and target-lesion revascularization compared with use of bare-metal stents (BMS).
- Based on the pivotal trials, DES have been widely used for percutaneous coronary intervention (PCI) in clinical practice.
- However, some longer-term studies have reported that DES are associated with increased rates of late stent thrombosis, mortality or myocardial infarction compared to BMS.

BACKGROUND

- Early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis with drug-eluting stents.
- Current PCI guidelines recommend that clopidogrel 75 mg daily should be given for at least 12 months after implantation of DES if patients are not at high risk of bleeding.
- However, the optimal duration of dual antiplatelet therapy and the risk–benefit ratio of long-term dual antiplatelet therapy remain uncertain for patients receiving DES

OBJECTIVE

- The findings of observational studies have been inconsistent, and no randomized trials have been performed to address this issue.

- Accordingly, we evaluated the effect of extended dual antiplatelet therapy beyond 12 months on long-term clinical outcomes in patients who underwent initial PCI with drug-eluting stents.

METHODS

STUDY DESIGN

- The current analysis merged data from two concurrent randomized, clinical trials comparing continuation and discontinuation of clopidogrel in patients who were free of major adverse cardiac or cerebrovascular events and major bleeding for at least 12 month period after implantation of drug-eluting stents.

STUDY DESIGN

- The first trial was called **REAL-LATE** (Correlation of Clopidogrel Therapy Discontinuation in *REAL*-world Patients treated with Drug-Eluting Stent Implantation and *L*ate Coronary *A*rterial *T*hrombotic *E*vents; ClinicalTrilas.gov number, NCT00484926)

- The second trial was called **ZEST-LATE** (Evaluation of the Long-term Safety After *Z*otarolimus-*E*luting Stent, *S*irolimus-Eluting Stent, or Pacli*T*axel-Eluting Stent Implantation for Coronary Lesions - *L*ate Coronary *A*rterial *T*hrombotic *E*vents; ClinicalTrilas.gov number, NCT00590174)

STUDY DESIGN

- The study designs of the two trials were similar; the main difference was that the ZEST-LATE trial included only individuals who had participated in another randomized trial, the ZEST(Comparison of the Efficacy and the Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions, NCT00418067).

- The REAL-LATE trial enrolled a broader population of patients without limiting the clinical or lesion characteristics.

STUDY DESIGN

- These two trials (the REAL-LATE and ZEST-LATE) were merged as the result of a decision of the executive committees, on the basis of the slower-than-anticipated enrollment in each of the trials and substantial similarities in their designs.

- The data and safety monitoring board, which was the same for both trials, agreed to the merger.

STUDY DESIGN

REAL-LATE

Broader population of patients who had received any DES

ZEST-LATE

Patients who had participated in ZEST trial

Data Merged

Patients who were free of MACCE with dual therapy (clopidogrel plus aspirin) for 12 months

R

Clopidogrel + Aspirin

Aspirin Alone

1

2 year F/U

STUDY POPULATION

Inclusion Criteria

Patients were eligible to enroll in the REAL-LATE and ZEST-LATE trials if they had undergone implantation of a drug-eluting stents at least 12 months before enrollment, had not had a major adverse cardiovascular event (myocardial infarction, stroke, or repeat revascularization) or major bleeding since implantation, and were receiving dual antiplatelet therapy at the time of enrollment.

STUDY POPULATION

Exclusion Criteria

- Contraindications to use of antiplatelet drugs.
- Concomitant vascular disease requiring long-term use of clopidogrel or other established indications for clopidogrel therapy (e.g., a recent acute coronary syndrome)
- Non-cardiac co-morbid conditions with life expectancy <1 year
- Participants in another drug or coronary-device study.

TRIAL PROCEDURES AND FOLLOW-UP

- Patients in both trials were randomly assigned either to clopidogrel (75 mg per day) plus low-dose aspirin (100 to 200 mg per day) or low-dose aspirin alone.
- The treatment allocation was performed using a preestablished, computer-generated randomization scheme, stratified according to site and type of DES.
- Both were open-label trials without blinding of either the study subjects or the investigators.
- Follow-up evaluations were performed every 6 months. At these visits, data pertaining to patients' clinical status, all interventions, outcome events, adverse events, and drug compliance were recorded.

END POINTS

The Primary End Points

The first occurrence of myocardial infarction or death from cardiac cause after treatment assignment.

The Principal Secondary End Points

- Each component of death, myocardial infarction, stroke (of any cause), definite stent thrombosis, or repeat revascularization
- Composite death or myocardial infarction
- Composite death, myocardial infarction or stroke
- Composite cardiac death, myocardial infarction, or stroke
- Major bleeding, according to the TIMI definition.

SAMPLE SIZE ESTIMATION

- Assuming an event rate of 5.0% at 2 years for the primary end point among patients who were assigned to the aspirin-alone group, we estimated that 1,812 patients (906 per group) would need to be enrolled for the detection of a 50% reduction in relative risk of the primary end point in the dual-therapy group as compared with aspirin-alone group, with a statistical power 80% power at a two-sided significance level of 0.05.
- The assumed rates of the primary end point and the assumed relative risk reduction were based on historical data (the BASEKET-LATE study and the Duke registry data).
- The planned sample size was increased by 10 % to allow for noncompliance and loss to follow-up, for a total overall enrollment goal of 2000 patients for each trial.

STATISTICAL ANALYSIS

- All enrolled patients from both trials were included in the analysis of primary and secondary clinical outcomes according to the intention-to-treat principle.
- Differences between treatment groups were evaluated by Student's t-test for continuous variables and by the chi-square or Fisher's exact test for categorical variables.
- Cumulative event curves were generated by means of the Kaplan-Meier method.
- We used a Cox proportional-hazards model to compare clinical outcomes between the groups.
- An additional stratified Cox regression analysis was performed to test whether merging of the data from the two trials would influence the primary outcome.

PARTICIPANTS

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CLINICAL TRIAL ORGANIZATION

Principal Investigators	Seung-Jung Park, MD, PhD Asan Medical Center
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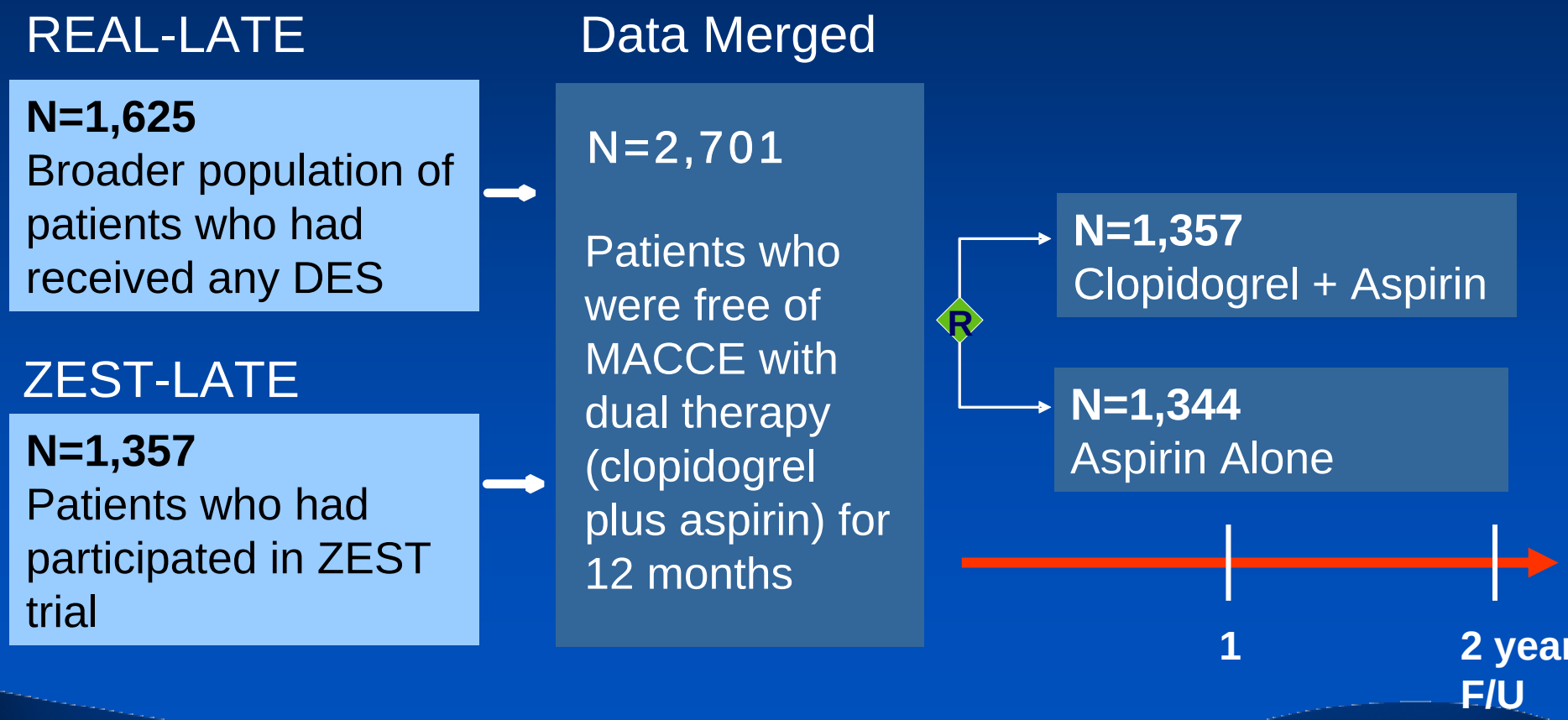
RESULTS

STUDY PATIENTS

From July 2007 through September 2008



Baseline Patients Characteristics

Characteristic	Clopidogrel + Aspirin (n=1357)	Aspirin Alone (n=1344)	P Value
Demographics			
Age (yr)	62.0±9.8	61.9±9.9	0.97
Male sex	950 (70.0)	933 (69.4)	0.74
Clinical Characteristics			
Diabetes mellitus	340 (25.1)	364 (27.1)	0.23
Hypertension	775 (57.1)	765 (56.9)	0.92
Hyperlipidemia	586 (43.2)	584 (43.5)	0.89
Current smoker	404 (29.8)	431 (32.1)	0.20
Previous coronary angioplasty	177 (13.0)	159 (11.8)	0.34
Previous myocardial infarction	51 (3.8)	45 (3.3)	0.57
Previous stroke	57 (4.2)	45 (3.3)	0.25

Characteristic	Clopidogrel + Aspirin (n=1357)	Aspirin alone (n=1344)	P Value
Ejection fraction (%)	59.2±9.3	59.7±8.5	0.20
Multivessel disease	667 (49.2)	633 (47.1)	0.29
Clinical indication			0.79
Stable angina	514 (37.9)	500 (37.2)	
Unstable angina	543 (40.0)	559 (41.6)	
NSTEMI	145 (10.7)	144 (10.7)	
STEMI	155 (11.4)	141 (10.5)	
Discharge medications			
Aspirin	1353 (99.7)	1399 (99.6)	0.73
Clopidogrel	1353 (99.7)	1343 (99.9)	0.38
ACE inhibitor	633 (46.6)	603 (44.9)	0.35
ß-blockers	917 (67.6)	869 (64.7)	0.11
Calcium channel blocker	730 (53.8)	739 (55.0)	0.54
Statin	1081 (79.7)	1058 (78.7)	0.55

Baseline Lesions Characteristics

Characteristic	Clopidogrel + Aspirin (n=1357)	Aspirin Alone (n=1344)	P Value
Lesions stented, No	**1872**	**1847**	
Vessel treated			0.35
Left anterior descending artery	912 (48.7)	921 (49.9)	
Left circumflex artery	372 (19.9)	334 (18.1)	
Right coronary artery	533 (28.5)	546 (29.6)	
Left main disease	55 (2.9)	44 (2.4)	
Bifurcation	226 (12.1)	231 (12.5)	0.69
Ostial location	125 (6.7)	128 (6.9)	0.76
B2 or C type	1494 (79.8)	1461 (79.1)	0.59
Calcification	80 (4.3)	91 (4.9)	0.34
Total occlusion	219 (11.7)	190 (10.3)	0.17

Baseline Procedural Characteristics

Characteristic	Clopidogrel +Aspirin (n=1357)	Aspirin Alone (n=1344)	P Value
Lesions stented, No	**1872**	**1847**	
Stents per lesion, No.	1.3±0.5	1.2±0.5	0.13
Stent length per lesion, mm	31.8±16.4	30.9±15.4	0.07
Type of drug-eluting stents			0.98
Sirolimus-eluting stents	1057 (56.6)	1052 (57.0)	
Paclitaxel-eluting stents	456 (24.4)	439 (23.8)	
Zotarolimus-eluting stents	350 (18.7)	347 (18.8)	
Others	9 (0.5)	9 (0.5)	

Timing of Randomization after the Index PCI

Characteristic	Clopidogrel + Aspirin (n=1357)	Aspirin Alone (n=1344)	P Value
Time to randomization			0.86
12 Mo – 18 Mo after procedure	1189 (87.6)	1187 (88.3)	
18 Mo – 24 Mo after procedure	167 (12.3)	156 (11.6)	
>24 Mo after procedure	1 (0.1)	1 (0.1)	
Median (interquartile range)	12.8 (12.2–14.6)	12.8 (12.2–14.8)	

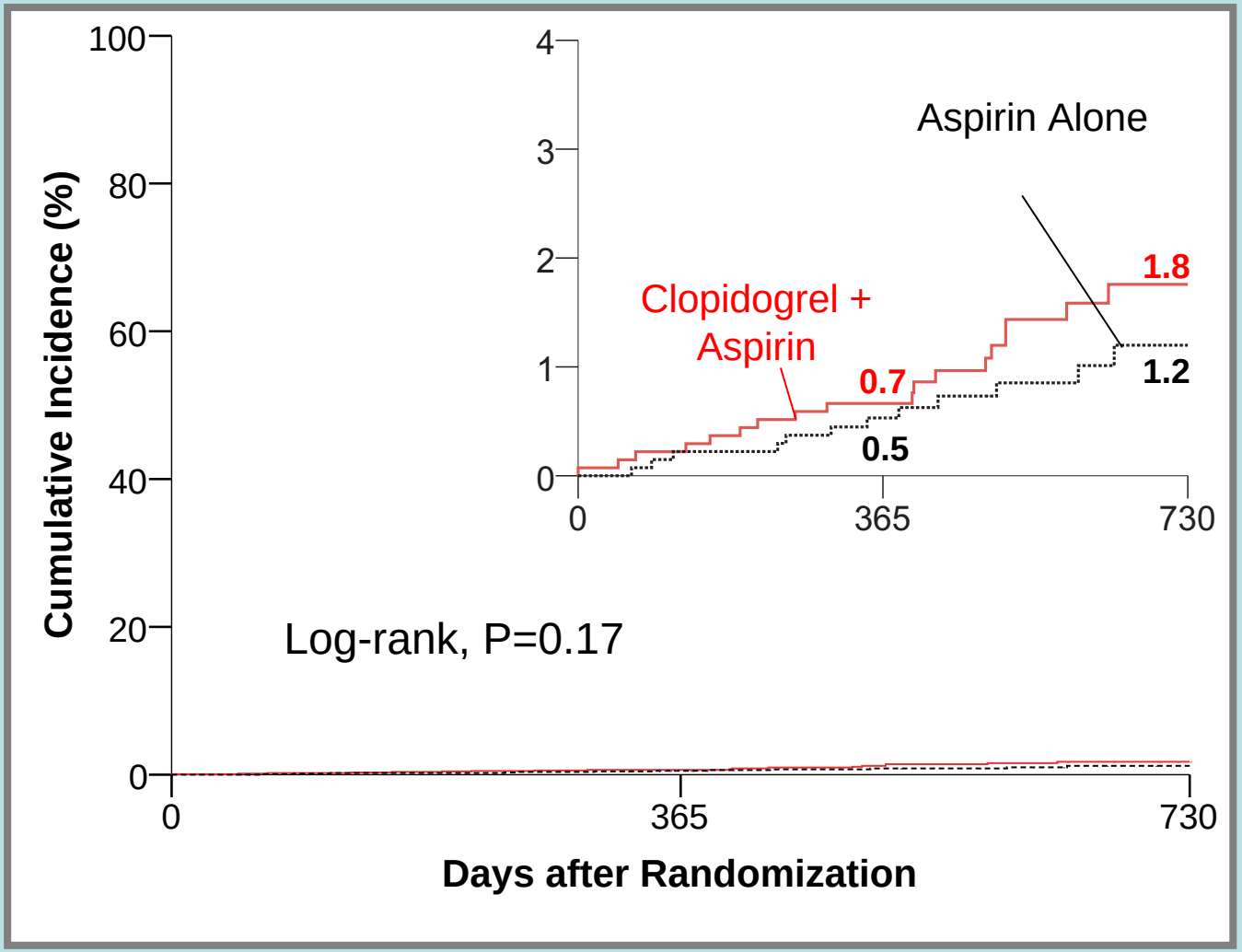
Status of Antiplatelet Therapy during Follow up

Characteristic	Clopidogrel + Aspirin (n=1357)	Aspirin Alone (n=1344)	P Value
Aspirin			
At randomization	1348/1357 (99.3)	1338/1344 (99.6)	0.45
6 Mo after randomization	1338/1349 (99.2)	1328/1333 (99.6)	0.14
12 Mo after randomization	1129/1143 (98.8)	1103/1117 (98.7)	0.95
18 Mo after randomization	752/759 (99.1)	722/730 (98.9)	0.37
24 Mo after randomization	327/333 (98.2)	313/318 (98.4)	0.82
Clopidogrel			
At randomization	1335/1357 (98.4)	59/1344 (4.4)	<0.001
6 Mo after randomization	1297/1349 (96.1)	78/1332 (5.9)	<0.001
12 Mo after randomization	1011/1143 (88.5)	72/1117 (6.4)	<0.001
18 Mo after randomization	654/758 (86.3)	46/730 (6.3)	<0.001
24 Mo after randomization	276/333 (82.9)	14/318 (4.4)	<0.001

FOLLOW UP AND CLINICAL OUTCOMES

Primary End Point:

Cardiac Death or Myocardial Infarction

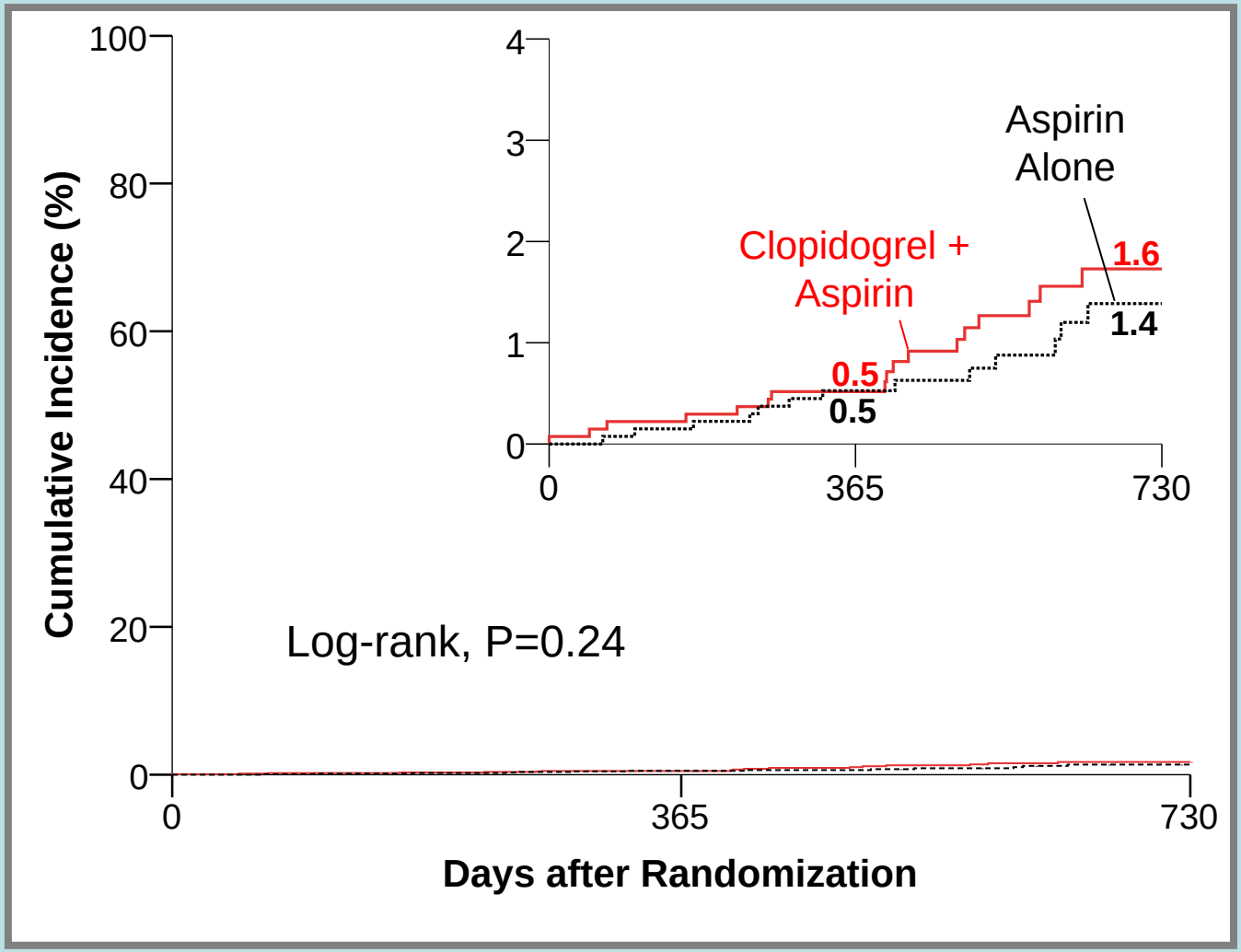


No. at Risk

Continuation group	1357	1122	299
Discontinuation group	1344	1100	301

Outcome	Total Events		Cumulative Event Rate At 12 Months		Cumulative Event Rate At 24 Months		Hazard Ratio (95% CI)	P Value
	Dual Therapy	Aspirin Only	Dual Therapy	Aspirin Only	Dual Therapy	Aspirin Only		
Primary End Point								
Cardiac death or MI	20	12	0.7	0.5	1.8	1.2	1.65 (0.80-3.36)	0.17
Secondary End Points								
Death	20	13	0.5	0.5	1.6	1.4	1.52 (0.75-3.5)	0.24
MI	10	7	0.4	0.3	0.8	0.7	1.41 (0.54-3.71)	0.49
Stroke	9	4	0.3	0.3	1.0	0.3	2.22 (0.68-7.20)	0.19
Stent thrombosis, definite	5	4	0.2	0.1	0.4	0.4	1.23 (0.33-4.58)	0.76
Repeat revascularization	36	26	1.7	1.1	3.1	2.4	1.37 (0.83-2.27)	0.22
Death or MI	27	17	0.8	0.8	2.3	1.7	1.57 (0.85-2.88)	0.15
Death, MI, or stroke	35	20	1.1	1.1	3.2	1.8	1.73 (0.99-3.0)	0.051
Cardiac death, MI, or stroke	28	15	1.0	0.8	2.7	1.3	1.84 (0.99-3.45)	0.06
Major bleeding, TIMI criteria‡	3	1	0.2	0.1	0.2	0.1	2.96 (0.31-28.46)	0.35

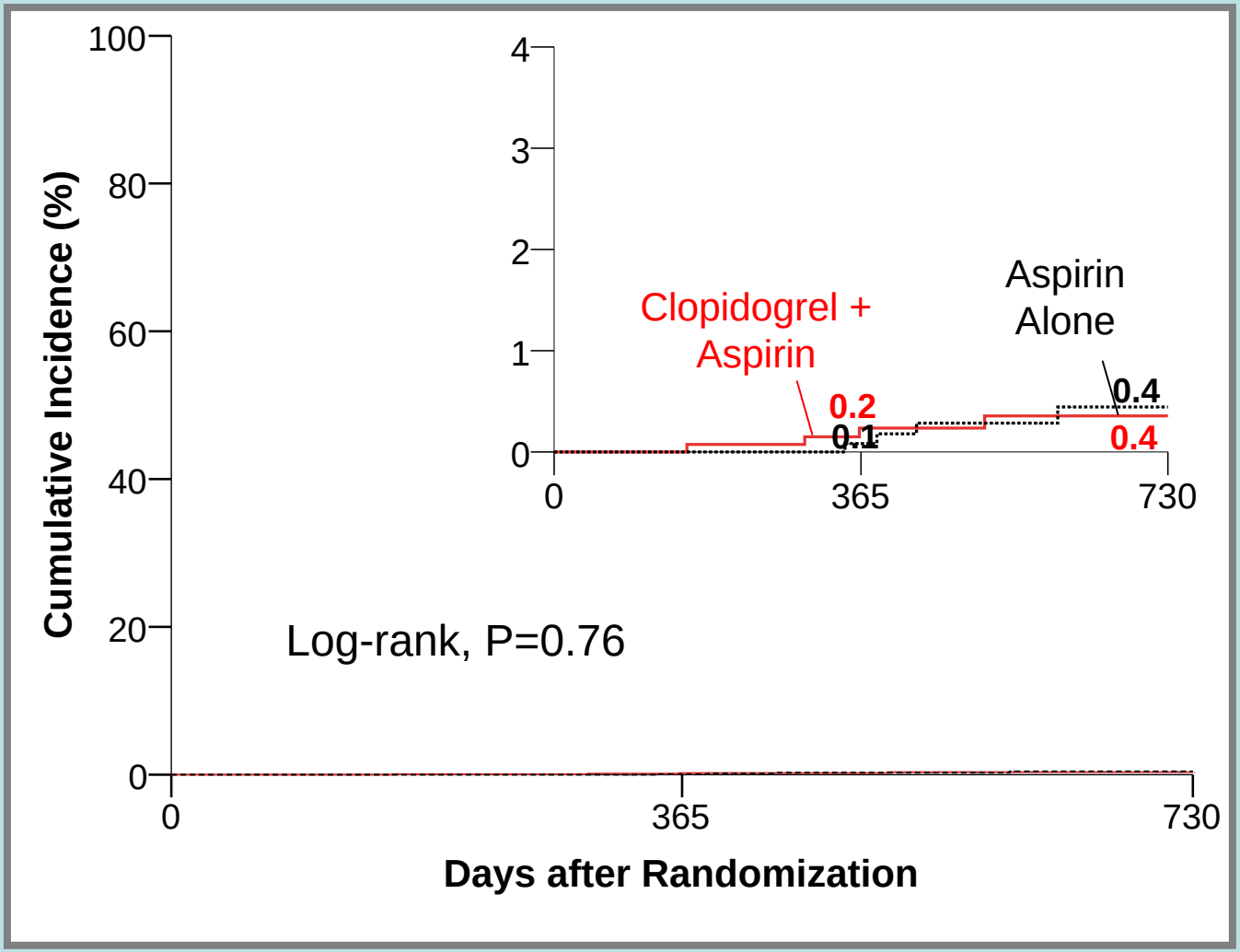
Death from Any Cause



No. at Risk

Continuation group	1357	1125	302
Discontinuation group	1344	1103	303

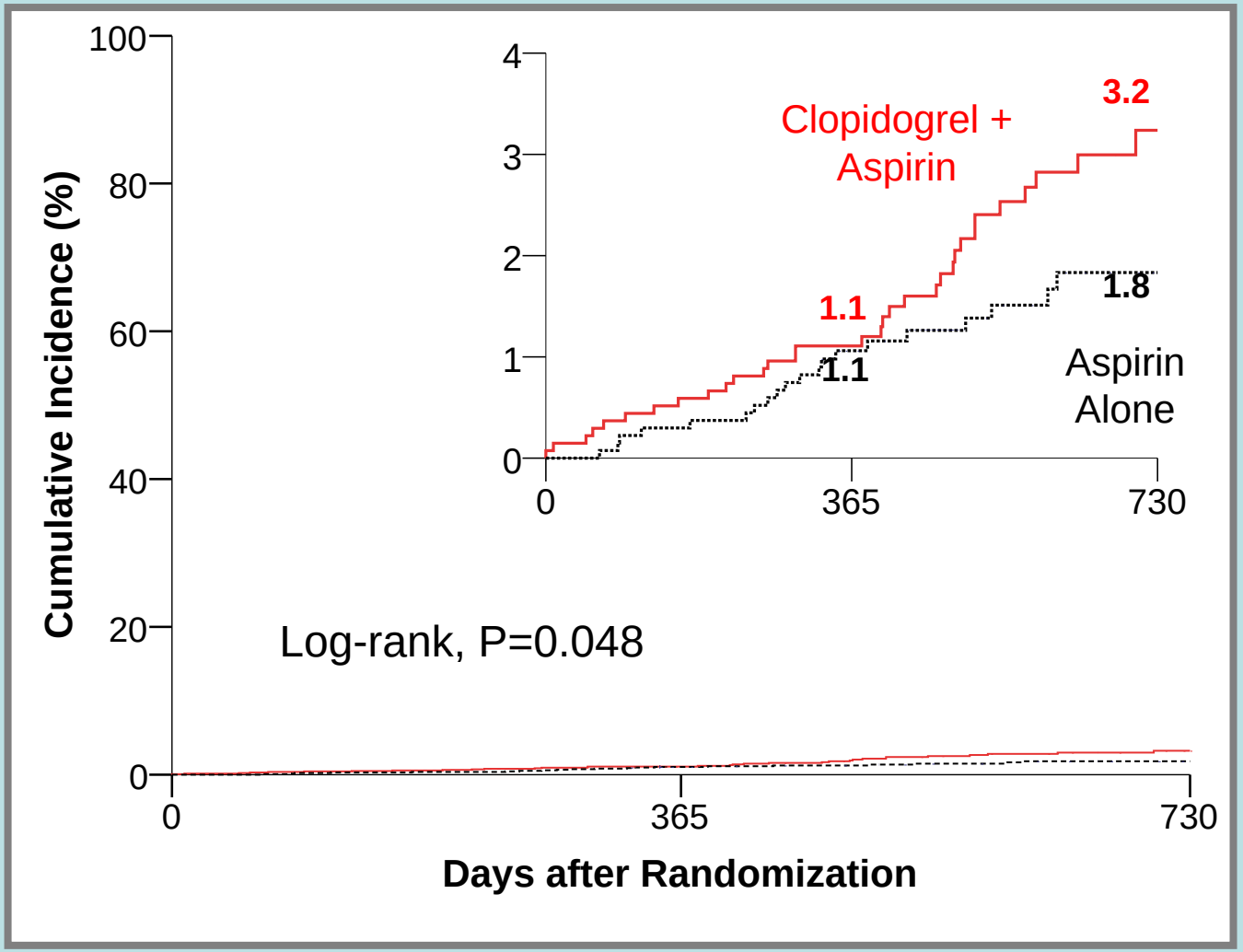
Definite Stent Thrombosis



No. at Risk

Continuation group	1357	1124	301
Discontinuation group	1344	1102	303

Death, Myocardial Infarction, or Stroke



No. at Risk

Continuation group	1357	1119	295
Discontinuation group	1344	1097	300

CONCLUSIONS

- In this combined analysis of two randomized multi-center trials, we found no significant benefit associated with clopidogrel continuation as compared with clopidogrel discontinuation after 12 months in reducing the incidence of cardiac death or myocardial infarction for patients who had received drug-eluting coronary stents.

CONCLUSIONS

- The rate of composite outcomes (all-cause or cardiac death, myocardial infarction, or stroke) was greater with clopidogrel continuation than with clopidogrel discontinuation, but this difference was not statistically significant.
- However, the study had insufficient statistical power to allow a firm conclusion regarding the safety of clopidogrel discontinuation after 12 months. Larger clinical trials will be necessary to resolve this issue.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