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

CardioVascular Research Foundation
UNIVERSITY OF ULSAN COLLEGE MEDICINE
ASAN Medical Center

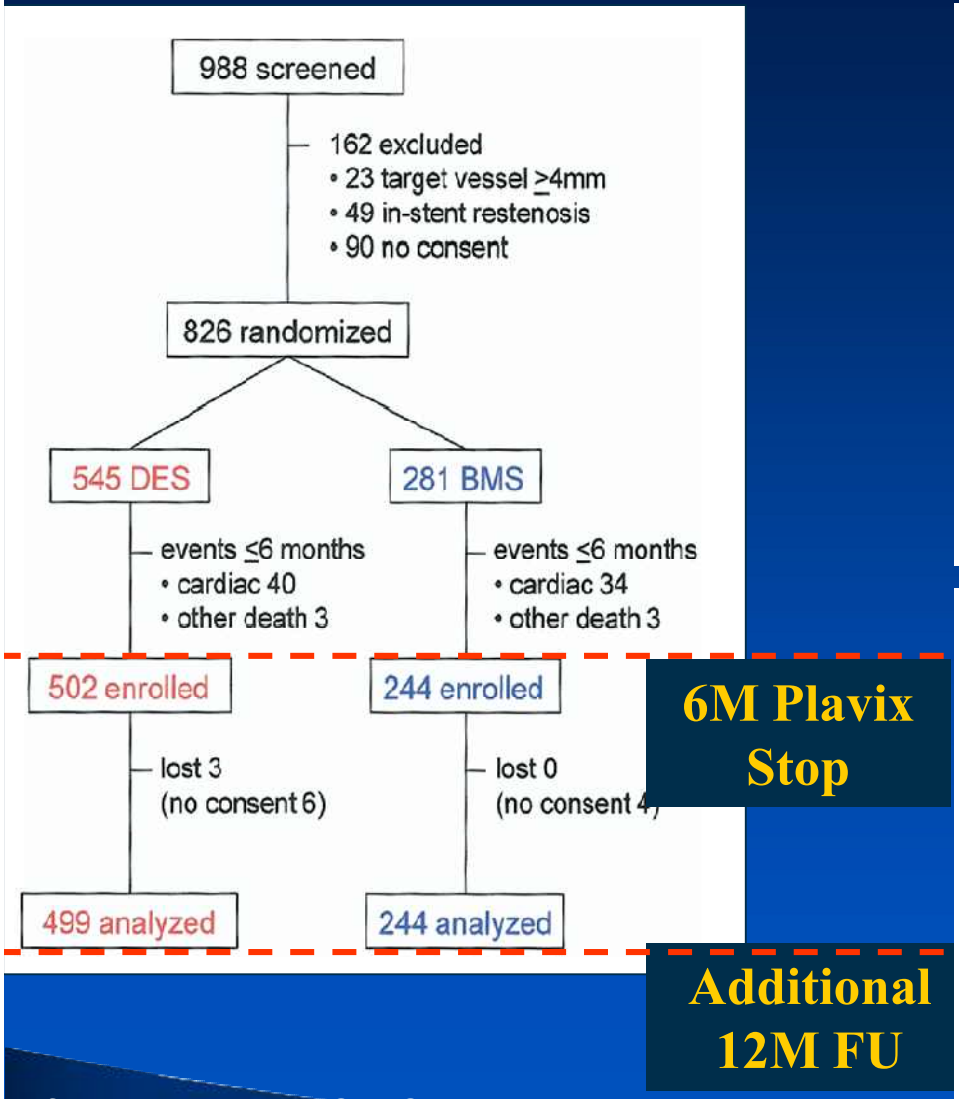
How Long ?

Duration of *D*ual *A*nti*P*latelet *T*herapy **(DAPT)** After Drug-Eluting Stent Implantation

BACKGROUND

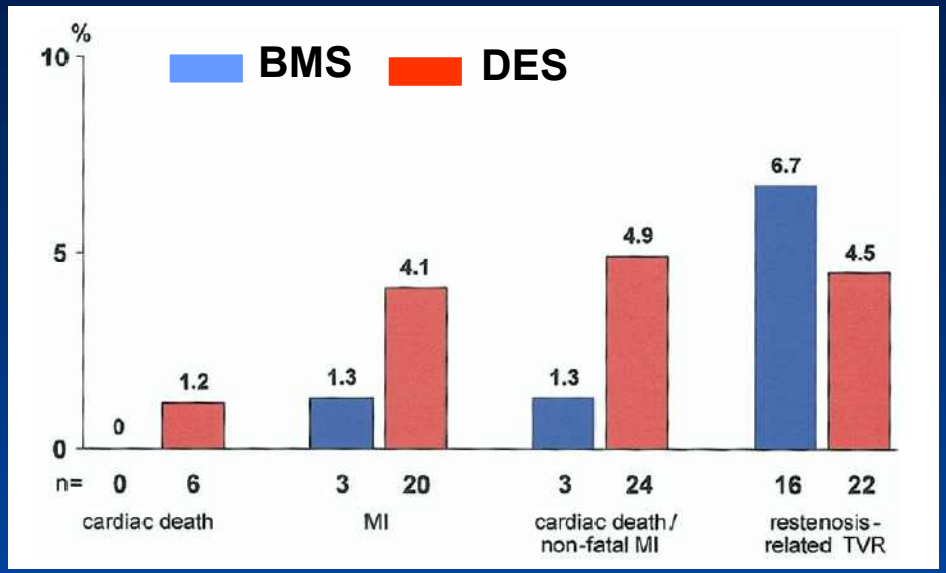
- The optimal duration and the risk–benefit ratio of long-term dual antiplatelet therapy remain uncertain for patients receiving DES

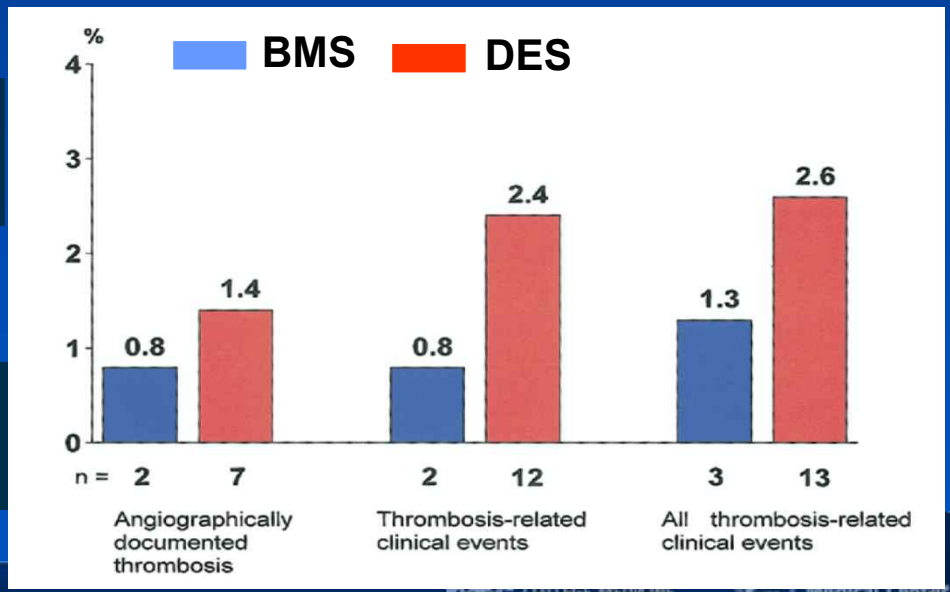
First Concern : BASKET-LATE



6M Plavix Stop

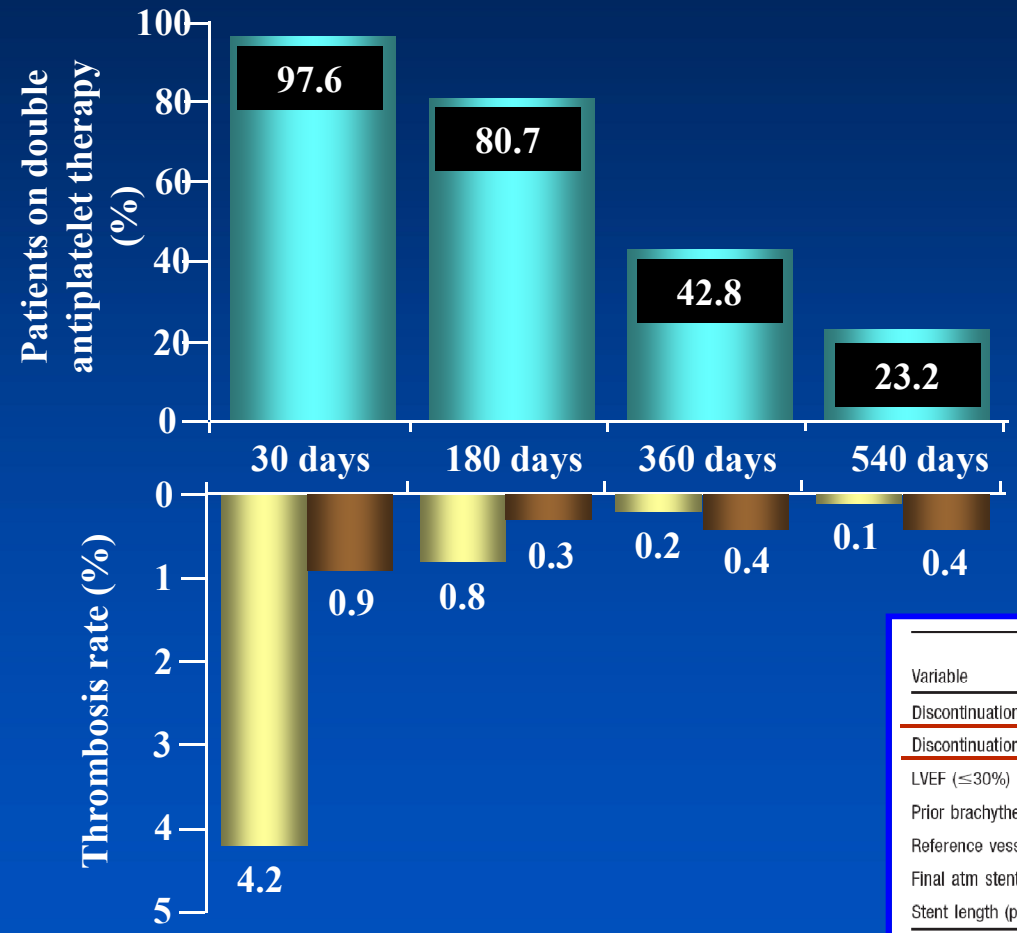
Additional 12M FU

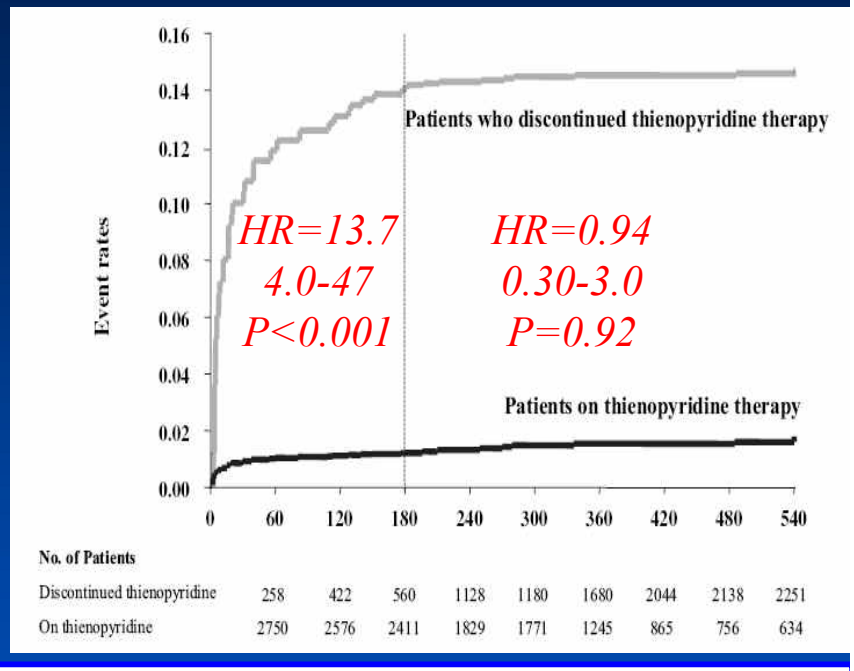




Pfisterer et al. J Am Coll Cardiol 2006;48:2584

Do We Need Dual Antiplatelet Therapy Beyond 6 Months After DES?





Variable	No. of Patients	HR	95% Lower Confidence Limit	95% Upper Confidence Limit	*P*
Discontinuation of thienopyridine (0–6 months)*	583	13.74	4.04	46.68	<0.001
Discontinuation of thienopyridine (6–18 months)*	1737	0.94	0.30	2.98	0.92
LVEF (≤30%)	96	3.72	1.50	9.27	0.005
Prior brachytherapy	31	9.70	2.99	31.44	<0.001
Reference vessel diameter (per 1 mm)†	...	0.27	0.06	1.13	0.07
Final atm stent implantation (per 1 atm)†	...	0.39	0.18	0.85	0.02
Stent length (per 10 mm)†	...	2.75	1.55	4.88	<0.001

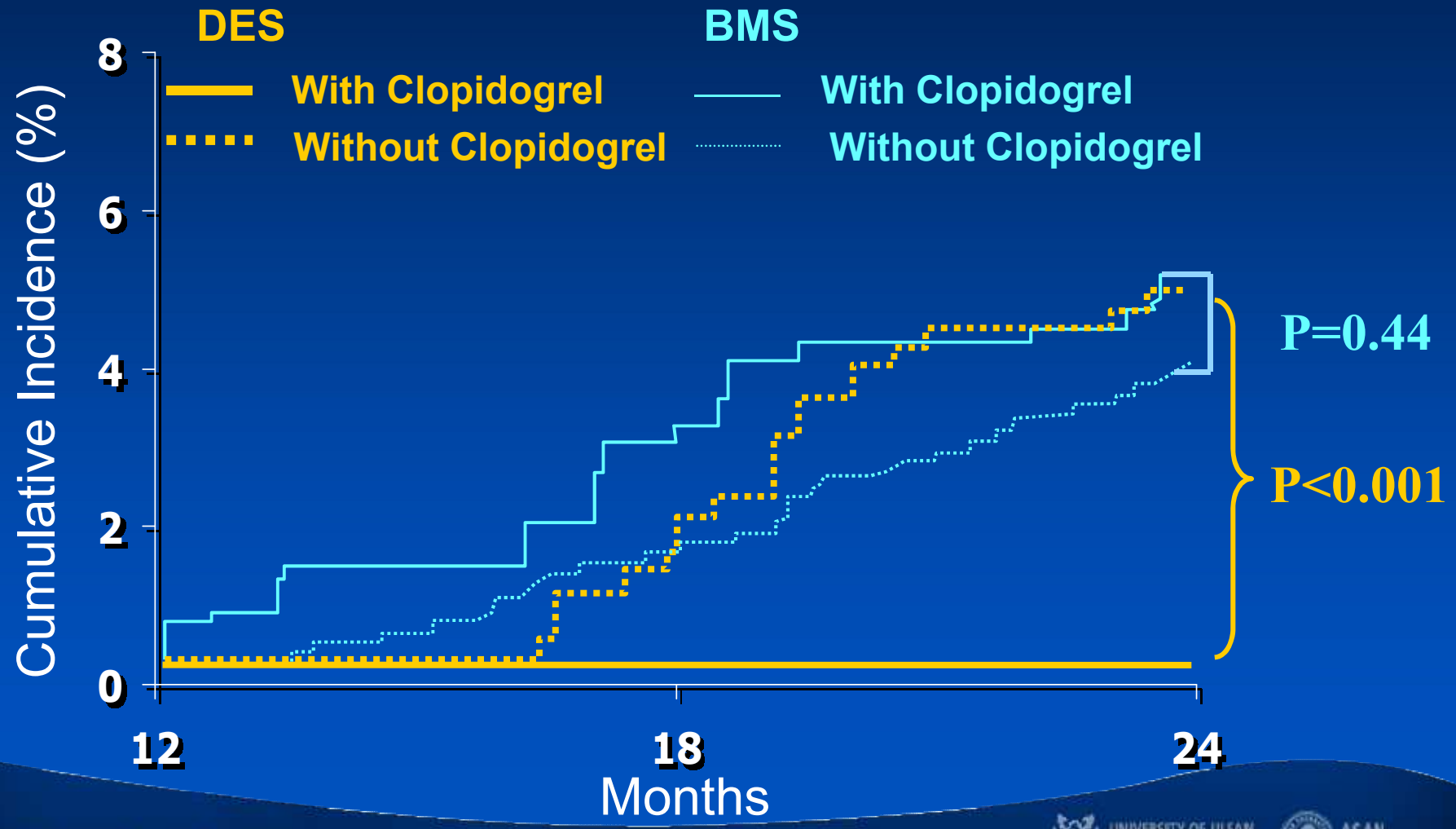
Airoldi F et al. Circulation, 2007;116:745

How Long ?

Premature discontinuation of DAPT (<6 months) associated marked increase risk of stent thrombosis

Clopidogrel Use and Composite of Death or MI
At 12-month Landmark

The Duke-Registry Landmark analysis



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Eisenstein et al, JAMA 2007;297

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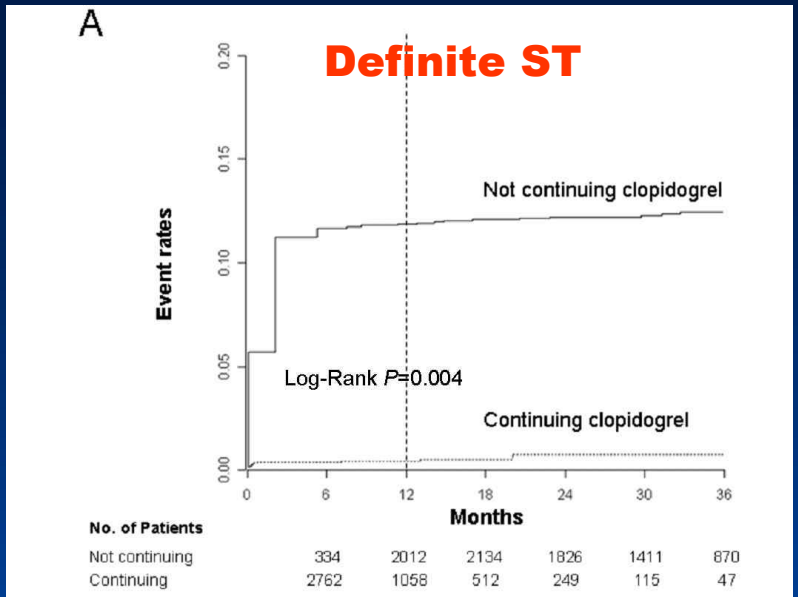
Asan Medical Center Registry Data

A



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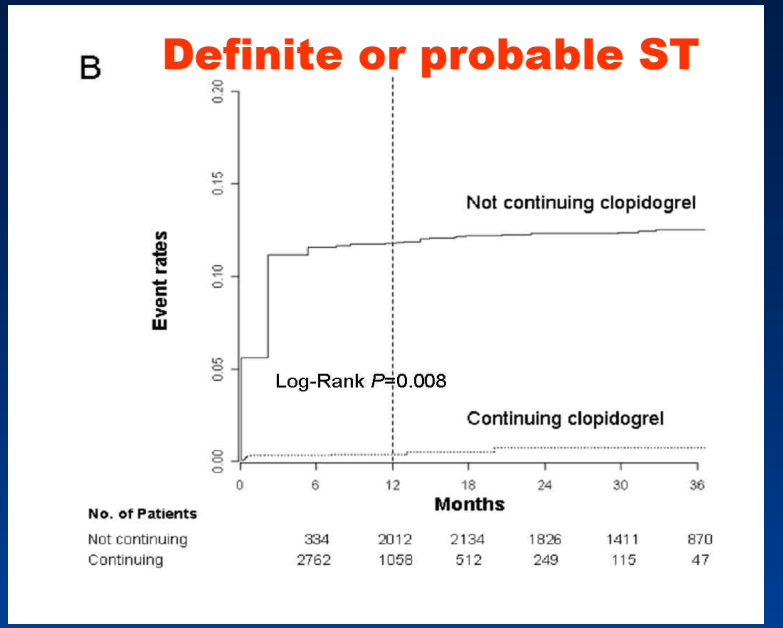

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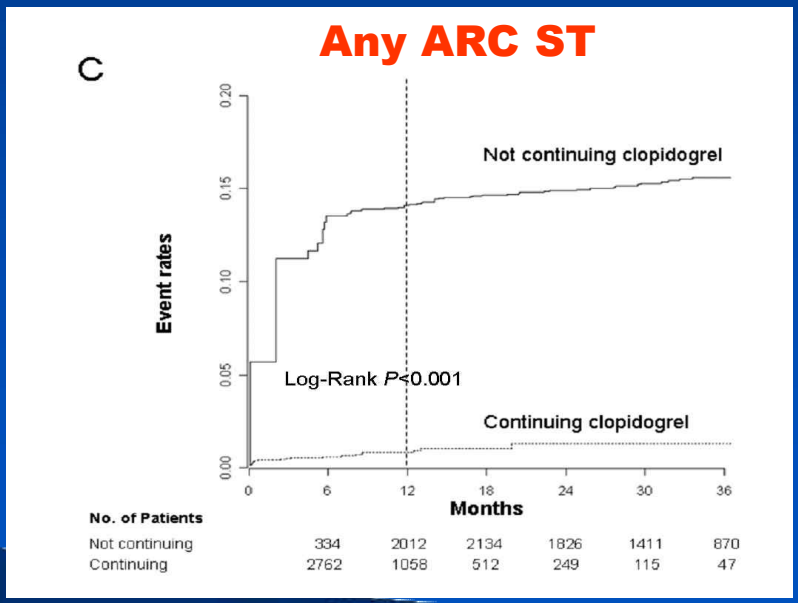


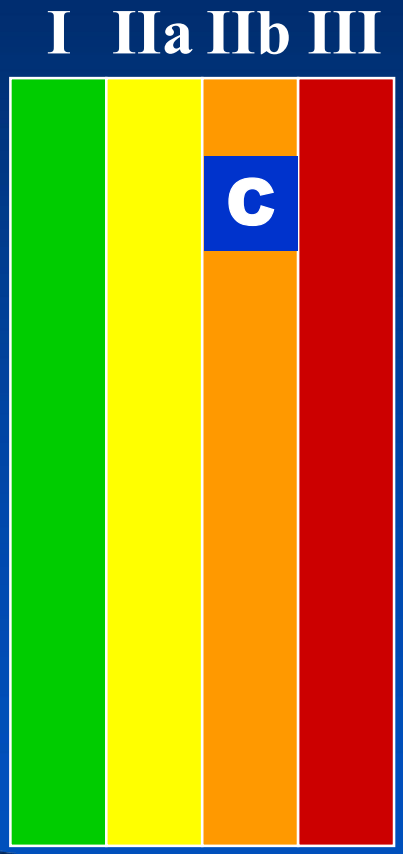
Close relationship between ST and Clopidogrel use before 1 year, but not after 1 year

Park et al. J Am Coll Cardiol Intv, 2008;1

Summary of Registries Data:
Optimal Clopidogrel Duration

ACC/AHA/SCAI 2007 Focused Update for PCI
Oral Antiplatelet Adjunctive Therapies

(New Recommendation)



Continuation of Clopidogrel therapy beyond 1 Year may be considered in patients undergoing DES placement.

The Optimal duration of Clopidogrel therapy after 1 year has not been established and Should depend on the judgment of the risk-benefit ratio for the individual patient.

How Long ?

It is still not clear whether DAPT after 1 year (of even after 6 months) reduces the risk of stent thrombosis for DES

DES-LATE

Prospective, multicenter, randomized clinical study

Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

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

CardioVascular Research Foundation
UNIVERSITY OF ULSAN COLLEGE MEDICINE
ASAN Medical Center

OBJECTIVE

- 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.

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 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

REAL-LATE

Broader population of patients who had received any DES

ZEST-LATE

Patients who had participated in ZEST trial

Patients who were free of MACCE with Dual antiplatelet therapy for at least a 12 month after DES implantation

R

Clopidogrel + Aspirin

Aspirin Alone

Clinical follow-up every 6 months
Composite of MI or Death from cardiac causes

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

- 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).
- 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 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

Seung-Jung Park	Asan Medical Center, Seoul
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Junghan Yoon	Yonsei University Wonju Christian Hospital, Wonju
Do-Sun Lim	Korea University Hospital, Seoul

CLINICAL TRIAL ORGANIZATION

Principal Investigators	Seung-Jung Park, MD, PhD Asan Medical Center
Clinical Events Committee	Jae-Joong Kim, MD, PhD Asan Medical Center
Data Safety Monitoring Board	Moo-Song Lee, MD, PhD University of Ulsan Medical College
Data Coordination/ Site Management	Clinical Research Center Asan Medical Center
Angiographic Core Lab	CVRF in Korea

RESULTS

STUDY PATIENTS

REAL-LATE

N=1,625
Broader population of patients who had received any DES

ZEST-LATE

N=1,357
Patients who had participated in ZEST trial

N=2,701

Patients who were free of MACCE with dual antiplatelet therapy for at least a 12 month after DES implantation

R

N=1,357
Clopidogrel + Aspirin

N=1,344
Aspirin Alone

Clinical follow-up every 6 months
Composite of MI or Death from cardiac causes

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)	

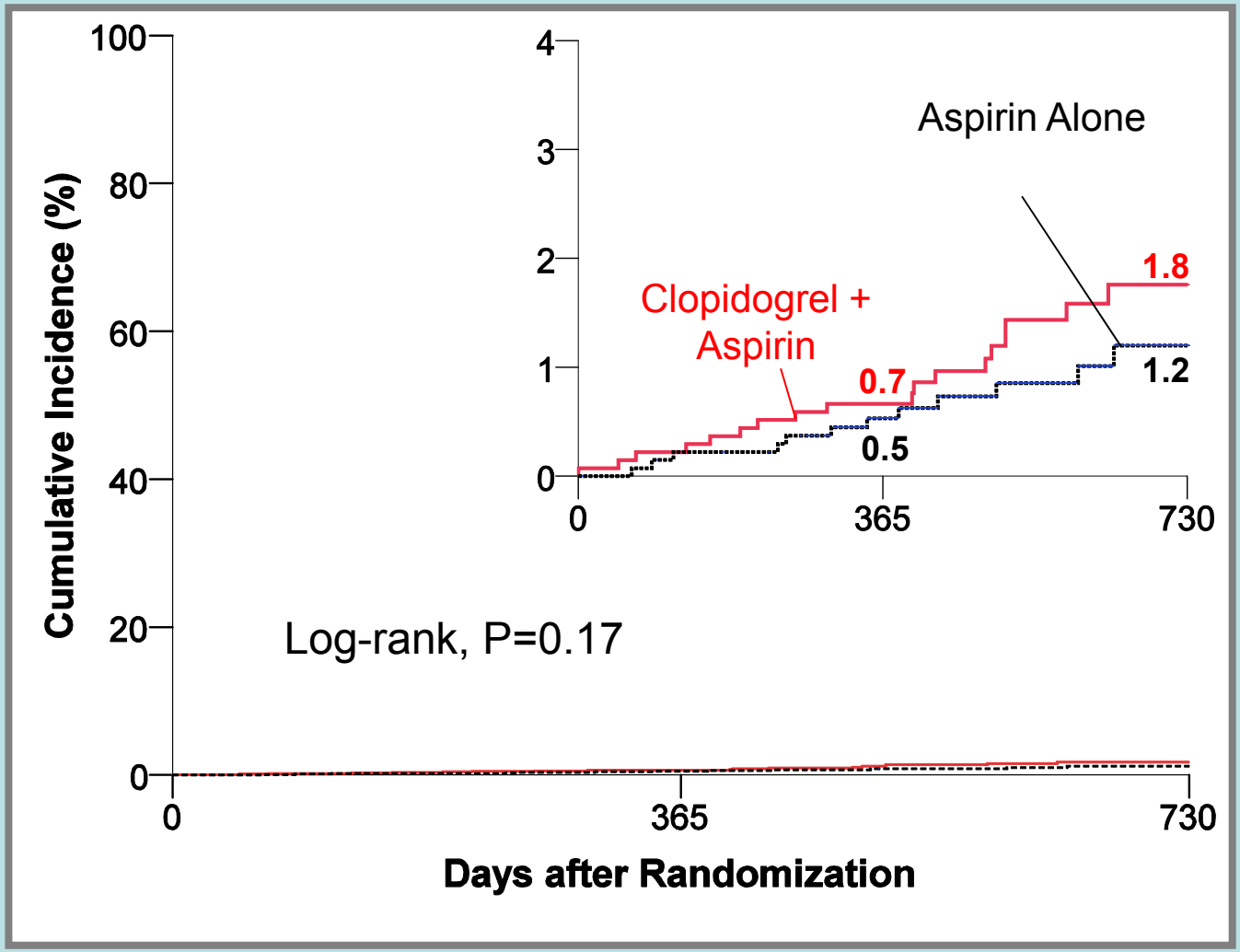
Timing of Randomization after the Index PCI

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)	

FOLLOW UP AND CLINICAL OUTCOMES

Primary End Point:

Cardiac Death or Myocardial Infarction

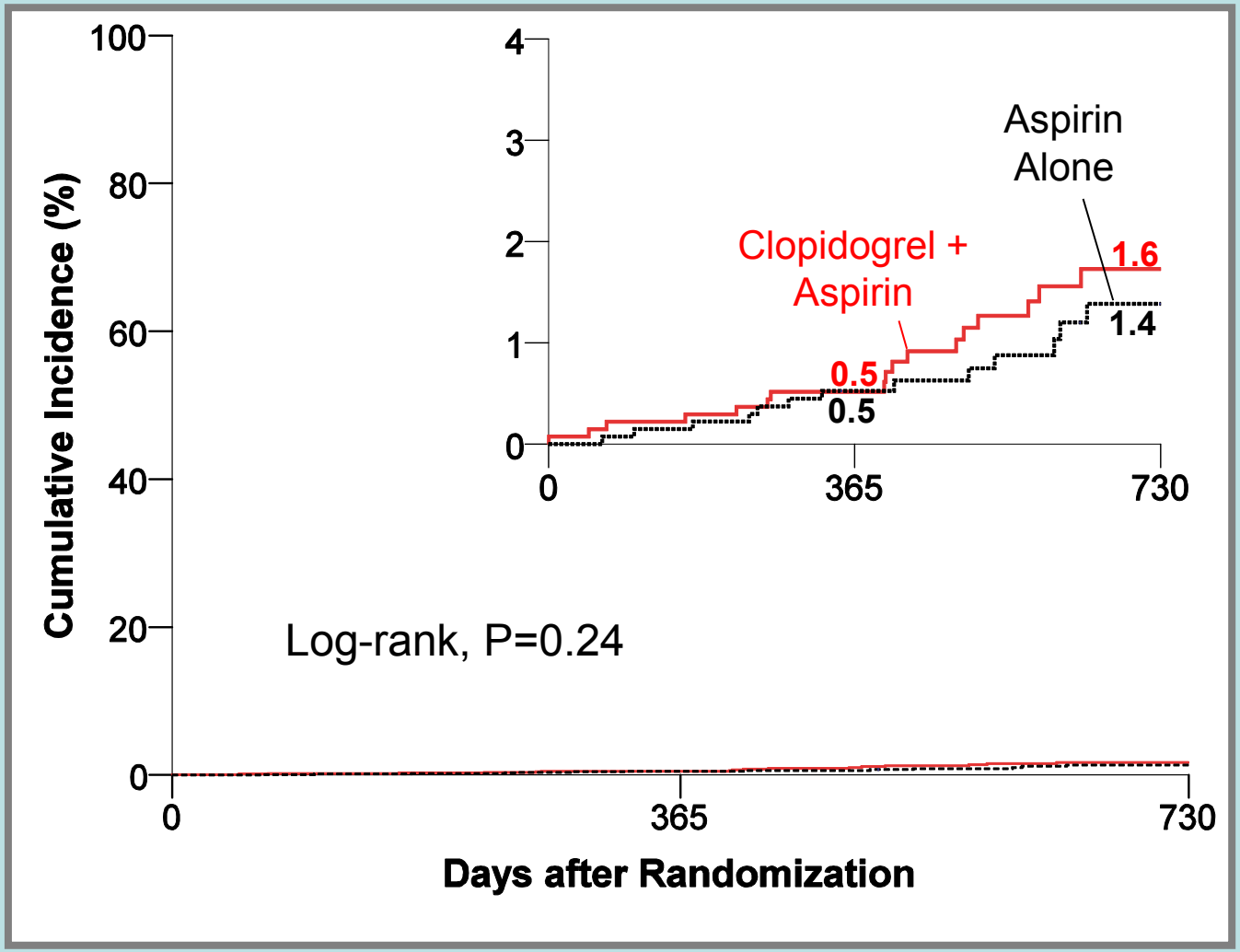


No. at Risk

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

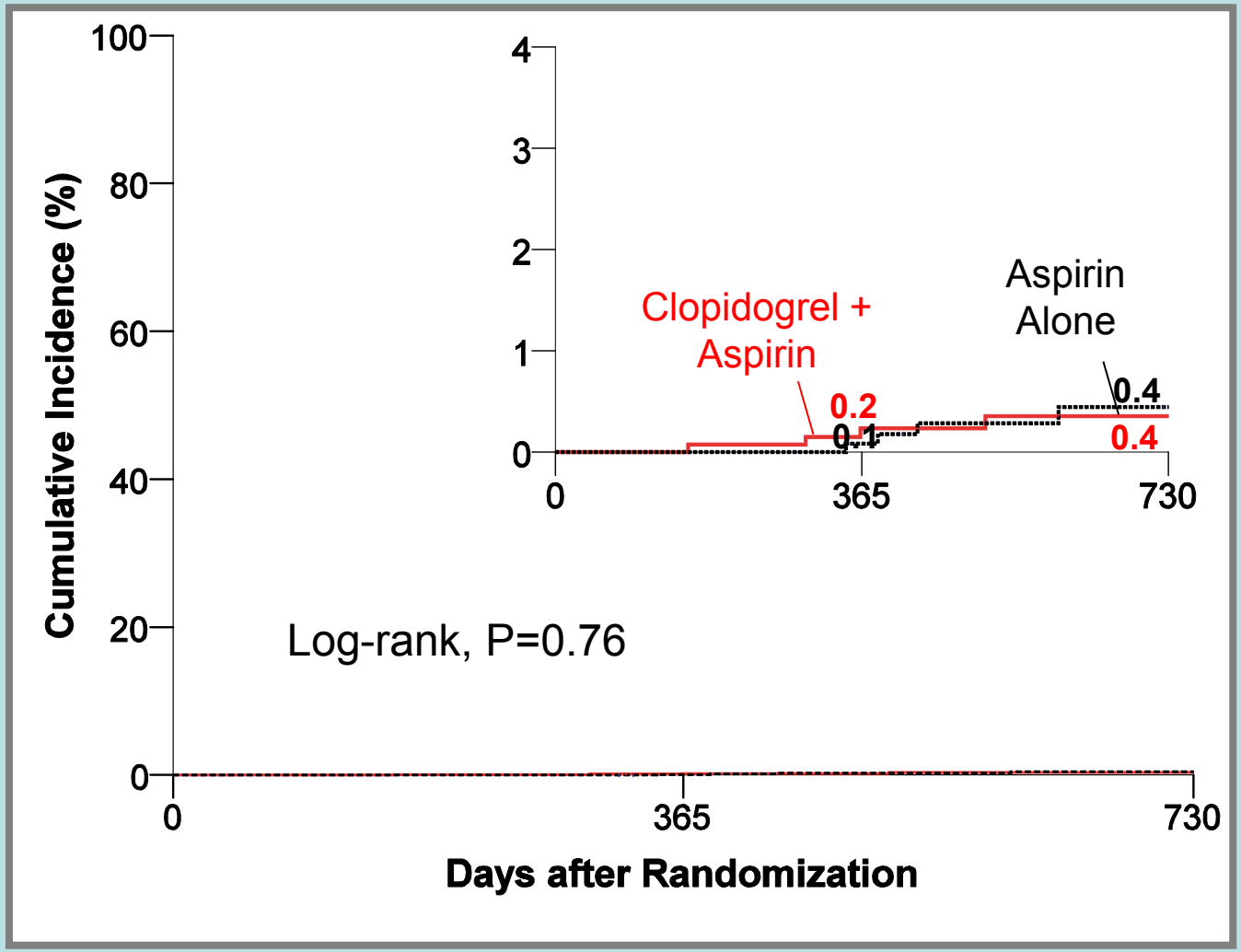
Death from Any Cause



No. at Risk

Continuation group	1357	1125	302
Discontinuation group	1344	1103	303

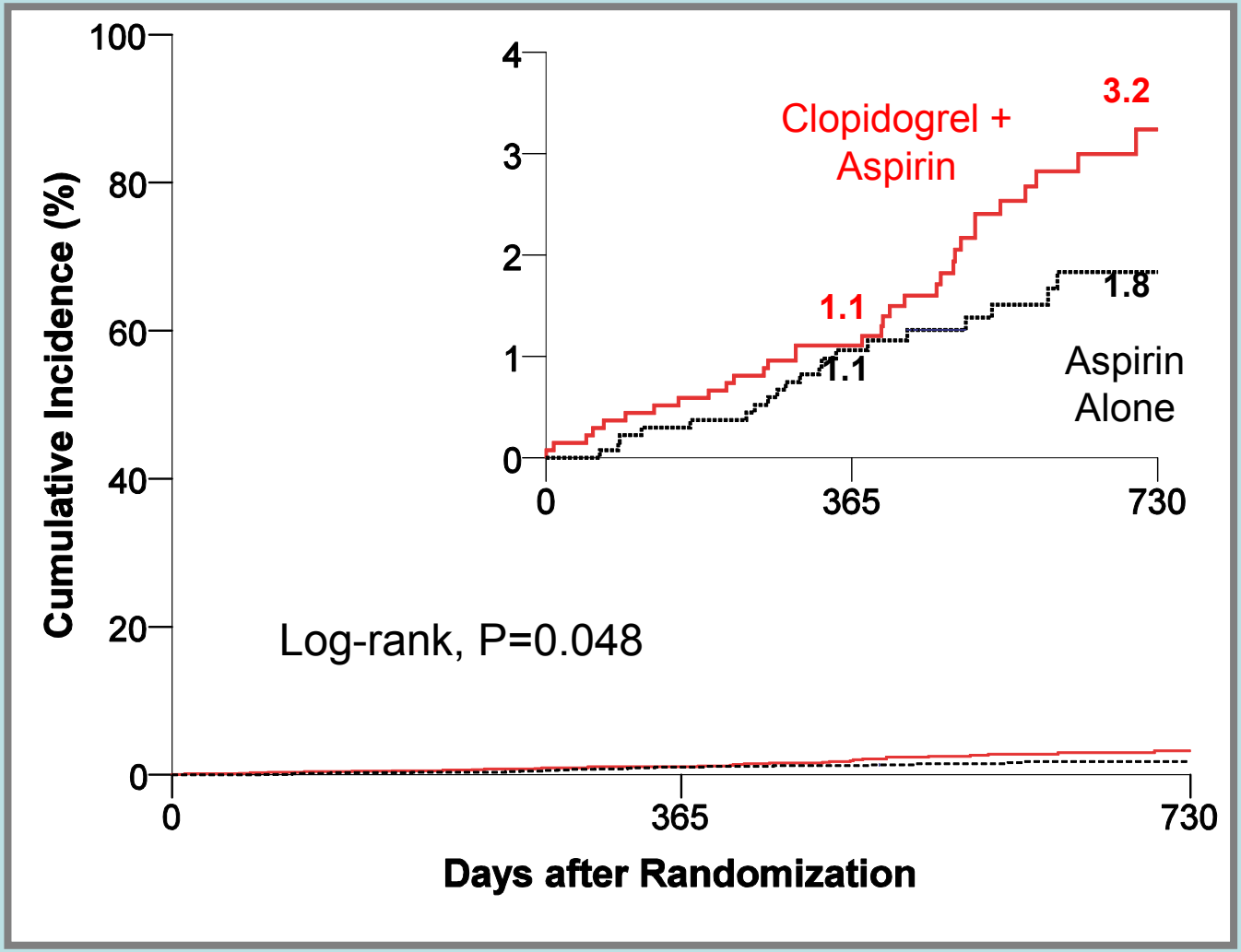
Definite Stent Thrombosis



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 conclusion, in our study, extended use of dual antiplatelet therapy, for more than 12 months, was not significantly more effective than aspirin monotherapy in reducing the risk of myocardial infarction or death from cardiac causes among patients who had received drug-eluting stents and had not subsequently had ischemic or bleeding events.

CONCLUSIONS

- In the group with dual antiplatelet therapy, there was a non-significant increase in the risk of composite end point of myocardial infarction, stoke, or death from any cause and of the composite end point of myocardial infarction, stoke, or death from cardiac causes.
- 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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stent

Seung-Jung Park, M.D, Duk-Woo Park, M.D., Young-Hak Kim, M.D., Soo-Jin Kang, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Ki-Hoon Han, M.D., Seong-Wook Park, M.D., Sung-Cheol Yun, Ph.D., Sang-Gon Lee, M.D., Seung-Woon Rha, M.D., In-Whan Seong, M.D., Myung-Ho Jeong, M.D., Seung-Ho Hur, M.D., Nae-Hee Lee, M.D., Junghan Yoon, M.D., Joo-Young Yang, M.D., Bong-Ki Lee, M.D., Young-Jin Choi, M.D., Wook-Sung Chung, M.D., Do-Sun Lim, M.D., Sang-Sig Cheong, M.D., Kee-Sik Kim, M.D., Jei Keon Chae, M.D., Deuk-Young Nah, M.D., Doo-Soo Jeon, M.D., Ki Bae Seung, M.D., Jae-Sik Jang, M.D., Hun Sik Park, M.D., and Keun Lee, M.D.

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Thank You !!
summitMD.com

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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.