Optimal Duration of Clopidogrel Therapy with DES to Reduce Late Coronary Arterial Thrombotic Event

The DES LATE Trial

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BACKGROUND (I)

- Current guidelines recommend that dual antiplatelet therapy should be given for at least 6-12 months after drug-eluting stents (DES) implantation, unless patients are at high-risk for bleeding.

- However, these recommendations are largely based on registry data, and the optimal duration of dual antiplatelet therapy remains poorly defined.

BACKGROUND (II)

- Previously we reported that compared to aspirin alone, continuation of dual antiplatelet therapy for longer than 12 months after DES implantation is not beneficial (NEJM 2010;362:1374-82).

- Furthermore, the long-term dual-therapy arm was associated with a trend toward increased risk of cardiac death, MI, and stroke

AIM OF THE STUDY

We tested the hypothesis that 12-month dual antiplatelet therapy may provide better protection against CV events than > 12 months of dual antiplatelet therapy after implantation of DES.

STUDY DESIGN (I)

- DES LATE was a prospective, multicenter, open-label, randomised comparison trial that was conducted in 24 clinical centers in Korea.
- The study was an extension of the previous conducted research according to the executive committee's recommendation to clarify our previous findings (NCT01186146).

STUDY DESIGN (II)

Cohort 1:
2,701 Patients
Jul 2007-Sept 2009

5,045 Patients

Cohort 2:
2,344 Patients
Aug 2010-Jul 2011

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 Stroke, MI or Death from cardiac causes

STUDY POPULATION (I)

Inclusion Criteria

Patients were eligible if they had undergone DES implantation at least 12 months before enrollment, had not had a major adverse CV event (MI, stroke, or repeat revascularization) or major bleeding since DES implantation, and were receiving dual antiplatelet therapy at the time of enrollment.

STUDY POPULATION (II)

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 ACS)
- Co-morbid conditions with life expectancy <1 year

TRIAL PROCEDURES AND FOLLOW-UP

- Patients were randomly assigned either to clopidogrel (75 mg per day) plus aspirin (100 to 200 mg per day) or aspirin alone.
- 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, outcome, adverse events, and drug compliance were recorded.

END POINTS

Primary End Points

A composite of death from cardiac causes, myocardial infarction, or stroke 24 months after randomisation.

Secondary End Points

- Each component of death, myocardial infarction, stroke, definite stent thrombosis, or TIMI major bleeding
- Composite death or myocardial infarction
- Composite death, myocardial infarction or stroke
- Composite cardiac death, MI, stroke, or TIMI major bleeding

SAMPLE SIZE ESTIMATION

- The sample size was calculated by assuming primary endpoint incidence of 1.3% and 2.7% for the aspirin-alone and dual-therapy groups, respectively (relative risk 0·5) at 24 months based on the log-rank test.

- A final sample size of 5,000 patients for two groups would provide statistical power of 80%, with a 2-sided α level of 0·05, on the assumption that 10% would be lost to follow-up.

STATISTICAL ANALYSIS

- The data of all patients enrolled in the first cohort and the extended second cohort were included in the analysis, and all analyses were based on the intention-to-treat principle.

- To determine whether merging of the data from the two cohorts would be appropriate, we conducted a homogeneity test using a likelihood test, indicating that the assumption of homogeneity was not violated (chi square=0·034, degree of freedom=1, P=0·85).

Baseline Patients Characteristics

Characteristic	Aspirin Alone (n=2514)	Clopidogrel + Aspirin (n=2531)	P Value
Age (yr)	62.3±10.1	62.5±10.0	0.48
Men	1749 (69.6%)	1749 (69.1%)	0.74
Current smoker	722 (28.7%)	693 (27.4%)	0.30
Diabetes mellitus	709 (28.2%)	709 (28.0%)	0.90
Hypertension	1423 (56.6%)	1479 (58.4%)	0.19
Hypercholesterolemia	297 (11.8%)	303 (12.0%)	0.86
Previous MI	92 (3.7%)	103 (4.1%)	0.47
Previous stroke	89 (3.5%)	15 (4.5%)	0.07
Previous angioplasty	276 (11.0%)	313 (12.4%)	0.13

***total cholesterol > 200 mg/dl**

Characteristic	Aspirin Alone (n=2514)	Clopidogrel+ Aspirin (n=2531)	P Value
Ejection fraction (%)	59.4±8.7	59.3±9.4	0.69
Multivessel disease	1184 (47.1)	1279 (50.5)	0.014
Clinical indication			0.79
Stable angina	956 (38.0)	1011 (39.9)	
Unstable angina	971 (38.6)	930(36.7)	
NSTEMI	266(10.6)	268 (10.6)	
STEMI	314 (12.5)	314 (12.4)	
Discharge medications			
Aspirin	2504 (99.6)	2521 (99.6)	>0.99
Clopidogrel	2502 (99.5)	2521 (99.6)	0.68
ACE inhibitor	1253 (49.8)	1298 (51.3)	0.31
ß-blockers	1623 (64.6)	1685 (66.6)	0.14
Calcium channel blocker	1237 (49.2)	1210 (47.8)	0.32
Statin	2070 (82.3)	2080 (82.2)	0.91

Baseline Lesions Characteristics

Characteristic	Aspirin Alone (n=2514)	Clopidogrel + Aspirin (n=2514)	P Value
Vessel treated			0.09
Left anterior descending artery	1768 (50.6)	1781 (49.5)	
Left circumflex artery	651 (18.6)	715 (19.9)	
Right coronary artery	972 (27.8)	976 (27.1)	
Left main disease	90 (2.6)	112 (3.1)	
B2 or C type	2734 (78.2)	2838 (78.8)	0.53
Calcification	172 (4.9)	168 (4.7)	0.62
Bifurcation	475(13.6)	477 (13.2)	0.67
Total occlusion	393 (11.2)	407 (11.3)	0.94

Baseline Procedural Characteristics

Characteristic	Aspirin Alone (n=2514)	Clopidogrel + Aspirin (n=2531)	P Value
Lesions stented, No	3603	3498	
Stents per lesion, No.	1.2±0.5	1.3±0.5	0.013
Stent length per lesion, mm	29.9±15.4	30.8±16.3	0.028
Type of drug-eluting stents			0.25
Sirolimus-eluting stents	1551 (44.3)	1566 (43.5)	
Paclitaxel-eluting stents	709 (20.3)	738 (20.5)	
Zotarolimus-eluting stents	664 (19.0)	682 (18.9)	
Everolimus	364 (10.4)	427(11.9)	
Others	210 (6.0)	190 (5.3)	

Timing of Randomization after the Index PCI

Characteristic	Aspirin Alone (n=2514)	Clopidogrel + Aspirin (n=2531)	P Value
Time to randomization			0.66
12 Mo – 18 Mo after procedure	2046 (81.4)	2039 (80.6)	
18 Mo – 24 Mo after procedure	292 (11.6)	315 (12.4)	
> 24 Mo after procedure	176 (7.0)	177 (7.0)	
Median (interquartile range)	13.2 (12.1,16.1)	13.3 (12.1,16.4)	

Status of Antiplatelet Therapy during Follow up

Characteristic	Aspirin Alone (n=2514)	Clopidogrel + Aspirin (n=2531)	P Value
Aspirin			
At randomization	2503/2514 (99.6)	2516/2531 (99.4)	0.44
6 Mo after randomization	2400/2426(98.9)	2442/2473(98.7)	0.55
12 Mo after randomization	2361/2405 (98.2)	2380/2361 (97.7)	0.29
18 Mo after randomization	2218/2257(98.3)	2248/2299 (97.8)	0.23
24 Mo after randomization	1975/2032 (97.2)	1958/2045 (95.7)	0.012
Clopidogrel			
At randomization	81/2514 (3.2)	2494/2531 (98.5)	<0.001
6 Mo after randomization	140/2285 (5.8)	2359 /2473(95.4)	<0.001
12 Mo after randomization	169/2407(7.0)	2157/2435 (88.6)	<0.001
18 Mo after randomization	172/2102 (7.6)	1909/2329 (82.0)	<0.001
24 Mo after randomization	164/2032 (8.1)	1625/2046 (79.4)	<0.001

Follow-Up and Compliance

Follow-up rate

Median length of follow-up: 42.0 months (IQR, 24.7 -50.7).

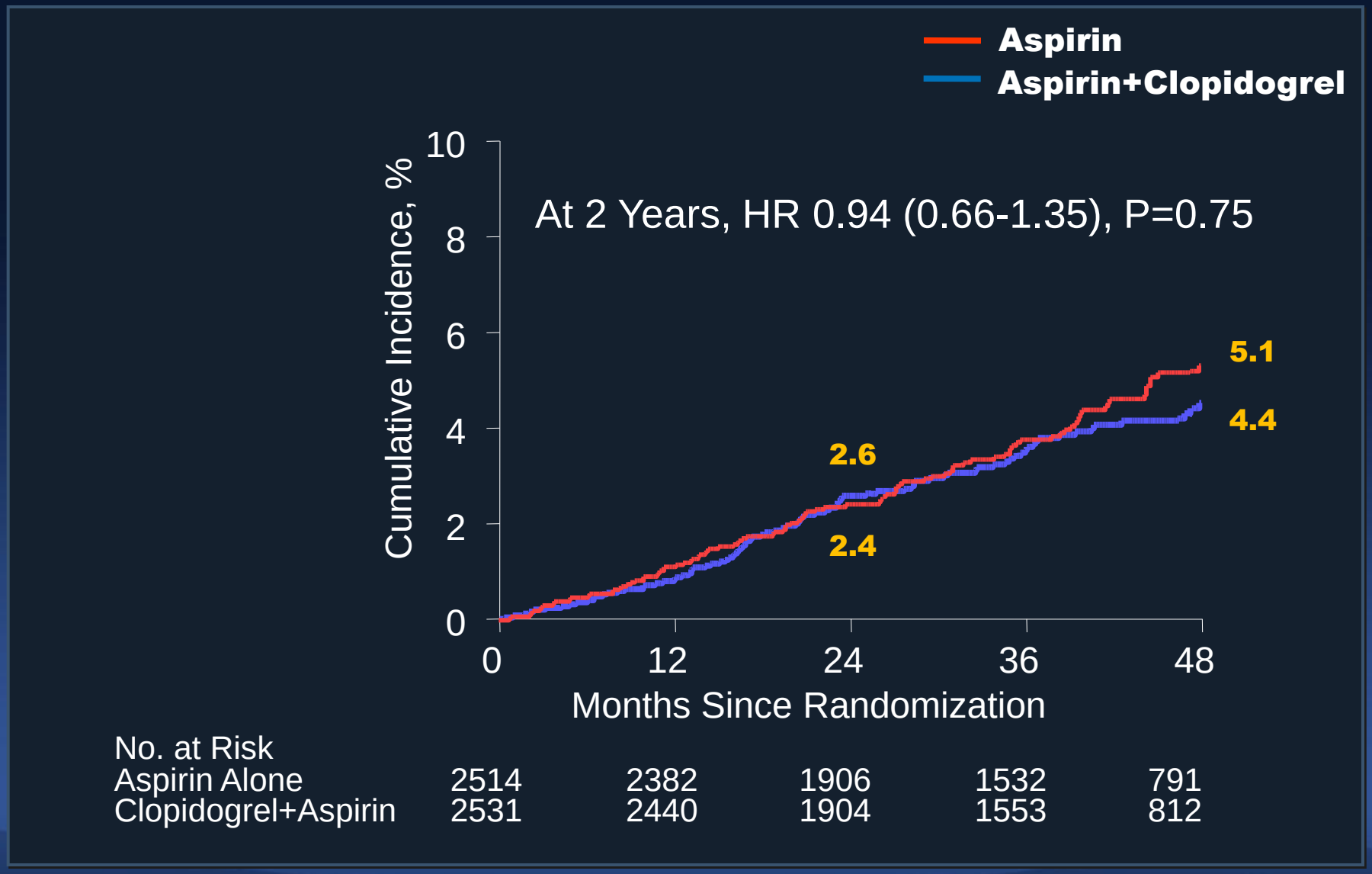
Follow-up: complete for 97.2%, 95%, & 87.7% of the eligible patients at 12, 24, and 48 months, respectively.

Adherence to the assigned study treatments

Aspirin-alone group: 98.2%, 97.2% at 12 and 24 months

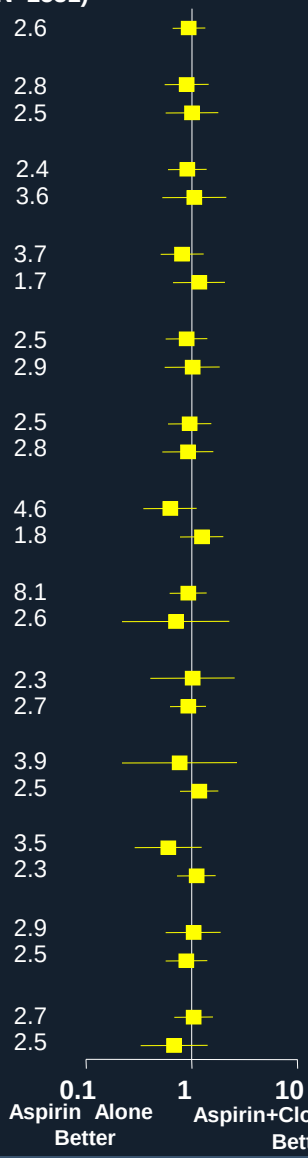
Dual-therapy group: 88.6%, 79.4% at 12 and 24 months

Primary End Point: Cardiac Death, MI, Stroke



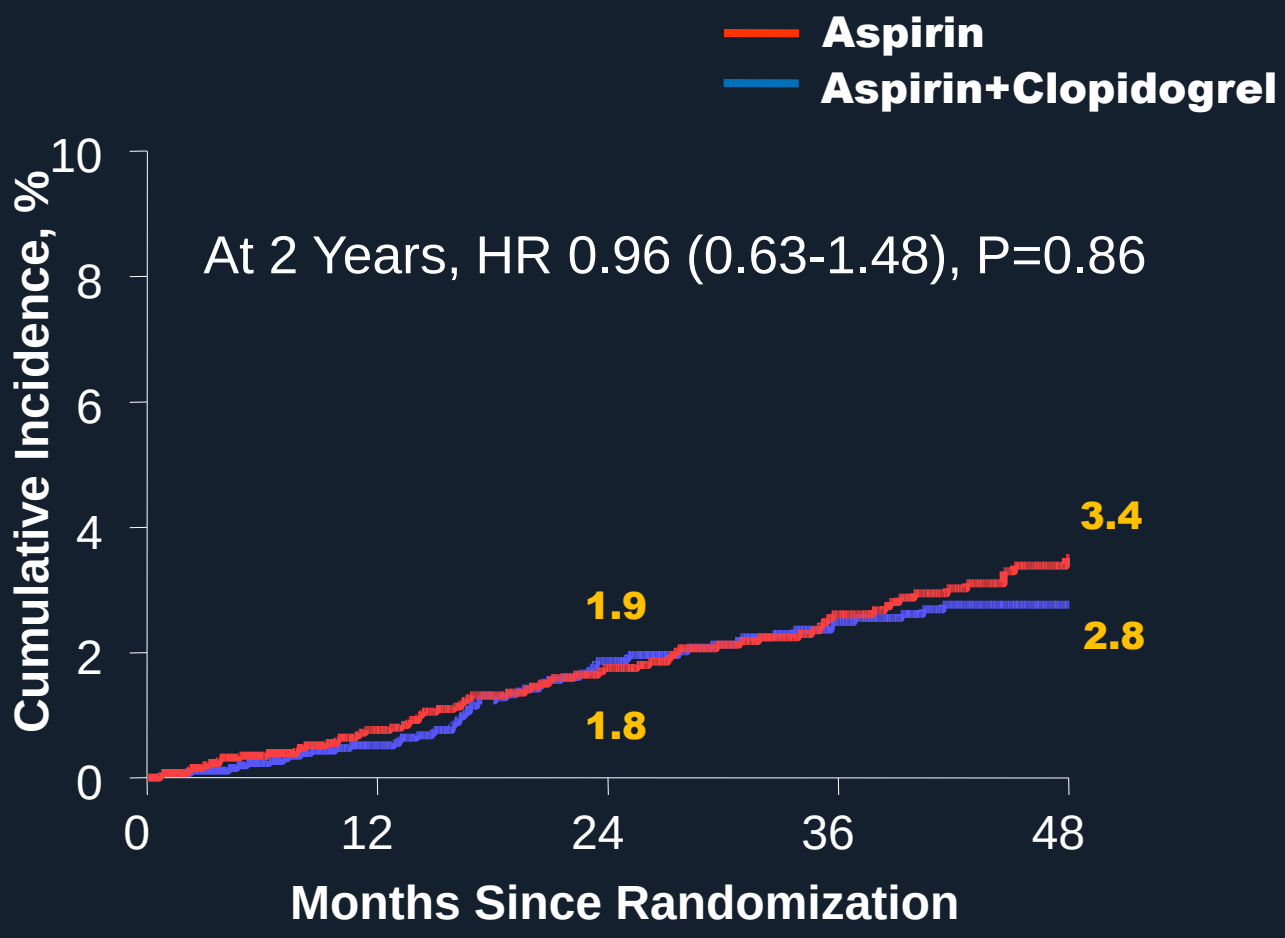
Subgroup Analysis

	Mono (N=2514)	Dual (N=2531)	Hazard Ratio (95% CI)	P value	Interaction P value
Overall	2.4	2.6	0.94 (0.66, 1.35)	0.75	
Cohort					0.76
First (N=2701)	2.5	2.8	0.90 (0.56, 1.45)	0.66	
Second (N=2344)	2.4	2.5	1.01 (0.57, 1.79)	0.98	
Time of Randomization					0.73
≤18 mon (N=4097)	2.2	2.4	0.91 (0.60, 1.39)	0.67	
>18 mon (N=948)	3.6	3.6	1.06 (0.53, 2.13)	0.87	
Age					0.32
≥65 yo (N=2739)	2.9	3.7	0.81 (0.51, 1.30)	0.38	
<65 yo (N=2306)	2.0	1.7	1.18 (0.67, 2.08)	0.58	
Sex					0.73
Male (N=3498)	2.2	2.5	0.90 (0.57, 1.41)	0.64	
Female (N=1547)	2.9	2.9	1.02 (0.56, 1.85)	0.95	
Acute coronary syndrome					0.92
Yes (N=3063)	2.4	2.5	0.96 (0.60, 1.54)	0.85	
No (N=1982)	2.5	2.8	0.92 (0.53, 1.61)	0.78	
Diabetes					0.07
Yes (N=1418)	2.9	4.6	0.63 (0.35, 1.12)	0.12	
No (N=3627)	2.3	1.8	1.25 (0.78, 2.00)	0.37	
Ejection fraction					0.66
≤40% (N=191)	5.6	8.1	0.93 (0.62, 1.39)	0.57	
>40% (N=4172)	2.4	2.6	0.71 (0.22, 2.27)	0.73	
Bifurcation					0.85
Yes (N=839)	2.3	2.3	1.02 (0.41, 2.56)	0.96	
No (N=4206)	2.5	2.7	0.93 (0.63, 1.37)	0.71	
Left main disease					0.74
Yes (N=314)	3.0	3.9	0.77 (0.22, 2.70)	0.68	
No (N=4731)	2.4	2.5	1.18 (0.78, 1.79)	0.85	
Long (>40mm) stenting					0.15
Yes (N=1193)	2.1	3.5	0.60 (0.29, 1.25)	0.17	
No (N=3852)	2.5	2.3	1.11 (0.73, 1.69)	0.61	
Multivessel stenting					0.69
Yes (N=1604)	3.0	2.9	1.04 (0.57, 1.89)	0.45	
No (N=3441)	2.2	2.5	0.89 (0.57, 1.41)	0.64	
Type of DES					0.33
Previous DES (N=3318)	2.8	2.7	1.04 (0.69, 1.59)	0.83	
New DES (N=1727)	1.7	2.5	0.68 (0.33, 1.43)	0.32	



Outcome	Cumulative Event Rate at 24 Months		Hazard Ratio (95% CI)	P Value
	Aspirin Alone	Dual therapy		
Primary End Point				
Cardiac death, MI, Stroke	2.4	2.6	0.94 (0.66-1.35)	0.75
Secondary End Points				
Death	1.4	2.0	0.71 (0.45-1.10)	0.12
MI	1.2	0.8	1.43 (0.80-2.58)	0.23
Stroke	0.9	0.9	1.01 (0.55-1.85)	0.98
Stent thrombosis, definite	0.5	0.3	1.59 (0.61-4.09)	0.34
TIMI Major Bleeding	1.1	1.4	0.71 (0.42-1.20)	0.20
Repeat revascularization	2.8	3.5	081 (0.58-1.12)	0.20
Death, MI or Stroke	3.0	3.3	0.89 (0.65-1.24)	0.49
Cardiac death, MI, stroke, TIMI Bleeding	3.2	3.8	0.84 (0.62-1.14)	0.26

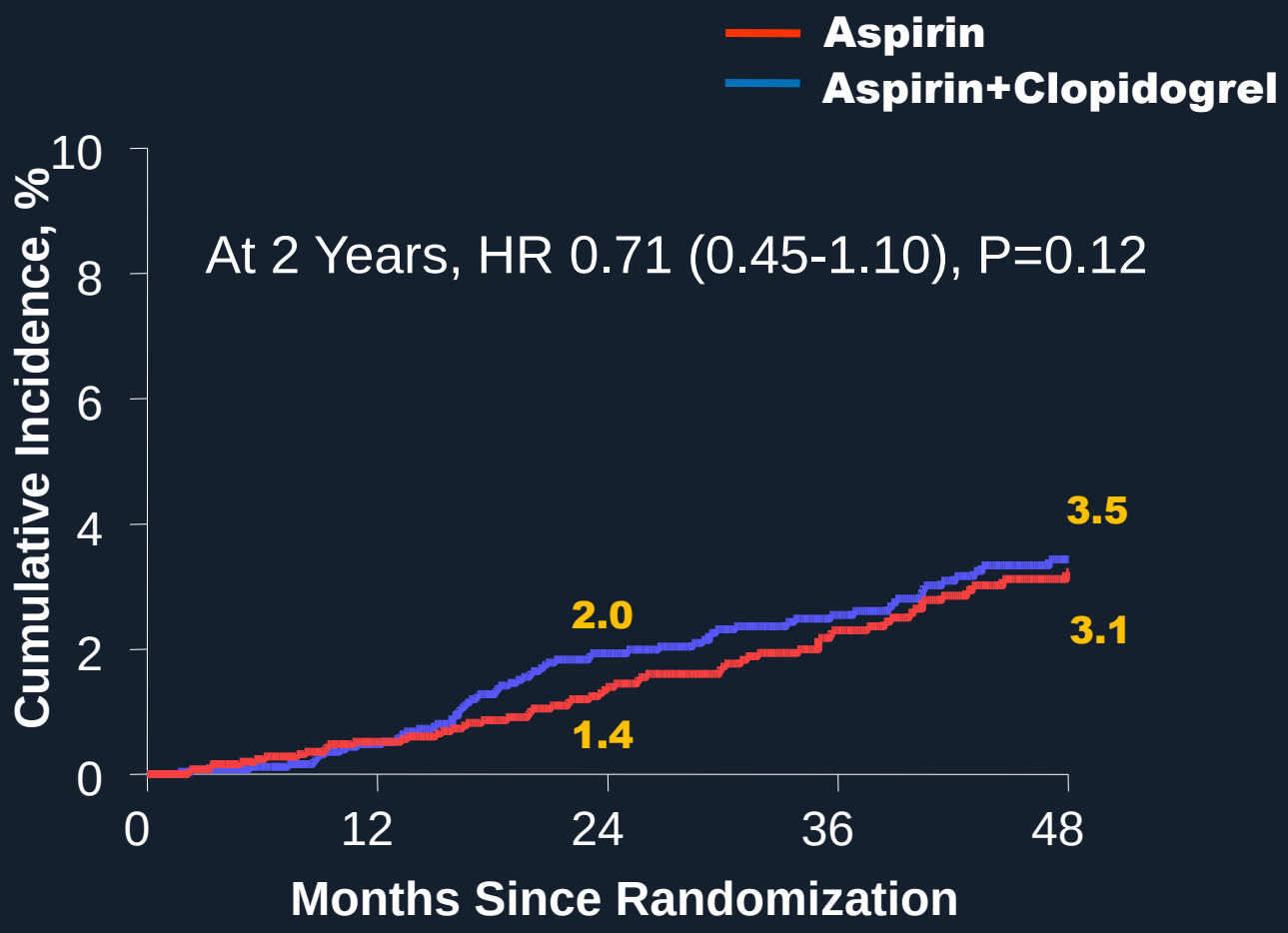
Cardiac Death or MI



No. at Risk

Aspirin Alone	2514	2384	1917	1545	795
Clopidogrel+Aspirin	2531	2442	1912	1597	811

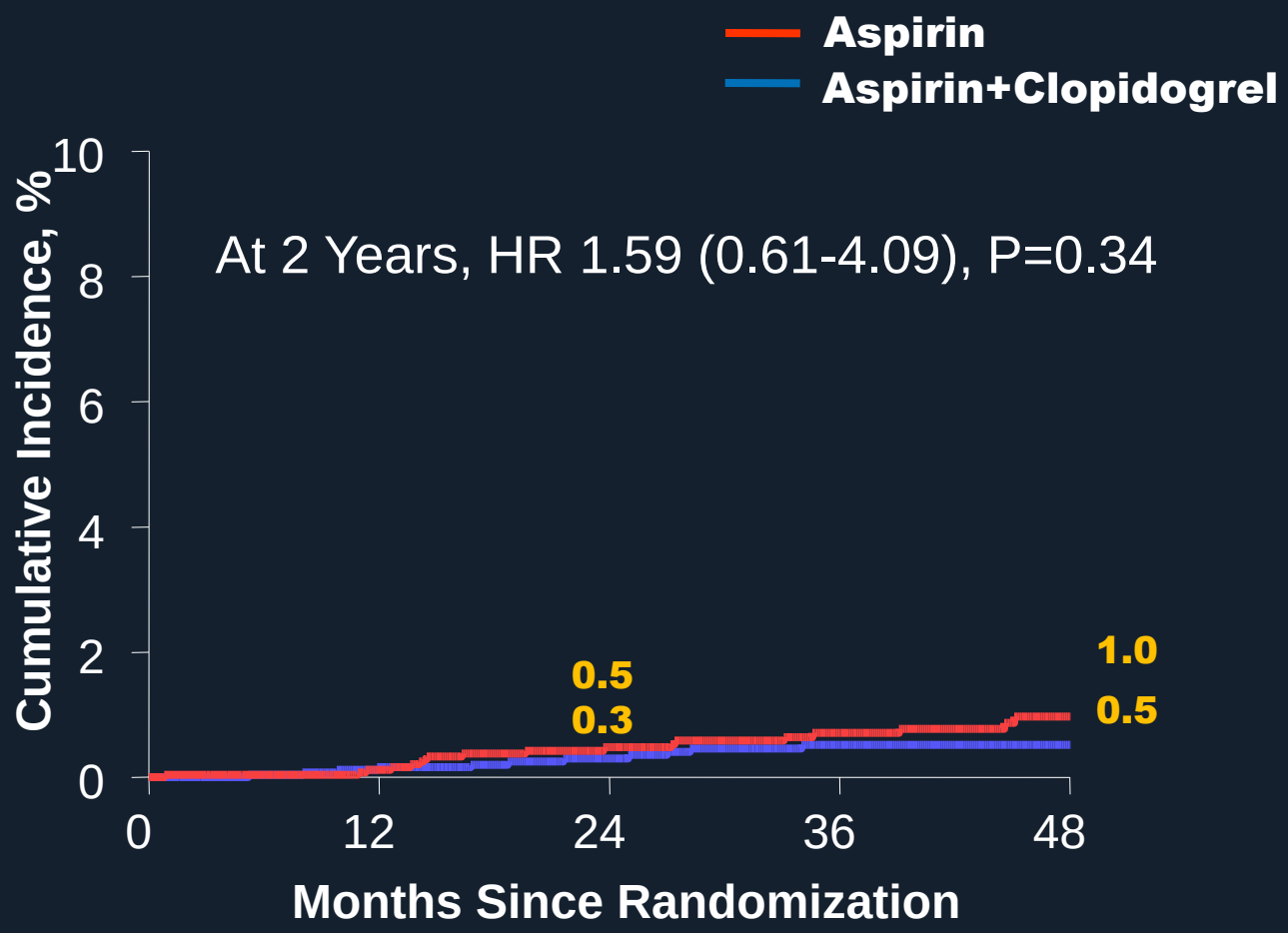
Death from Any Causes



No. at Risk

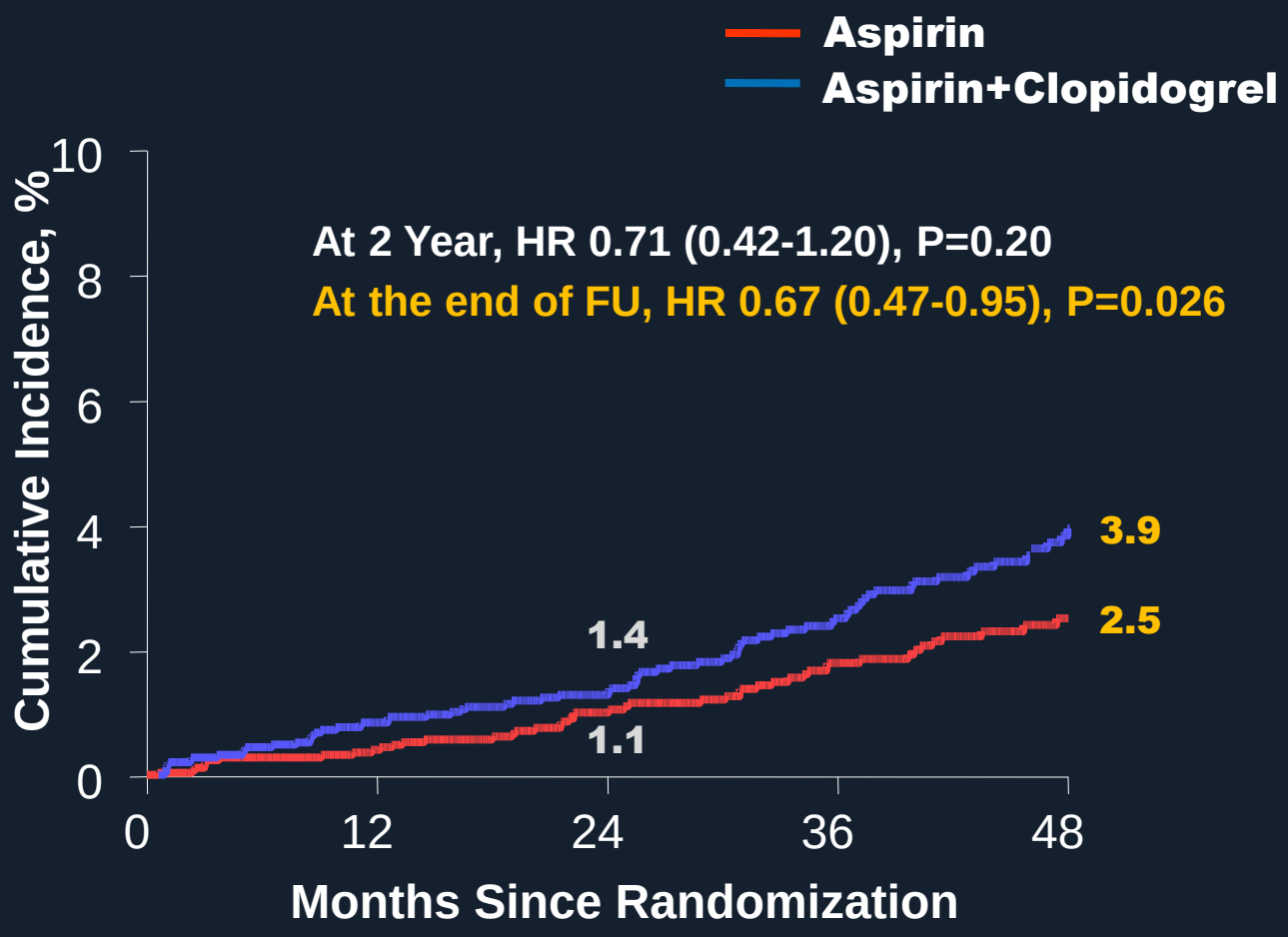
Aspirin Alone	2514	2399	1936	1568	815
Clopidogrel+Aspirin	2531	2455	1926	1582	834

Definite Stent thrombosis



No. at Risk					
Aspirin Alone	2514	2397	1930	1559	811
Clopidogrel+Aspirin	2531	2452	1922	1575	830

TIMI Major Bleeding



No. at Risk

Aspirin Alone	2514	2392	1924	1552	802
Clopidogrel+Aspirin	2531	2435	1912	1555	810

CONCLUSIONS

- In stable patients receiving DES, aspirin monotherapy compared with dual antiplatelet therapy for longer than 12 months did not reduce the risk of death from cardiac causes, MI, or stroke.

- Aspirin monotherapy was associated with lower risk of TIMI major bleeding during the follow-up period.

CONCLUSIONS

- These findings suggest that two antiplatelet strategies provide similar protection from ischemic events with less risk of bleeding in aspirin monotherapy.

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