Smart Antiplatelet Therapy after DES Implantation

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Contents

- Duration of dual antiplatelet therapy (DAPT)
  - Short vs. prolonged DAPT
  - Consideration in special subset patients

- Effective monotherapy after DAPT
  - Aspirin vs. clopidogrel

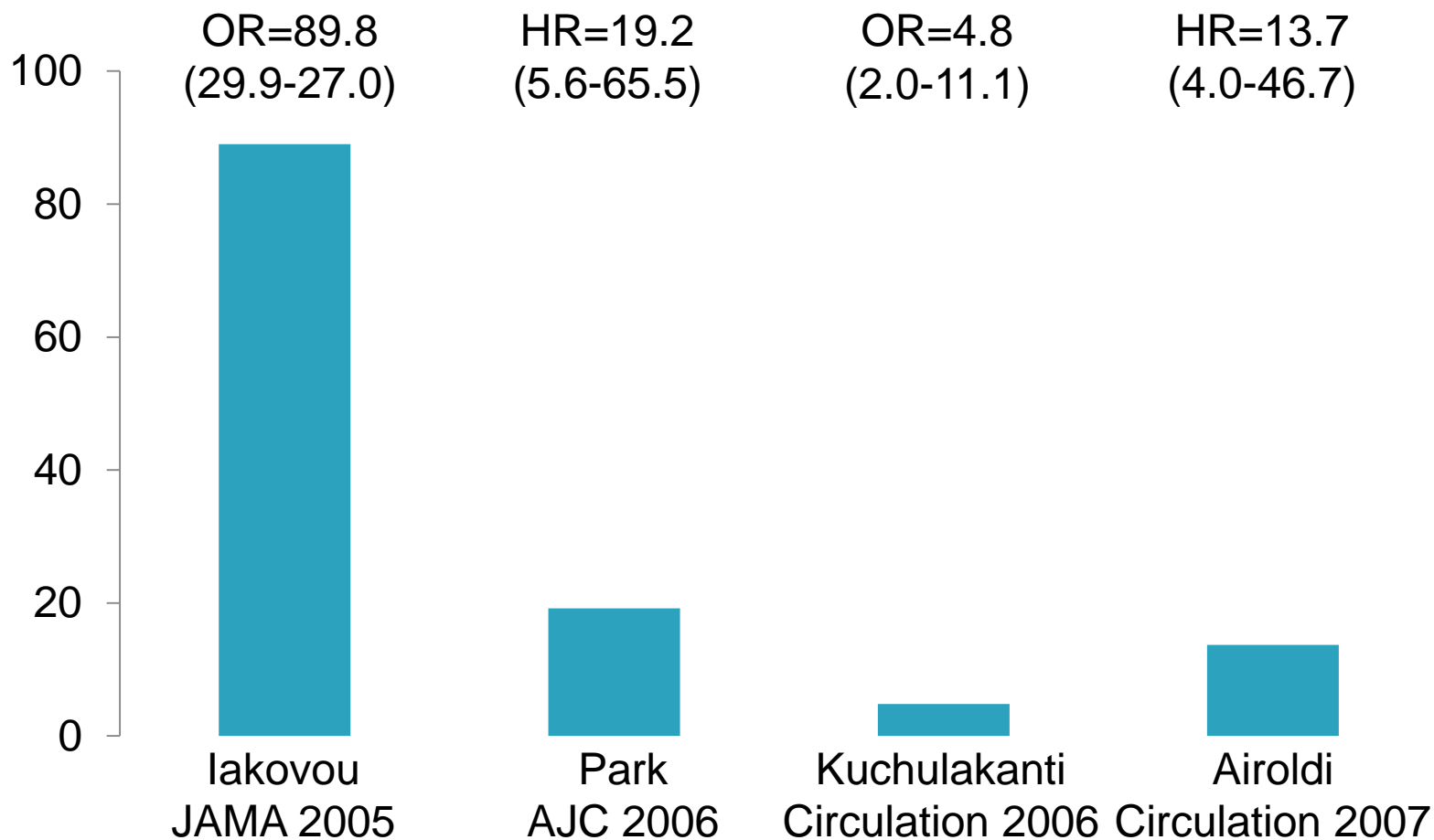Samsung Medical Center

Contents

▸ **Duration of dual antiplatelet therapy (DAPT)**
- ◦ Short vs. prolonged DAPT
- ◦ Consideration in special subset patients

▸ Effective monotherapy after DAPT
- ◦ Aspirin vs. clopidogrel

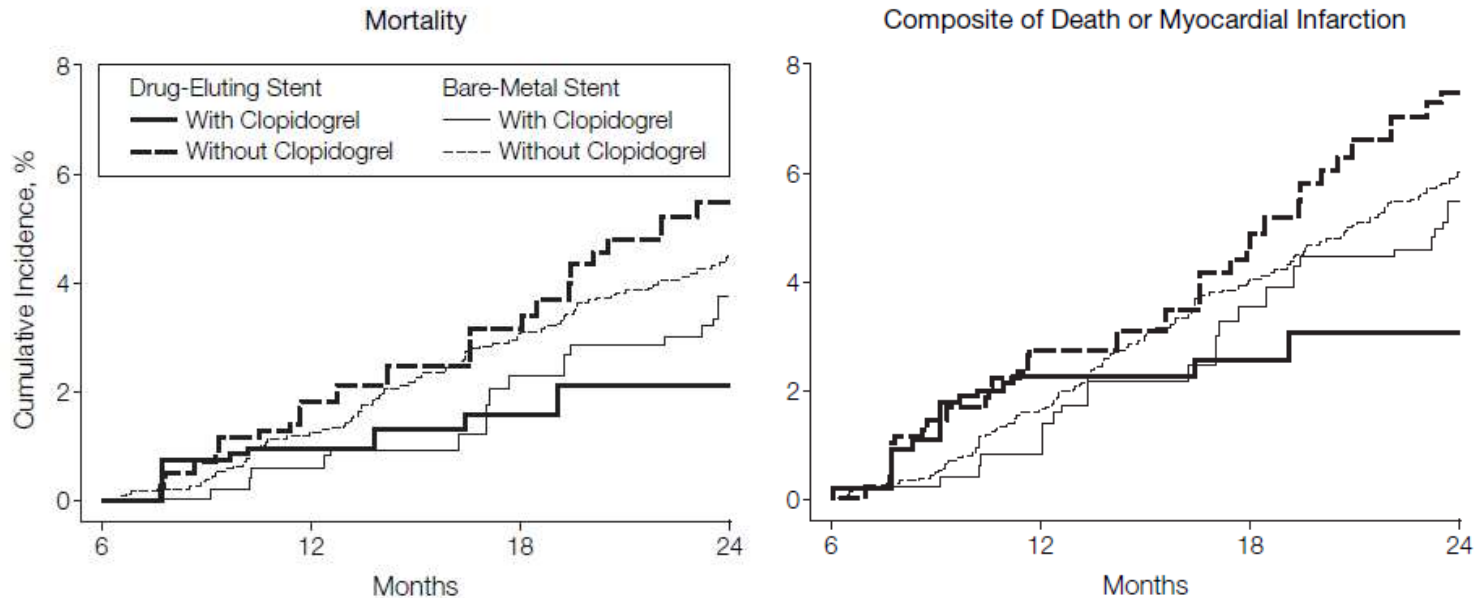# Premature discontinuation of clopidogrel

the most important predictor of stent thrombosis after DES implantation

OR=89.8 (29.9-27.0)   HR=19.2 (5.6-65.5)   OR=4.8 (2.0-11.1)   HR=13.7 (4.0-46.7)

Iakovou JAMA 2005 — Park AJC 2006 — Kuchulakanti Circulation 2006 — Airoldi Circulation 2007

Clopidogrel Use and Long-term Clinical Outcomes

Mortality

Composite of Death or Myocardial Infarction

JAMA. 2007;297:159-168

Milan-Siegburg Study
No increase of risk by the discontinuation of clopidogrel after 6 months:

▸ 3,021 patients treated with DES

HR =13.7
(4.0-47)
p<0.001

HR=0.94
(0.3-3.0)
p=0.98

Airoldi F, Circulation 2007
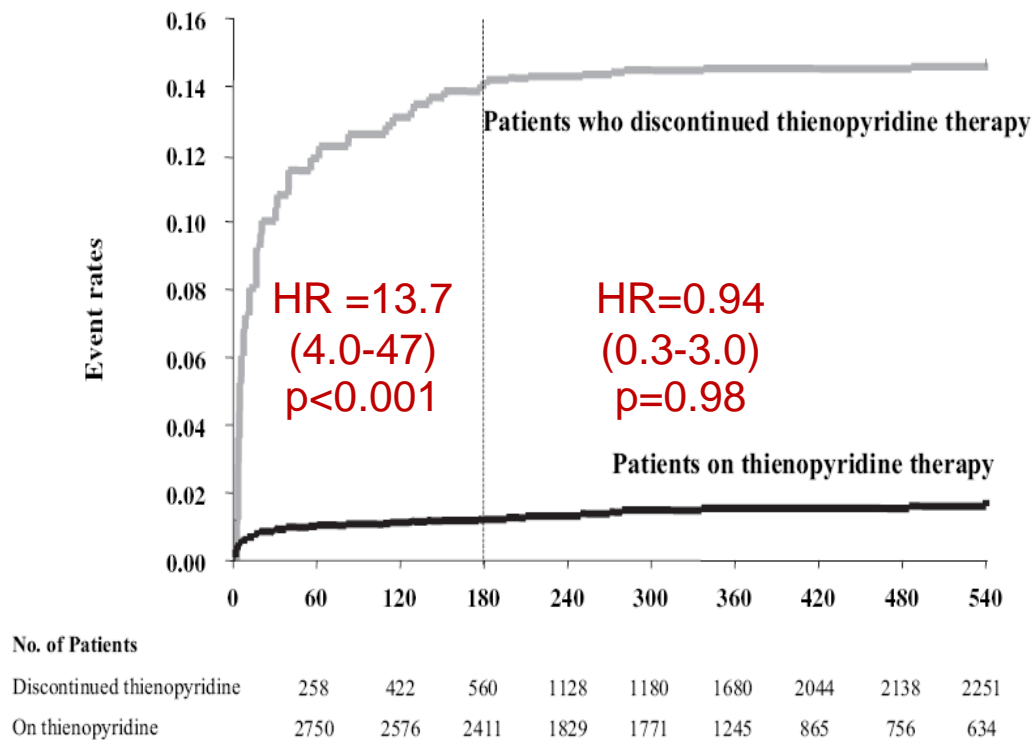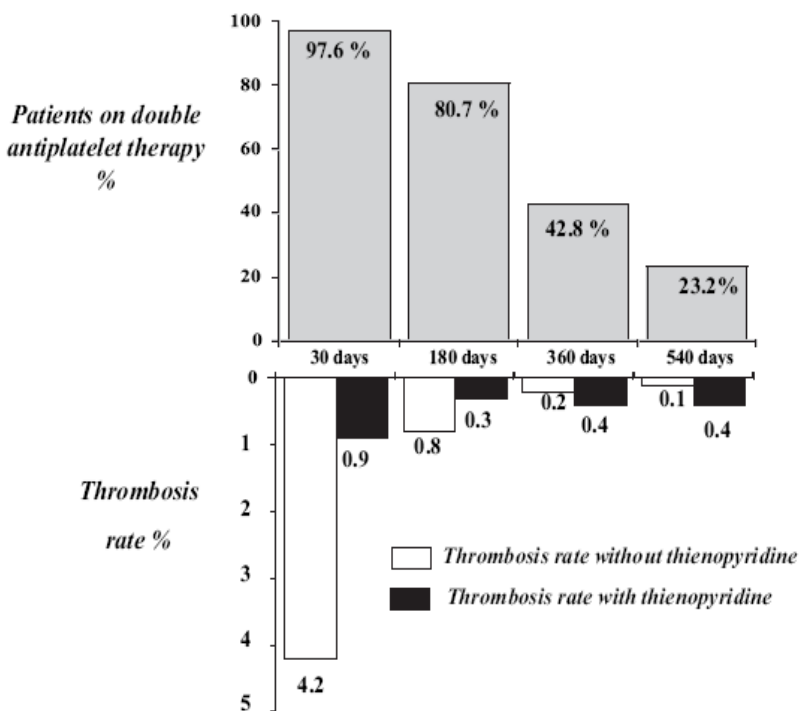
REAL-LATE and ZEST-LATE trials

A Primary End Point: MI or Death from Cardiac Causes

P=0.17
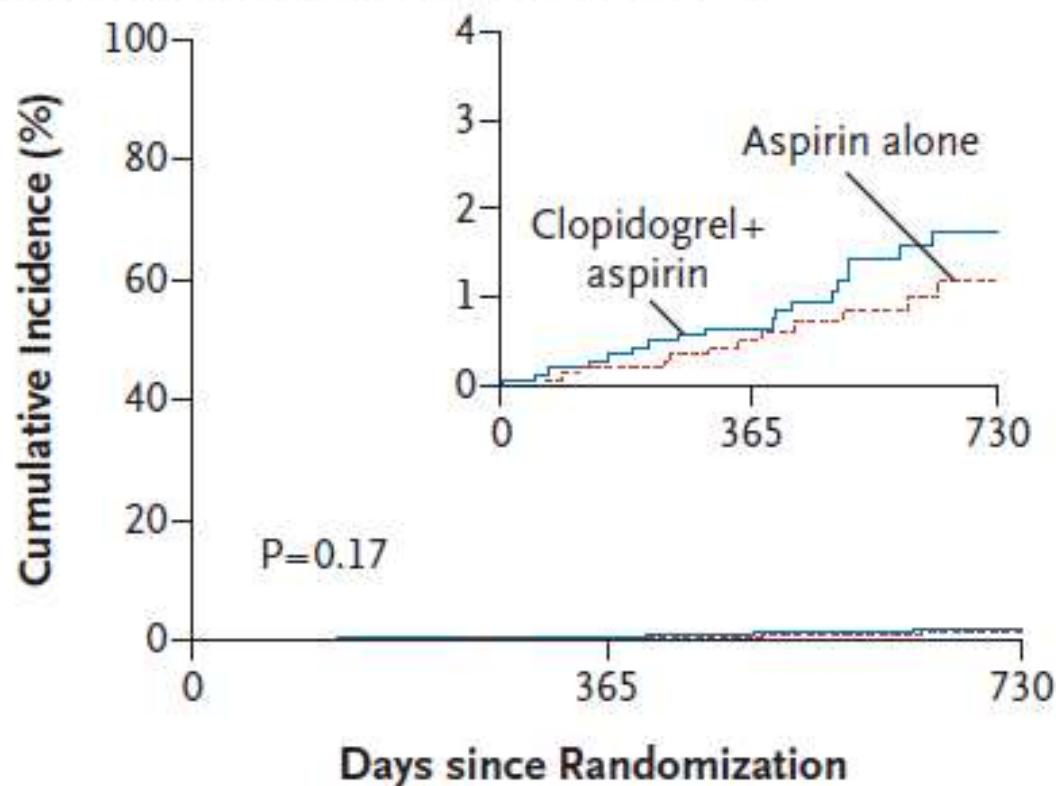
No. at Risk

Clopidogrel+aspirin	1357	1122	299
Aspirin alone	1344	1100	301

Park SJ et al. N Engl J Med 2010;362:1374-82   Samsung Medical Center

EXCELLENT Trial
1° EP: Target Vessel Failure (TVF)

N=1,443
HR = 1.10 (95% CI 0.68-1.79)
Superiority p=0.708
Non-inferiority p=0.001

6-mo DAPT
12-mo DAPT

4.7%
4.4%
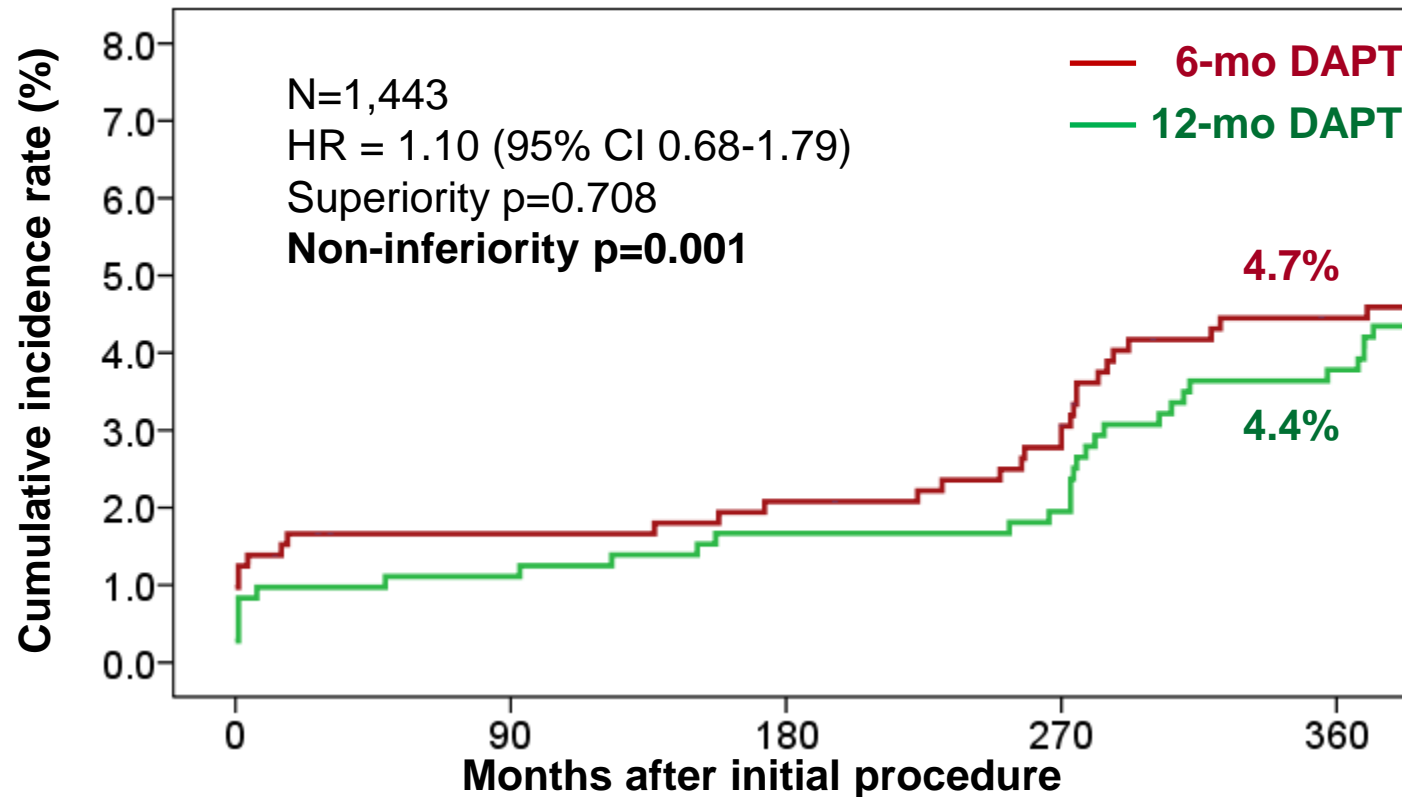
Patient Number at Risks

6-month	722	707	704	698	682
12-month	721	710	703	698	682

* DAPT = dual antiplatelet therapy

EXCELLENT Trial
2° EP: Death, MI, ST, CVA, or major bleeding

P=0.644
HR = 1.15 (95% CI 0.64 – 2.06)

6-mo DAPT
12-mo DAPT

3.4%
3.0%

Cumulative incidence rate (%)

Months after initial procedure
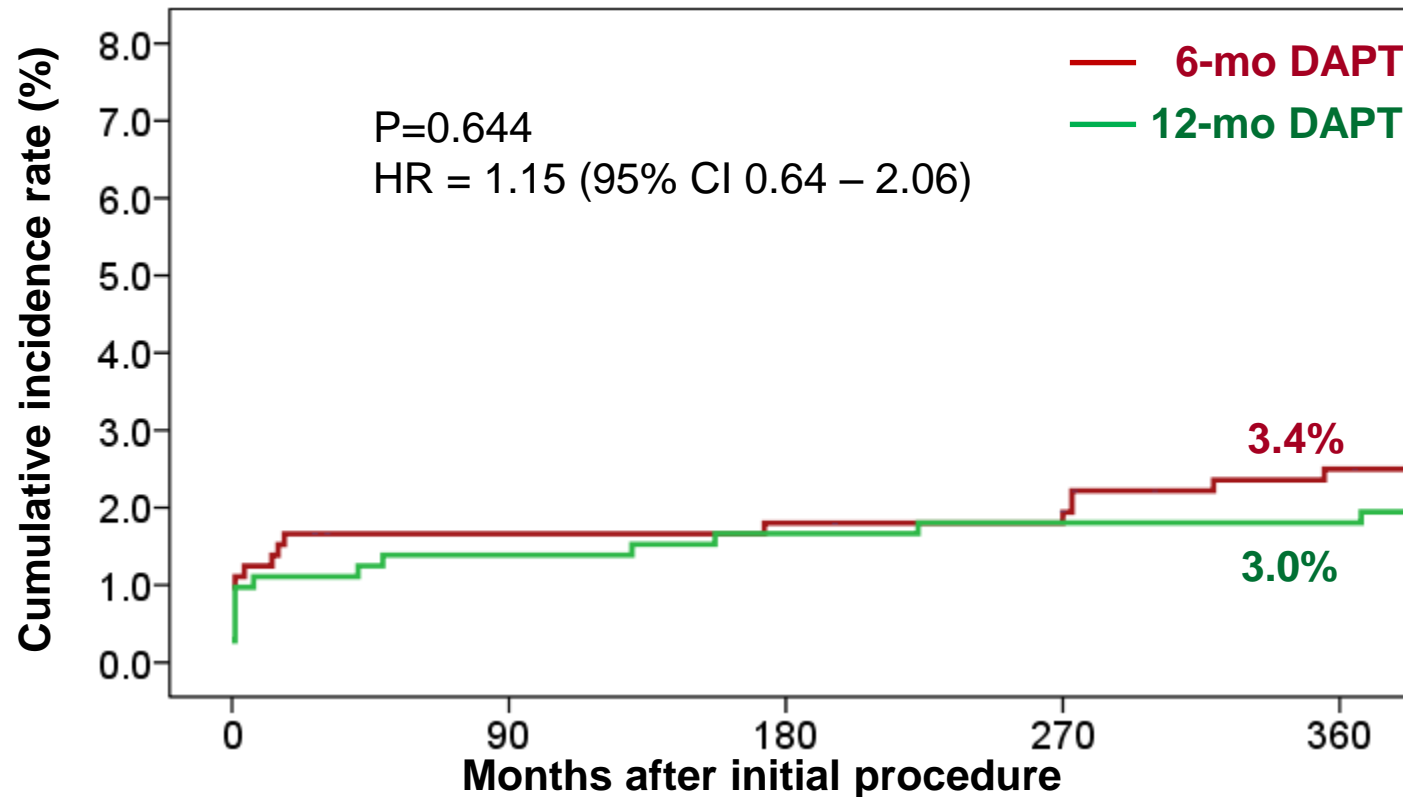
Patient Number at Risks

6-month	722	708	707	706	698
12-month	721	710	706	704	699

TCTAP 2014   Gwon HC, Hahn JY et al. Circulation 2012   Samsung Medical Center

PRODIGY Study

▸ N=2013, comparing 6- vs. 24-months DAPT

Death, MI or CVA
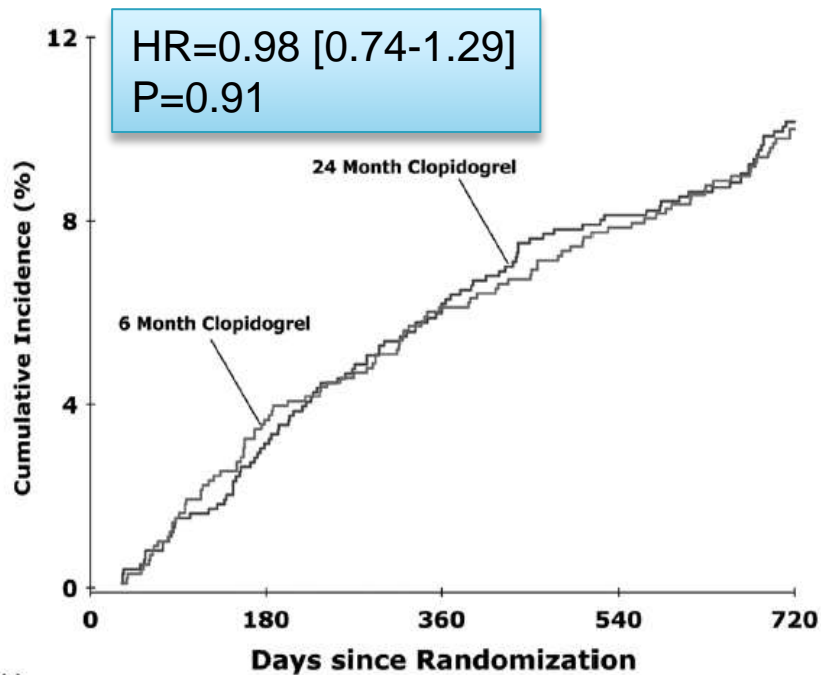
HR=0.98 [0.74-1.29]
P=0.91

24 Month Clopidogrel

6 Month Clopidogrel

No. at Risk
24-Month Clopidogrel 987 — 925 — 884
6-Month Clopidogrel 983 — 919 — 881

BARC Type 5,3,2 Bleeding

HR=2.17 [1.44-3.22]
P=0.0002

24 Month Clopidogrel

6 Month Clopidogrel

No. at Risk
24-Month Clopidogrel 987 — 911 — 858
6-Month Clopidogrel 983 — 923 — 892

Valgimigli M, Circulation 2012
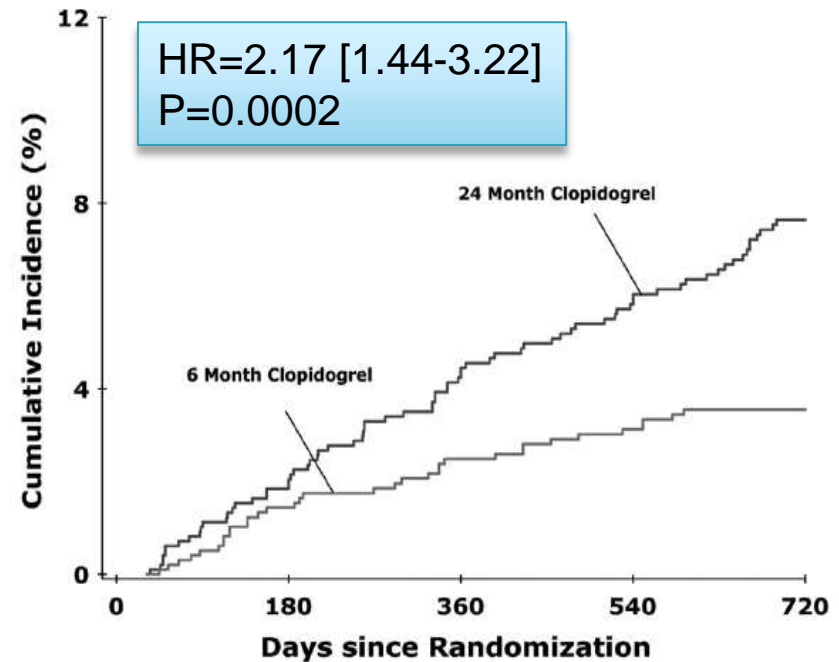
▸ Meta-analysis of LATE, EXCELLENT, and PRODIGY

a

Study

ID

Cardiac death/MI/stroke
OR=1.26 (0.88-1.80)

Events, Events, %

Park et al, 2010

Gwon et al, 2011

Valgimigli et al, 2011

Overall (I-squared =

NOTE: Weights are f

e

Study

ID

Definite or probable stent thrombosis
OR=0.73 (0.31-1.72)

Events, Events, %

Park et al, 2010

Gwon et al, 2011

Valgimigli et al, 2011

Overall (I-squared =

NOTE: Weights are fr

b

Study ID		OR (95% CI)	Events, Long DAPT	short DAPT	% Weight
Major bleeding OR=2.51(1.10-5.71)					
Park et al. 2010		2.98 (0.31, 28.64)	3/1357	1/1344	12.67
Gwon et al, 2011		2.01 (0.37, 11.00)	4/721	2/722	25.11
Valgimigli et al, 2011		2.61 (0.93, 7.37)	13/741	5/737	62.23
Overall (I-squared = 0.0%, p = 0.954)		2.51 (1.10, 5.71)	20/2819	8/2803	100.00

.01 .1 1 10 100

Long DAPT better   Short DAPT better

Valgimigli M, Int J Cardiol 2013

Risk factors of stent thrombosis

▸ **Procedure related**

  ◦ Stent underexpansion, stent malapposition, stent length, multiple stents, geographic miss, positive remodeling, persistent slow flow, residual stenosis, dissection

▸ **Lesion related**

  ◦ Necrotic core, bifurcation lesion, instent restenosis, chronic total occlusion, diffuse di...

▸ **Pati...**

  ◦ A...MI, ACS, diabetes, renal failure, low EF, young age, smoking

> The appropriate duration of DAPT may be different according to the risk profile.

▸ **Stent related**

  ◦ Antiproliferative agent, coating technology, polymer biocompatibility, strut/polymer thickness, stent structure, drug dosage

▸ **Dual antiplatelet therapy (DAPT) related**

  ◦ Premature discontinuation, interruption, CYP2C19 polymorphism, platelet reactivity, antiplatelet drug type, duration of therapy

EXCELLENT Trial
TVF according to diabetes (6-mo landmark analysis)

P for int. < 0.001

Non-diabetics

p=0.063
HR = 0.45 (0.19-1.04)

Diabetics

p=0.036
HR=2.99 (1.08-8.29)

Legend:
- 6-mo DAPT
- 12-mo DAPT
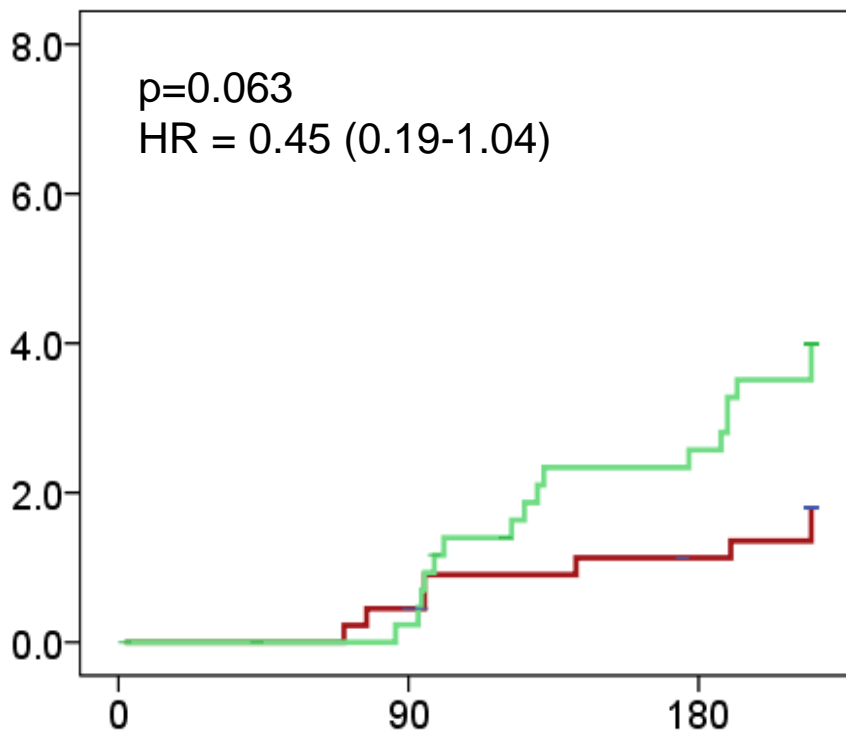
Patient Number at Risks

6-mo	444	442	436	259	255	245
12-mo	431	428	415	271	270	265

Gwon HC, Hahn JY et al. Circulation 2012

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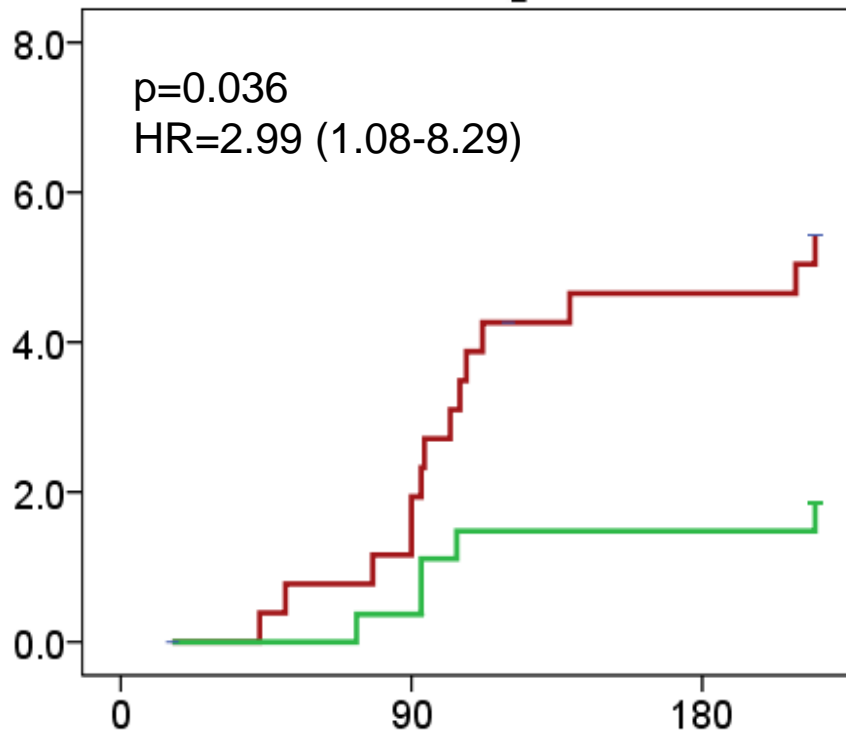
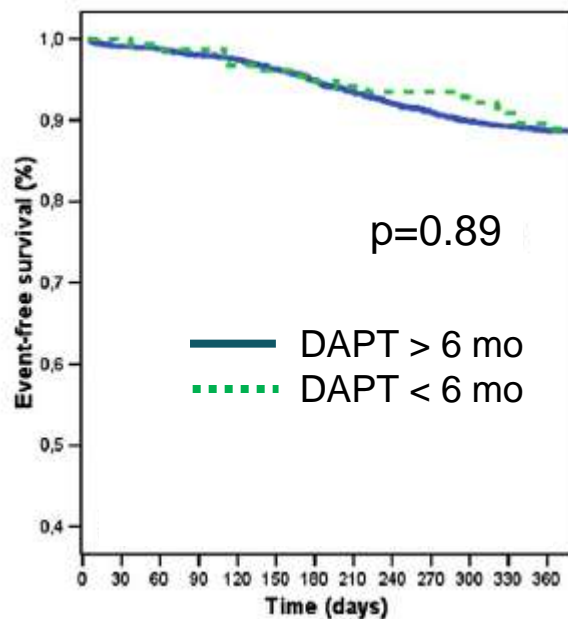# Italian Multicenter Registry on Bifurcations (I-BIGIS)

▸ N=4,314

One-year MACE

DES group	2-stent group	ACS group

DES group — p=0.89 — DAPT > 6 mo / DAPT < 6 mo

2-stent group — p=0.63 — DAPT > 6 mo / DAPT < 6 mo

ACS group — **p=0.04** — DAPT > 6 mo / DAPT < 6 mo
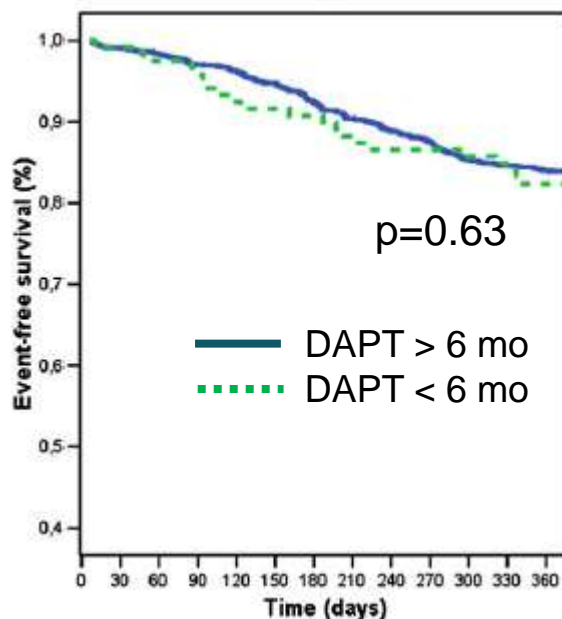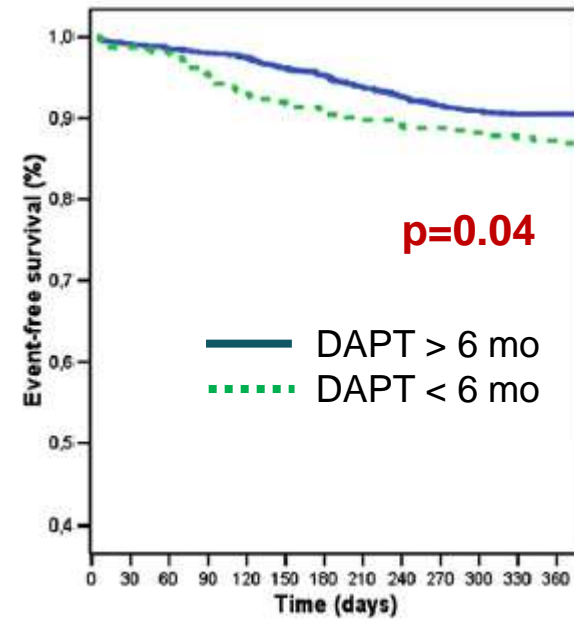
DAPT ≥12 months for all patients with ACS

CURE trial
CV Death or MI from Randomization

Placebo+Aspirin (N=6259) — 11.4%

Clopidogrel + Aspirin (N=6303) — 9.3%

P<0.001
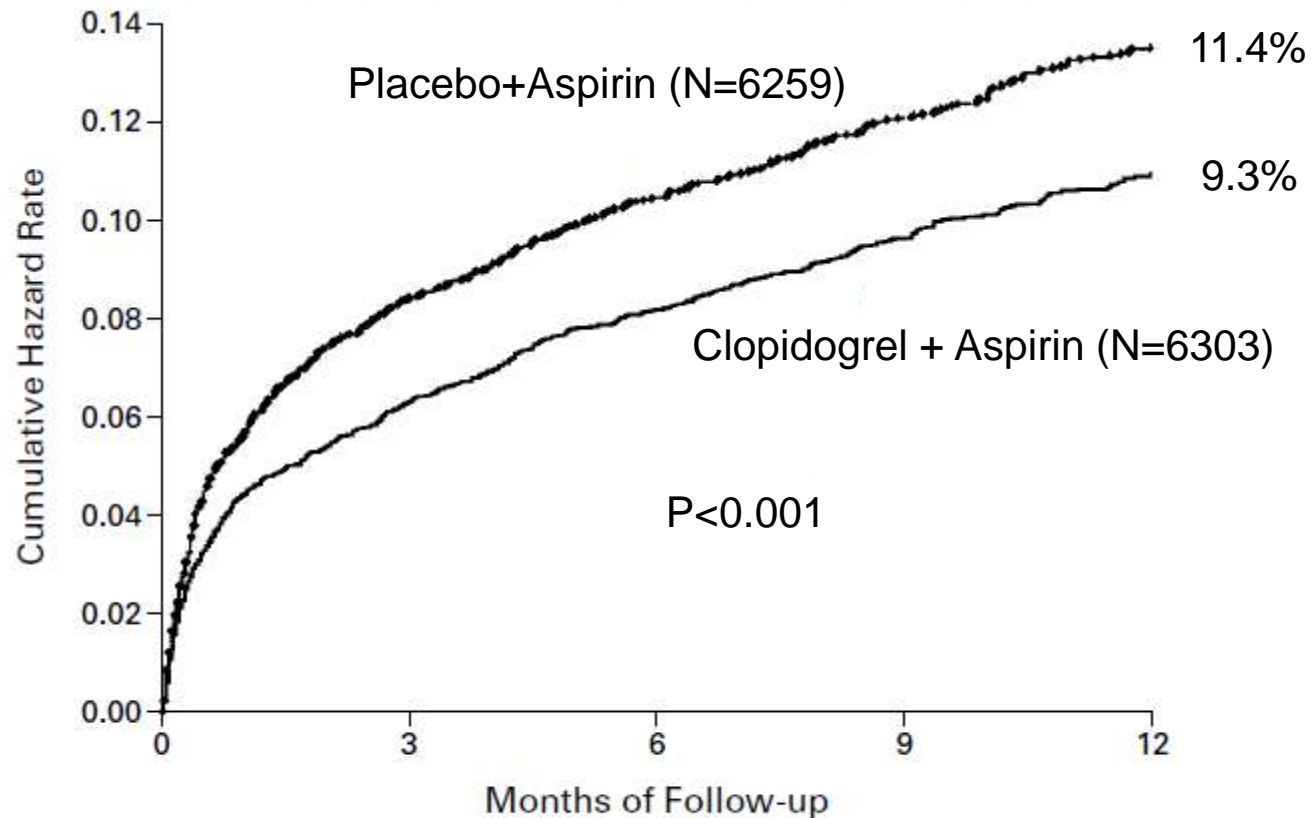
NO. AT RISK					
Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

Close look at CURE Study

- In clopidogrel group, 300 mg of clopidogrel was pre-loaded.

- Primary endpoint was MACE for 30 days, not for 12 months.

- Median duration of clopidogrel therapy was 9 months after randomization.

- Major benefit was observed in the first 30 days.

> The supporting evidence for prolonged DAPT in patients with ACS are not conclusive.

Real DATE registry: ACS patients
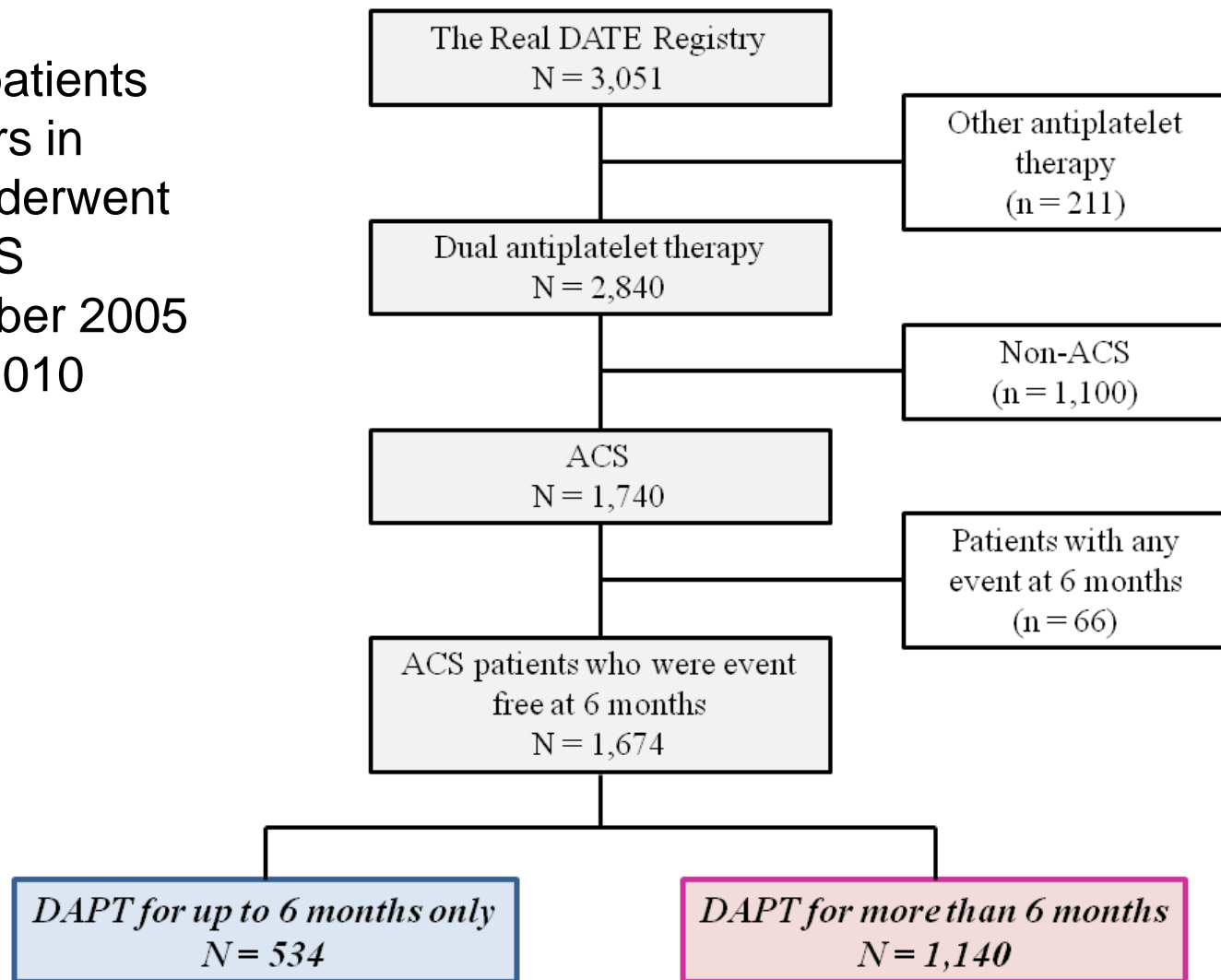
▸ Consecutive patients from 19 centers in Korea who underwent PCI with a ZES between October 2005 and January 2010

The Real DATE Registry
N = 3,051

Other antiplatelet therapy
(n = 211)

Dual antiplatelet therapy
N = 2,840

Non-ACS
(n = 1,100)

ACS
N = 1,740

Patients with any event at 6 months
(n = 66)

ACS patients who were event free at 6 months
N = 1,674

DAPT for up to 6 months only
N = 534

DAPT for more than 6 months
N = 1,140

Real DATE registry: ACS patients

Whole patients

Log-Rank, *P*=0.89
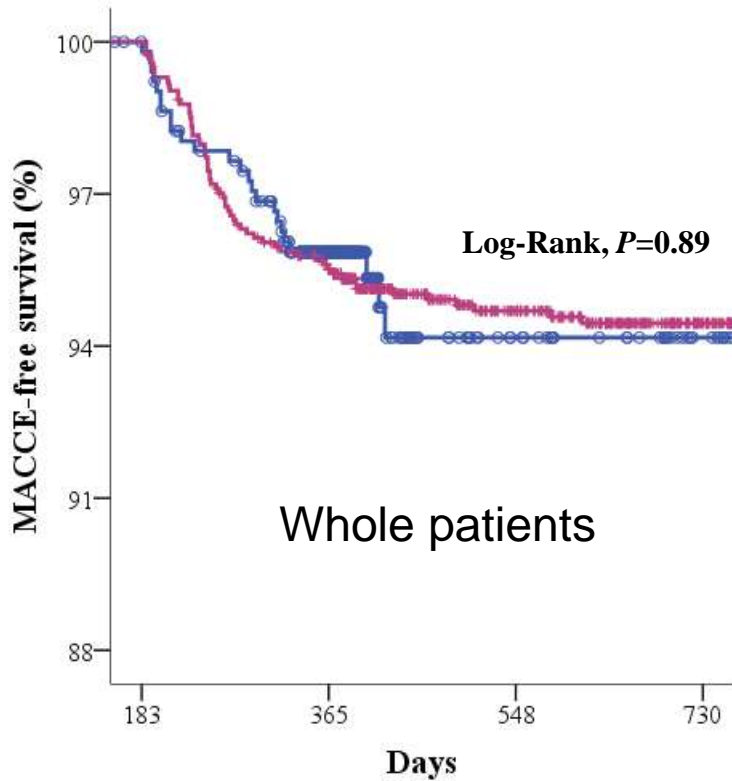
| 534 | 384 | 131 | 108 | ≤ 6M |
| 1140 | 1068 | 813 | 623 | > 6M |

No. at risk

PS matched patients

Log-Rank, *P*=0.27
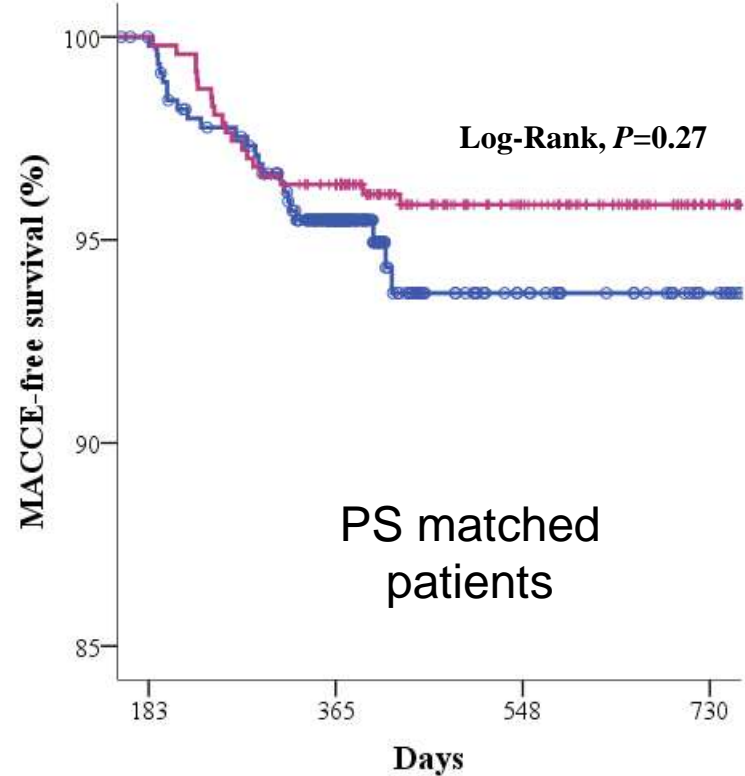
| 469 | 320 | 123 | 102 | ≤ 6M |
| 469 | 438 | 337 | 272 | > 6M |

No. at risk
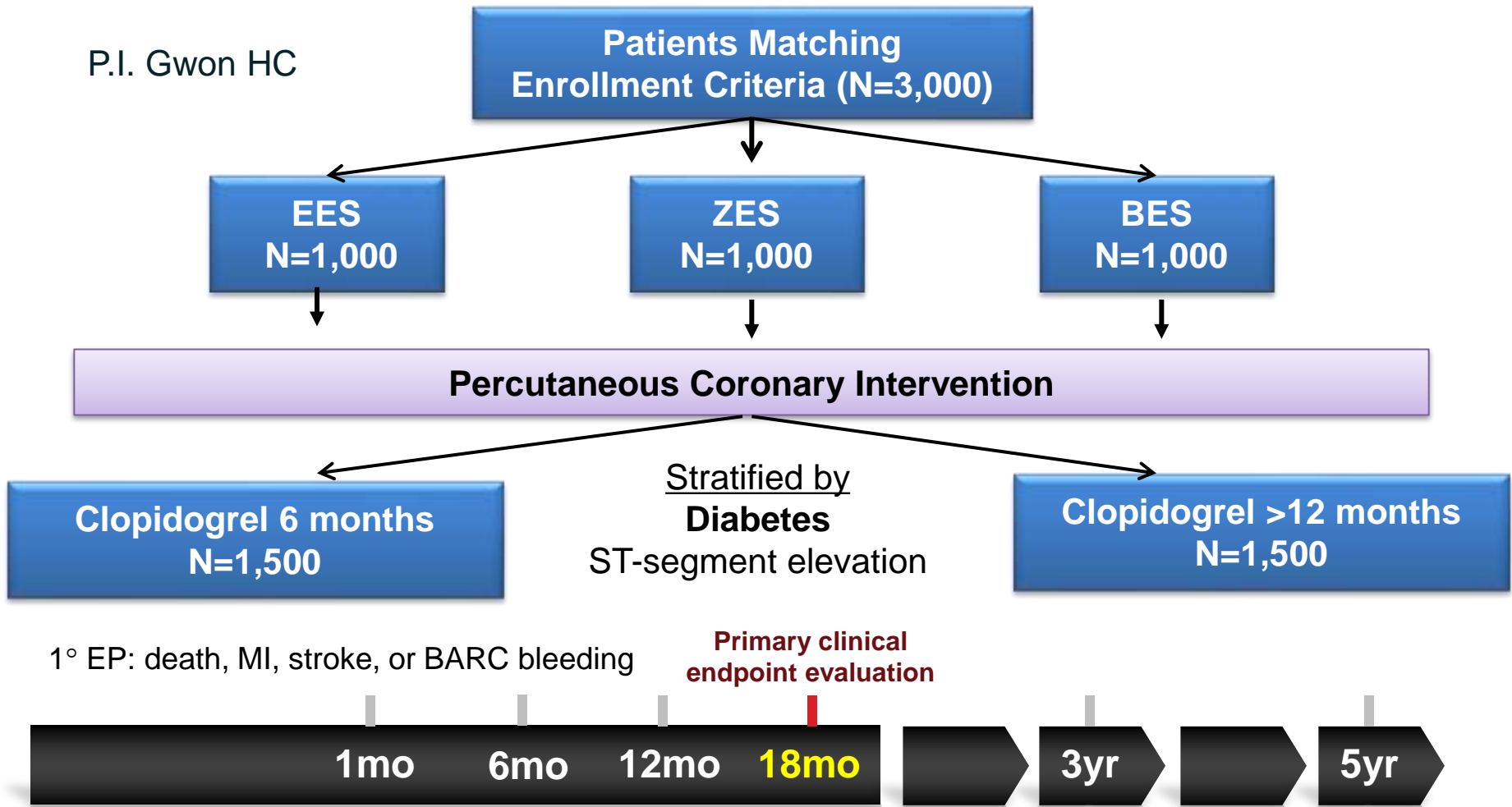
Stent-specific DAPT duration?
EXCELLENT Trial: TVF in stent subgroups

(Randomized to EES vs. SES in 3:1 fashion)

Everolimus-Eluting Stent

HR = 0.92 (0.53-1.59)
Superiority p=0.764
Non-inferiority p=0.0029

5.0%
4.6%

— **6-mo DAPT**
— **12-mo DAPT**
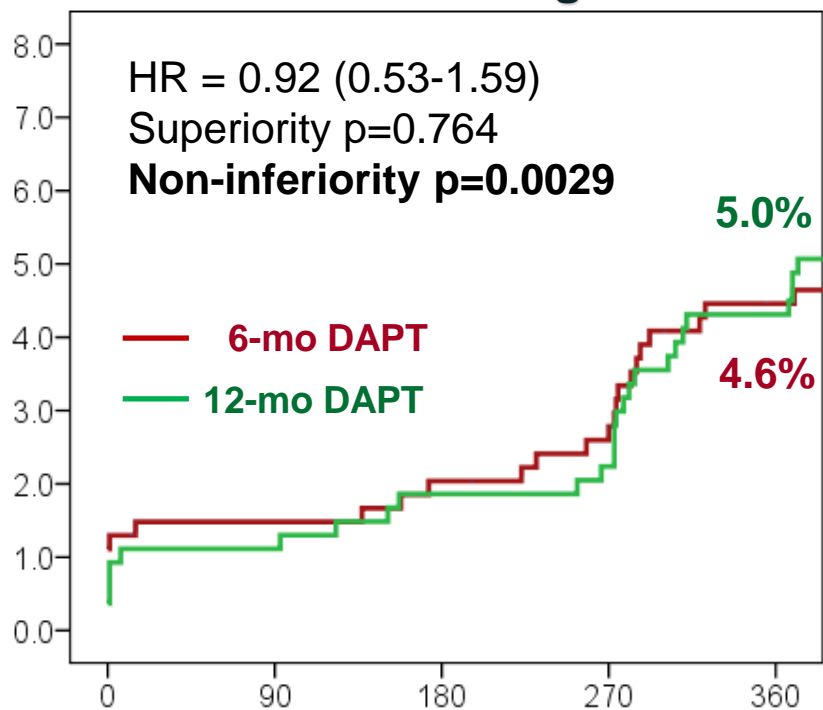
Patient Number at Risks

6-mo	540	531	528	524	511
12-mo	539	531	524	521	505

Sirolimus-Eluting Stent
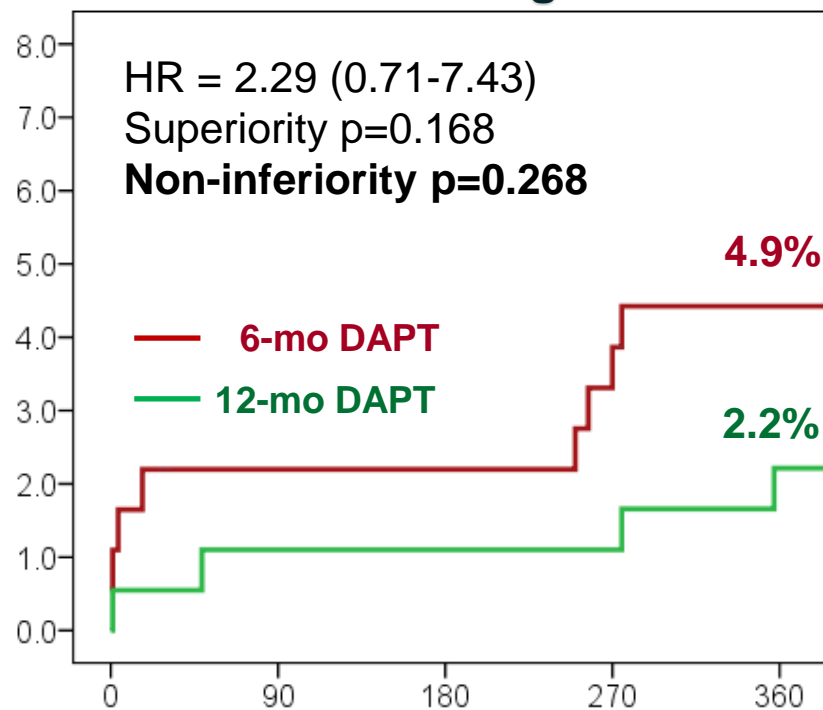
HR = 2.29 (0.71-7.43)
Superiority p=0.168
Non-inferiority p=0.268

4.9%
2.2%

— **6-mo DAPT**
— **12-mo DAPT**

Patient Number at Risks

182	176	176	174	171
182	179	179	178	176

TCTAP 2014   Gwon HC, Hahn JY, Circulation 2012   Samsung Medical Center

Stent-specific DAPT duration?
A pre-specified analysis from the PRODIGY trial

Optimal duration of DAPT may be stent-specific and it does not support a clear association between stent potency and vulnerability to shorter DAPT therapy

Valgimigli M, Eur Heart J 2013   Samsung Medical Center
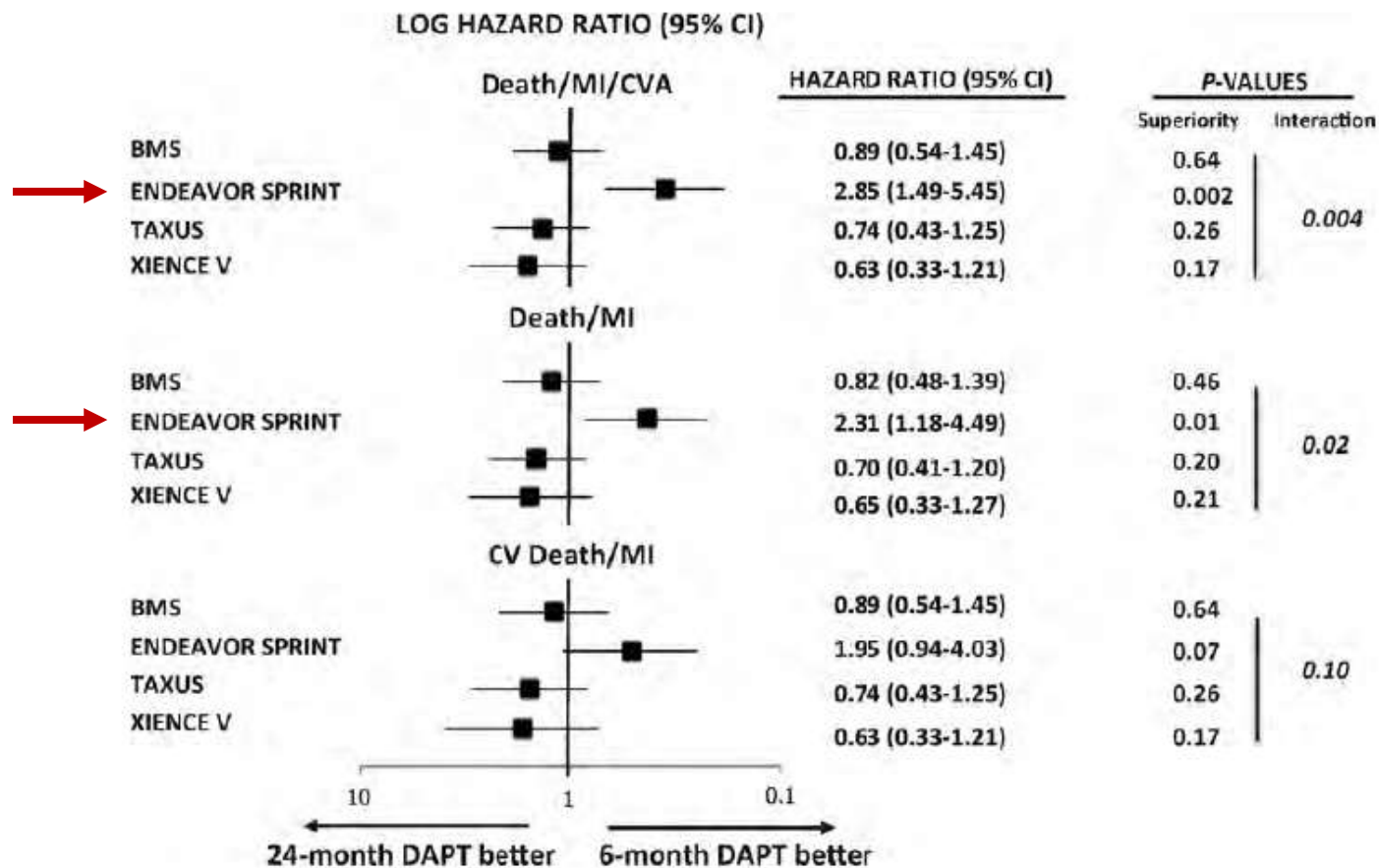
▸ N=3,119, NACCE = death, MI, stroke, major bleeding

0-360 d

HR, 1.03 (95% CI, 0.77-1.38)
Log-rank P = .84
Noninferiority P = .002

Antiplatelet therapy
— Short-term
- - - - Long-term

NACCE, %

Time After Initial Procedure, d

0-90 d

91-360 d
(Landmark analysis)

HR, 1.03 (95% CI, 0.71-1.51)
Log-rank P = .86

HR, 1.03 (95% CI, 0.66-1.60)
Log-rank P = .91

NACCE, %

Time After Initial Procedure, d
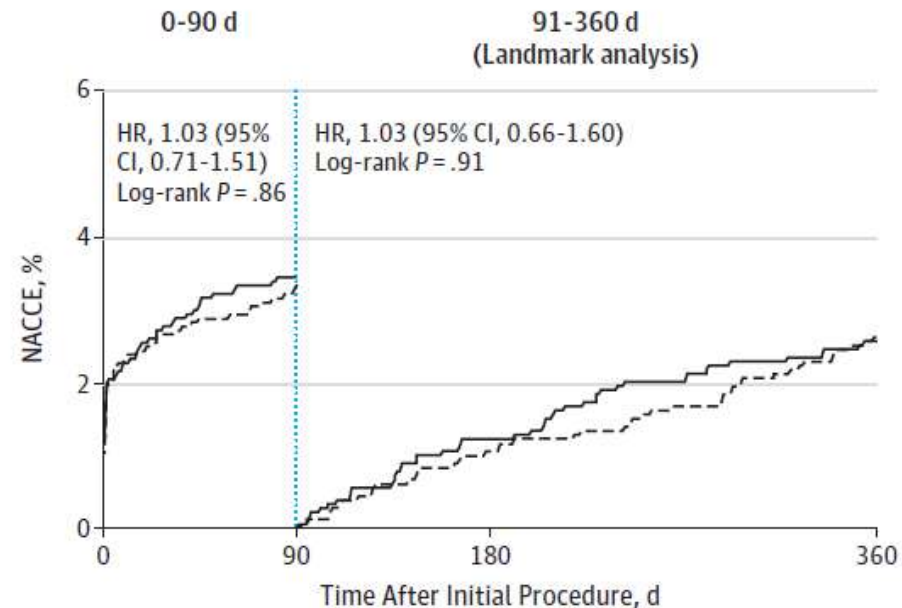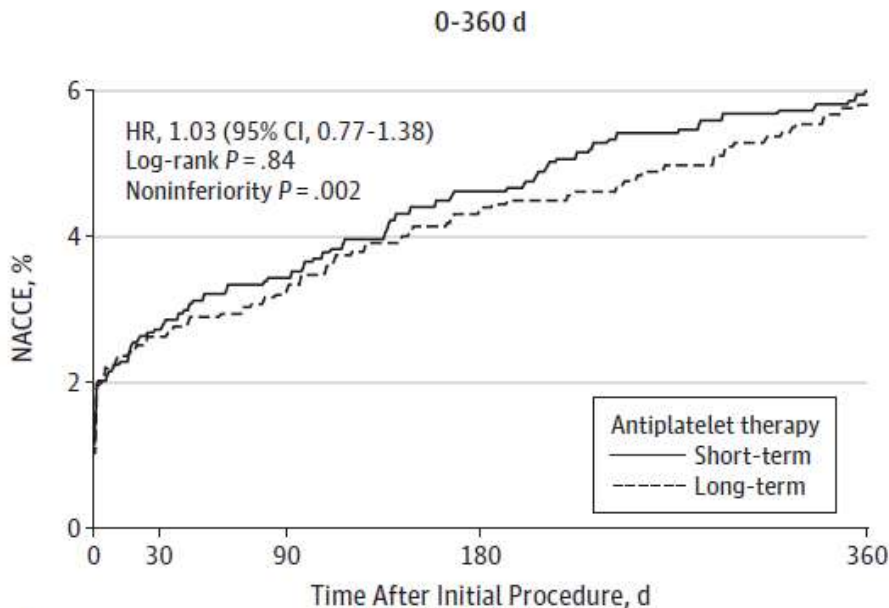
* A trend of increased rate of any bleeding with longer DAPT arms

Summary

▸ According to recent studies, a shorter duration of DAPT than recommended by the guidelines may be acceptable, especially after the implantation of new-generation DES.

▸ The prolonged DAPT, however, may be considered in specific subsets of high-risk patients, which is to be determined in future studies.

▸ It is prudent to await the results of ongoing trials before changing our practice.

Contents

▸ Duration of dual antiplatelet therapy (DAPT)
  ◦ Short vs. prolonged DAPT
  ◦ Consideration in special subset patients

▸ Effective monotherapy after DAPT
  ◦ Aspirin vs. clopidogrel

Monotherapy after DAPT

▸ In the guideline, aspirin is recommended to be continued indefinitely after the DAPT in patients undergoing PCI with DES.

▸ However, in the CAPRIE trial,
  ◦ Clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death in patients with atherosclerotic vascular disease.
  ◦ The overall safety profile of clopidogrel is at least as good as that of medium-dose aspirin.

CAPRIE: superior efficacy of clopidogrel versus aspirin

Cumulative Event Rate (Ischemic stroke, MI, vascular death)
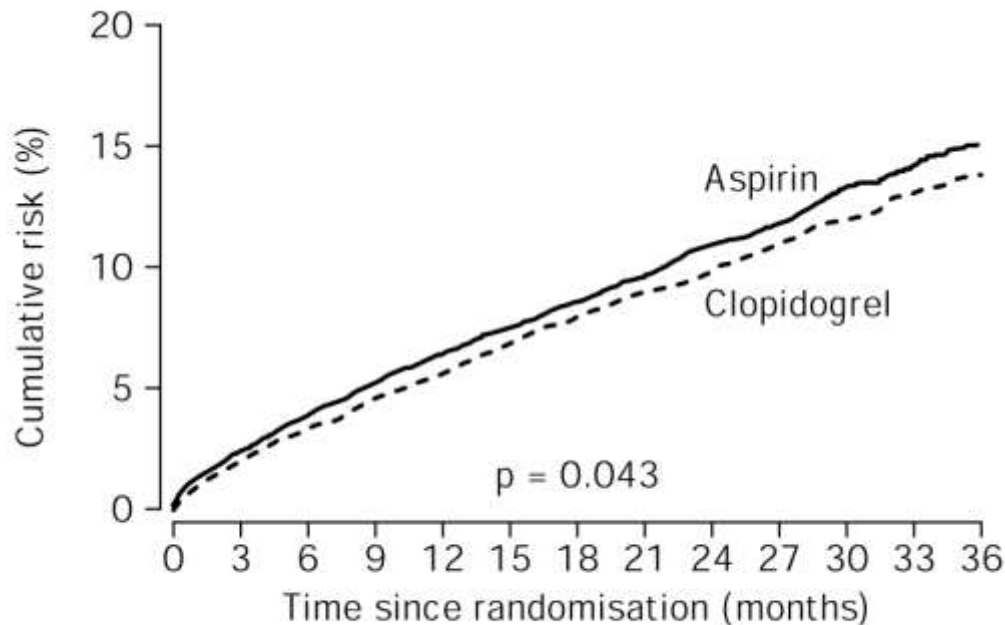
8.7% Relative risk reduction (p=.043)

**Aspirin = 5.83%
Clopidogrel = 5.32%**

Patients with recent ischemic stroke, recent MI, or symptomatic PAD (N = 19185)

CAPRIE Steering Committee. Lancet 1996; 348:1329-1339.

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CAPRIE Safety: Hemorrhagic Events

Number of Patients

Legend:
- **Clopidogrel** (blue)
- Aspirin (gray)

Hospitalization for GI Bleeding Events[1]
- 71 (0.74%) — Clopidogrel
- 104 (1.08%) — Aspirin

GI Hemorrhages (*p*<0.002)[2]
- 191 — Clopidogrel
- 255 — Aspirin
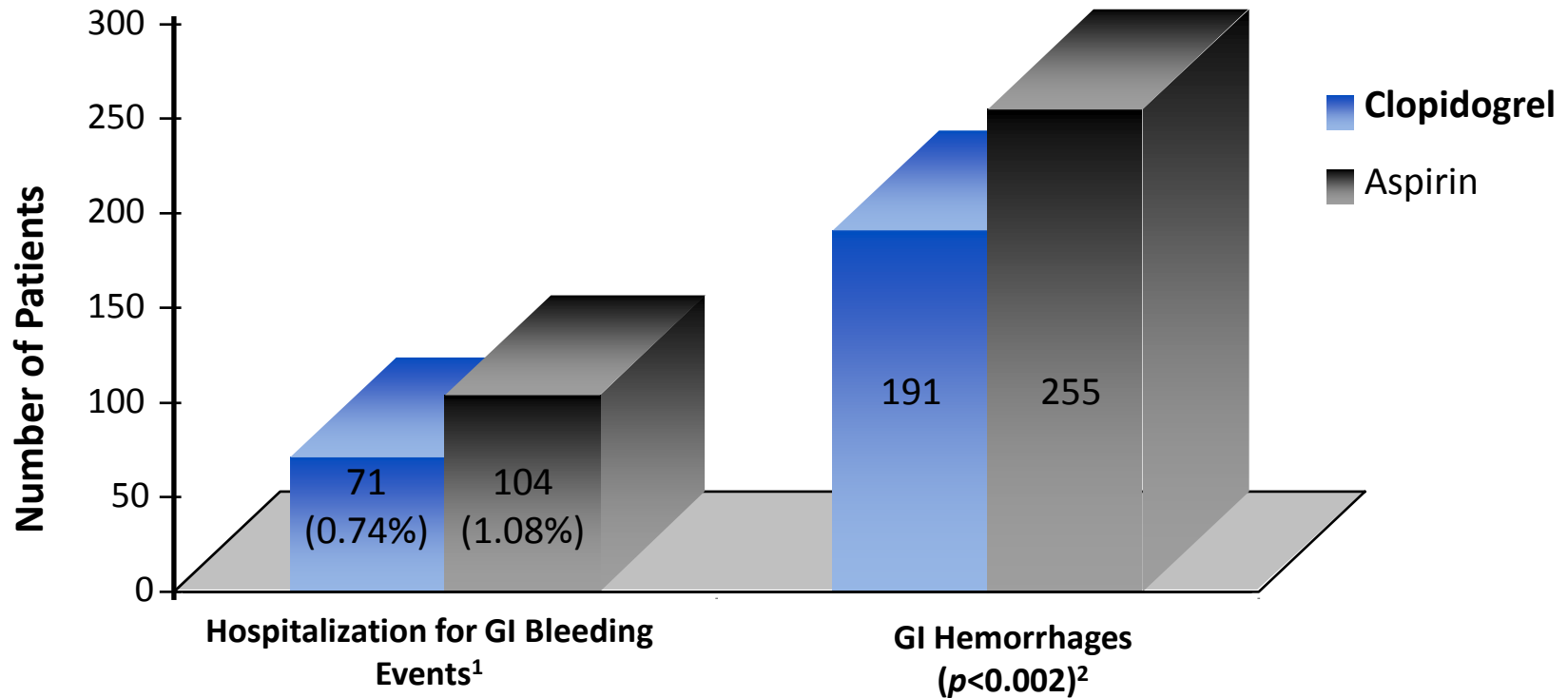
- Trend to more cerebral hemorrhages, fatal or non-fatal, and more hemorrhagic deaths in aspirin group: 37 versus 51 (0.39% vs. 0.53%)

1. Bogousslavsky. Cerebrovasc Dis 1998;8(suppl 4):43. Abstract CLI 76.
2. CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

Aspirin vs. Clopidogrel: SMC data

Single center, observational study
Choice of antiplatelet agent → the operator's discretion

PCI with DES **January 2003 ~ December 2010** **5505 patients at baseline**	▸ Events during initial 12-month: n = 647 ◦ Death: n = 214 ◦ Nonfatal MI: n = 57 ◦ Revascularization: n = 349 ◦ Cerebrovascular accident: n = 27
Event-Free at 12-month (n = 4858)	
Antiplatelet monotherapy after 12-month (n = 3261)	▸ **Unavailable information about antiplatelet agent: n = 835** ▸ **Continued DAPT: n = 672** ▸ **Receiving antiplatelet agent other than aspirin and clopidogrel: n = 90**

Aspirin (n = 2477)   **Clopidogrel (n = 784)**

Baseline patient characteristics

	Aspirin (n=2477)	Clopidogrel (n=784)	p value
Age, years	62 (53-69)	64 (56-71)	<0.001
Male gender	1814 (73.2)	597 (73.9)	0.733
Diabetes mellitus	836 (33.8)	333 (42.5)	<0.001
Hypertension	1318 (53.2)	503 (64.2)	<0.001
Dyslipidemia	707 (28.5)	262 (33.4)	0.009
Current smoker	431 (17.4)	177 (22.6)	0.001
Chronic renal failure	200 (8.1)	81 (10.3)	0.050
Previous myocardial infarction	470 (19.0)	145 (18.5)	0.765
Previous PCI	244 (9.9)	110 (14.0)	0.001
Previous bypass surgery	63 (2.5)	26 (3.3)	0.247
Previous CVA	79 (3.2)	49 (6.2)	<0.001
Clinical presentation			0.004
Silent ischemia/stable angina	1456 (58.8)	452 (57.7)	
UA/NSTEMI	657 (26.5)	246 (31.4)	
STEMI	364 (14.7)	86 (11.0)	
LVEF, %*	62 (55-67)	62 (56-68)	0.165

Values are expressed as median (interquartile range) or number of patients (%).
PCI indicates percutaneous coronary intervention; CVA, cerebrovascular acciden; UA, unstable angina; NSTEMI, Non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction.
*LVEF was available in 1610 (65.0%) patients with aspirin and 586 (74.7%) patients with clopidogrel.

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Lesion and procedural characteristics

	Aspirin (n=2477)	Clopidogrel (n=784)	p value
Angiographic disease extent			0.018
1-vessel disease	1111 (44.9)	307 (39.2)	
2-vessel disease	834 (33.7)	296 (37.8)	
3-vessel disease	532 (21.5)	181 (23.1)	
Left main or LAD as treated vessel	1304 (52.6)	397 (50.6)	0.327
Treated lesions per patient	1.5±0.8	1.6±0.9	<0.001
Number of stents per patient	1.5±0.8	1.7±0.9	<0.001
Number of stents per lesion	1.1±0.3	1.2±0.4	0.006
Stent diameter, mm*	3.21±0.41	3.23±0.45	0.410
Stent total length, mm	34.2±20.5	39.3±23.4	<0.001
Type of drug-eluting stent			<0.001
Sirolimus/Paclitaxel	1593 (64.3)	251 (32.0)	
Everolimus/Zotarolimus/Biolimus	884 (35.7)	533 (68.0)	

Values are expressed as mean ± SD or number of patients (%).

LAD indicates left anterior descending.
*The maximum diameter was presented in patients undergoing multiple stenting.
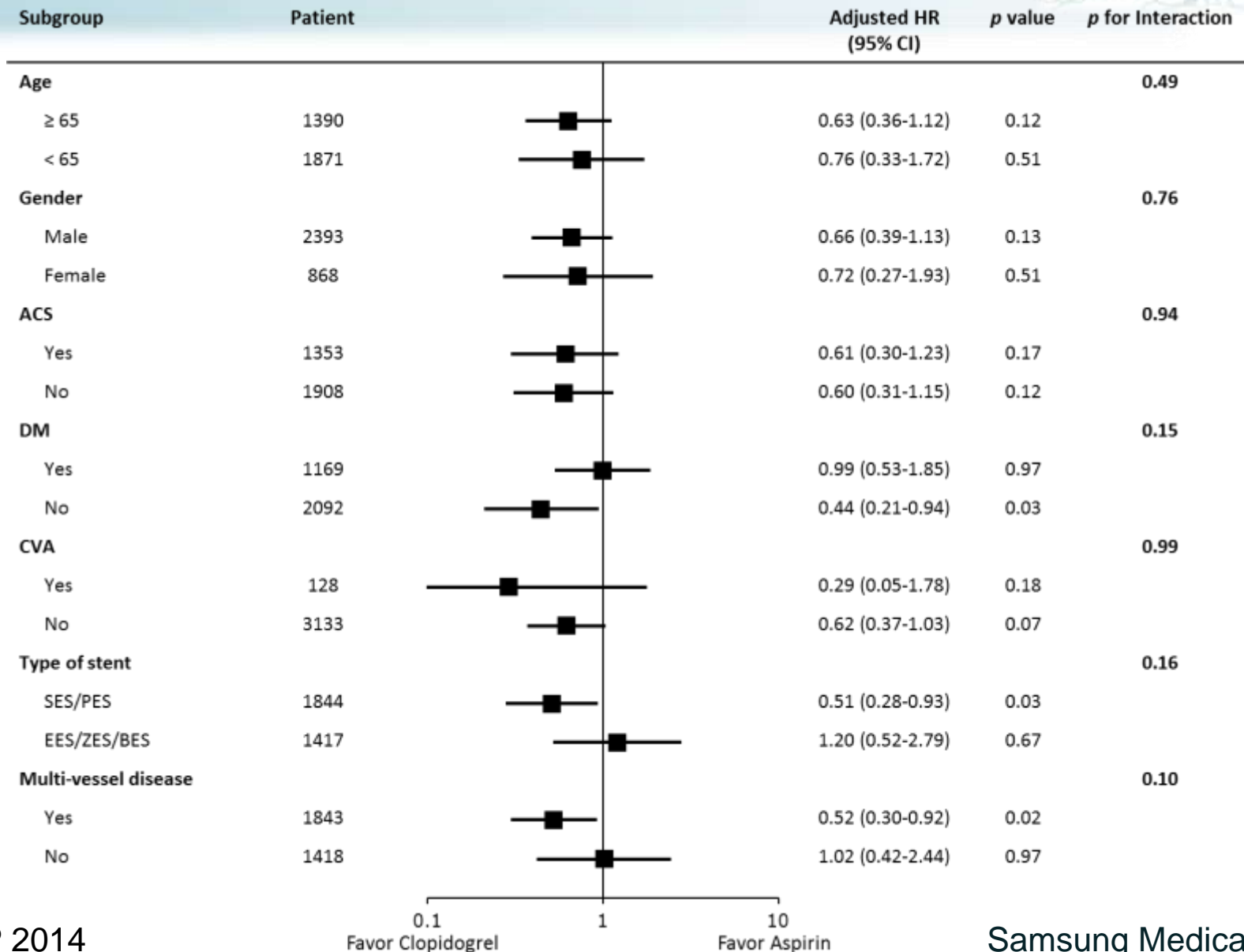
Clinical outcomes

Median f/u duration: 59 months

	Aspirin (n=2477)	Clopidogrel (n=784)	Before weighting		After IPTW	
			HR* (95% CI)	P value	HR* (95% CI)	P value
Total death	131 (5.3)	26 (3.3)	0.85 (0.55-1.33)	0.48	0.89 (0.61-1.31)	0.56
Cardiac death	50 (2.0)	7 (0.9)	0.51 (0.22-1.16)	0.11	0.54 (0.25-1.15)	0.11
MI	51 (2.1)	7 (0.9)	0.68 (0.30-1.54)	0.36	0.42 (0.17-1.04)	0.06
Stent thrombosis	18 (0.7)	1 (0.1)	0.29 (0.04-2.29)	0.24	0.12 (0.01-2.19)	0.15
TLR	109 (4.4)	14 (1.8)	0.71 (0.40-1.26)	0.24	0.63 (0.37-1.08)	0.09
TVR	184 (7.4)	23 (2.9)	0.64 (0.41-0.99)	0.05	0.53 (0.34-0.82)	0.004
CVA	60 (2.4)	11 (1.4)	0.73 (0.37-1.42)	0.36	0.62 (0.32-1.20)	0.16
Cardiac death or MI	93 (3.8)	13 (1.7)	0.61 (0.33-1.11)	0.11	0.51 (0.28-0.93)	0.03
Cardiac death, MI, or CVA	144 (5.8)	22 (2.8)	0.65 (0.41-1.04)	0.07	0.51 (0.32-0.83)	0.006

Values are expressed as number of patients (%).

IPTW indicates inverse probability of treatment weighting; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; CVA, cerebrovascular accident.
*Adjusted covariates included age, sex, clinical presentation, diabetes mellitus, hypertension, dyslipidemia, current smoker, chronic renal failure, previous MI, previous percutaneous coronary intervention, previous bypass surgery, previous CVA, angiographic disease extent, number of treated lesion, number of stent used, stent diameter, total stent length, left main or left anterior descending artery as a treated vessel, and type of drug-eluting stent.

Subgroup analysis

Subgroup	Patient		Adjusted HR (95% CI)	p value	p for Interaction
Age					0.49
≥ 65	1390		0.63 (0.36-1.12)	0.12	
< 65	1871		0.76 (0.33-1.72)	0.51	
Gender					0.76
Male	2393		0.66 (0.39-1.13)	0.13	
Female	868		0.72 (0.27-1.93)	0.51	
ACS					0.94
Yes	1353		0.61 (0.30-1.23)	0.17	
No	1908		0.60 (0.31-1.15)	0.12	
DM					0.15
Yes	1169		0.99 (0.53-1.85)	0.97	
No	2092		0.44 (0.21-0.94)	0.03	
CVA					0.99
Yes	128		0.29 (0.05-1.78)	0.18	
No	3133		0.62 (0.37-1.03)	0.07	
Type of stent					0.16
SES/PES	1844		0.51 (0.28-0.93)	0.03	
EES/ZES/BES	1417		1.20 (0.52-2.79)	0.67	
Multi-vessel disease					0.10
Yes	1843		0.52 (0.30-0.92)	0.02	
No	1418		1.02 (0.42-2.44)	0.97	

0.1   1   10
Favor Clopidogrel   Favor Aspirin

Summary

▸ The present study compared long-term clinical outcomes of patients receiving aspirin monotherapy versus clopidogrel monotherapy following 12-month of DAPT after PCI with DES

▸ Clopidogrel monotherapy was associated with a risk reduction in a composite of cardiac death, MI, or CVA.

▸ The treatment effect was consistent across various subgroups.

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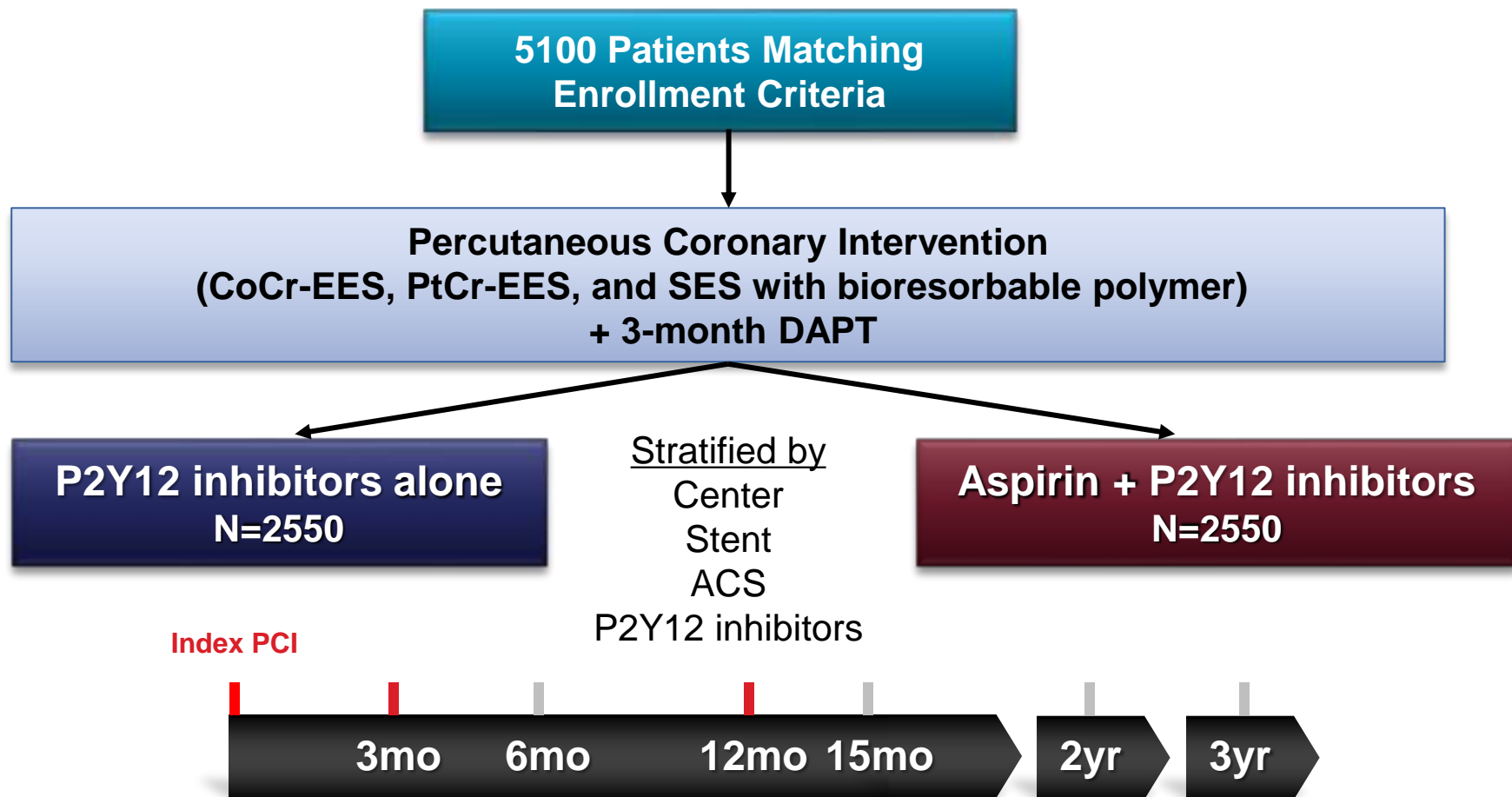
Thank you for your attention!
감사합니다.