SANOFI

Plavix
Take Protection Further. Today.

Optimal Duration of Dual Antiplatelet Therapy after Implantation of DES
: Shorter or Longer?

배장환
충북대학교병원 심장내과
충북권역 심뇌혈관질환센터

KR.PM.CLO.14.02.06[2015.02]

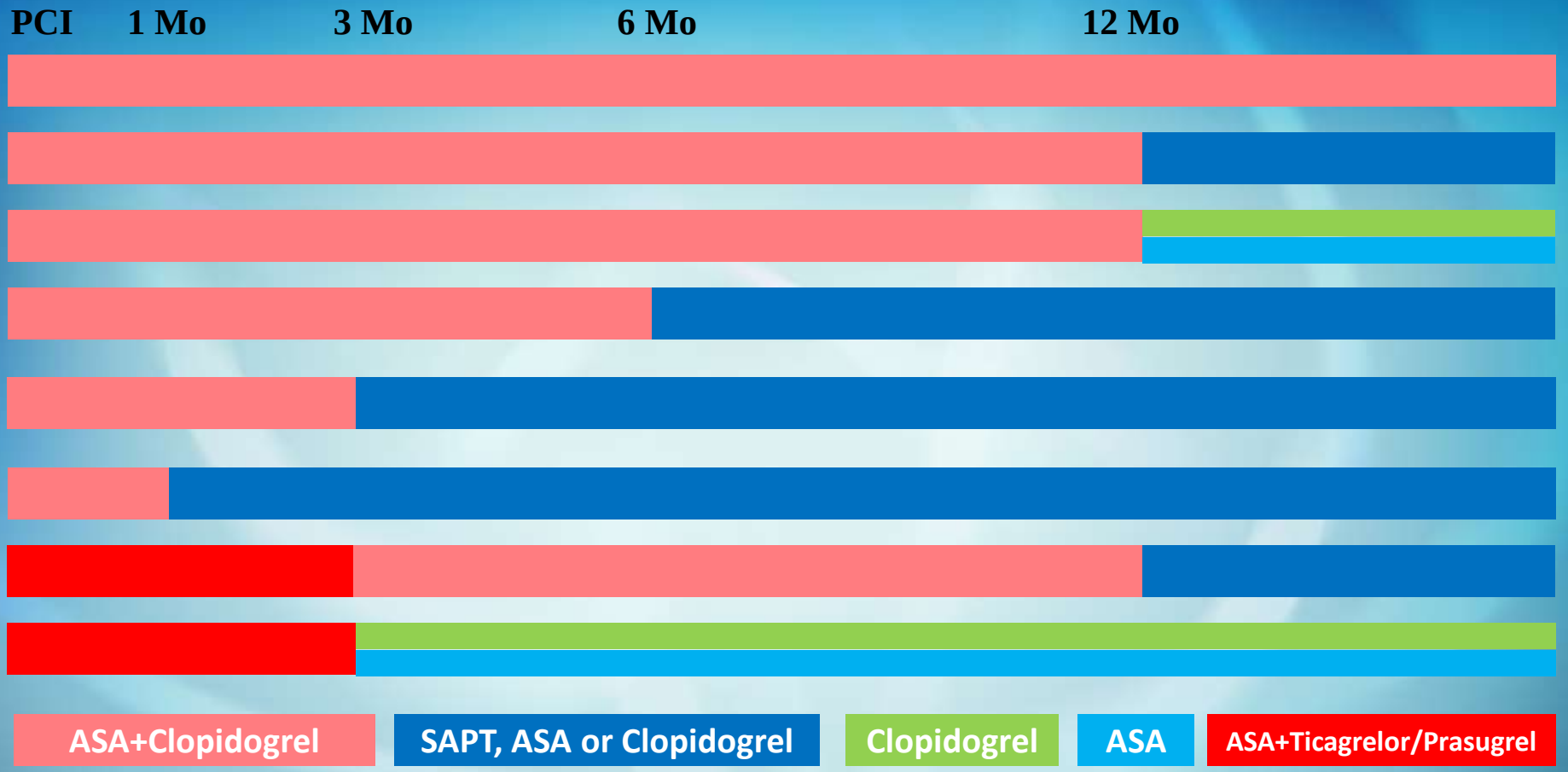
Contents

1. Current ACC/AHA guideline and Pitfall

2. Trials to find the optimal duration of DAPT after PCI implantation (in non-ACS/ ACS patients)
   - more than 12 months
   - 12 months
   - 6 months
   - 3 months

3. Which monotherapy is better following DAPT?
   - Aspirin vs. $P2Y_{12}$ antagonist

Ideas for DAPT usage after DES implantation



Ideas for DAPT usage after DES implantation

Lesion specific vs patients specific

- bifurcation, left main, complex stenting, stent type
- ACS, NIDDM, CKD, multiple CVD, atrial fibrillation

Bleeding

- high risk of bleeding population, chronic use of NSAIDs, OAC, UGIB

Potency of drugs

- clopidogrel
- prasugrel
- ticagrelor

Duration of DAPT after DES

< 12 months

> 12 months

Is shorter better?

Is longer better?

Similar early S.T.
Similar MI
Similar death

LESS BLEEDING

Less MI
Less late S.T.
Less death

MORE BLEEDING

Historical trials about duration of DAPT after DES

< 12 months

> 12 months

2012 **EXCELLENT** (6 vs. 12 mo)

2012 **RESET** (3 vs. 12 mo)

2013 **OPTIMIZE** (3 vs. 12 mo)

2014 **SECURITY** (6 vs. 12 mo)

2015 **ISAR-SAFE** (6 vs. 12 mo)

2010 **REAL-LATE/ ZEST-LATE** (24 vs. 12 mo)

2014 **DES-LATE** (36 vs. 12 mo)

2014 **ARCTIC-INTERRUPTION** (18~30 vs. 12 mo)

2014 **DAPT** (30 vs. 12 mo)

2013 **PRODIGY** (6 vs. 24 mo)

2015 **ITALIC** (6 vs. 24 mo)

35,088 patients

KR.PM.CLO.14.02.06[2015.02]

SANOFI

Plavix

ARCTIC-Interruption

Discontinuation of DAPT after 12 Months?

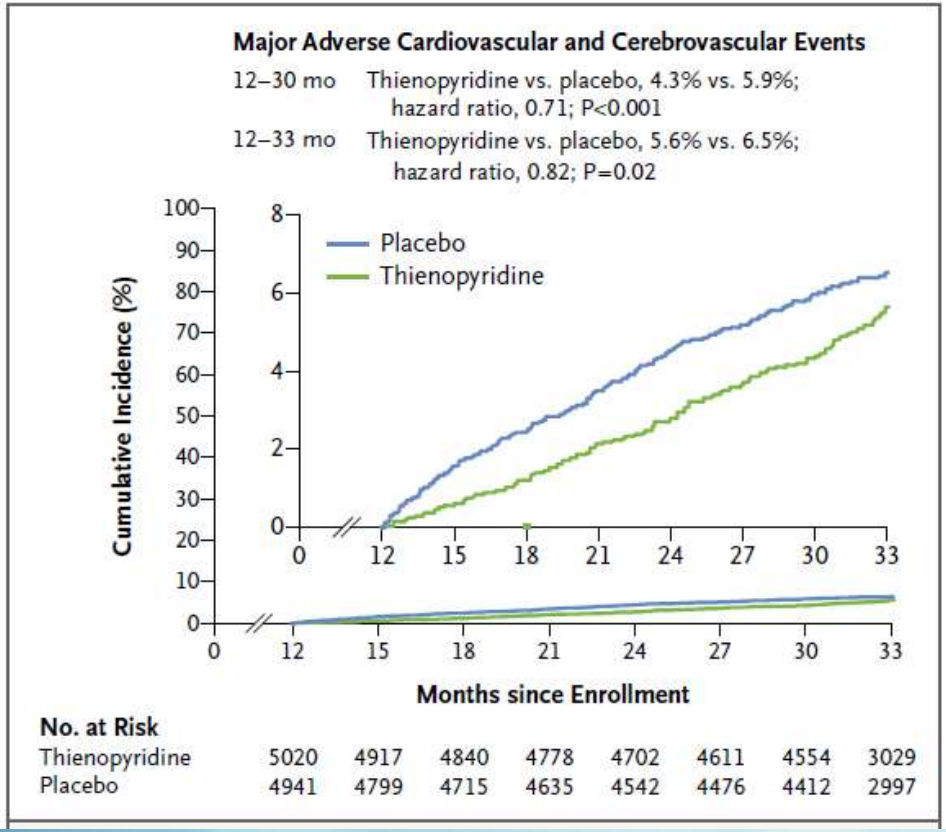
	Continuation (n=635)	Interruption (n=624)	Hazard ratio (95% CI)	p value
Any death, myocardial infarction, stent thrombosis, stroke or TIA, urgent revascularisation (primary endpoint)	24 (4%)	27 (4%)	1·17 (0·68–2·03)	0·58
Stent thrombosis (revascularised or not) or any urgent revascularsation (main secondary endpoint)	8 (1%)	10 (2%)	1·30 (0·51–3·30)	0·58
Any death, recurrent acute coronary syndrome, stroke or TIA	21 (3%)	24 (4%)	1·19 (0·66–2·13)	0·56
Death or resuscitated cardiac arrest	7 (1%)	9 (1%)	1·32 (0·49–3·55)	0·58
Death or myocardial infarction	14 (2%)	17 (3%)	1·26 (0·62–2·55)	0·52
Any death, myocardial infarction, stent thrombosis (revascularised or not), stroke or TIA, urgent revascularisation, TIMI major bleed (net clinical benefit)	30 (5%)	28 (5%)	0·97 (0·58–1·62)	0·90
Any death	7 (1%)	9 (1%)	1·32 (0·49–3·55)	0·58
Myocardial infarction	9 (1%)	9 (1%)	1·04 (0·41–2·62)	0·94
Stent thrombosis*	0 (0%)	3 (1%)		
Acute coronary syndrome	11 (2%)	13 (2%)	1·23 (0·55–2·74)	0·62
Stroke or TIA	6 (1%)	4 (1%)	0·69 (0·19–2·44)	0·57
Urgent revascularisation	8 (1%)	9 (1%)	1·17 (0·45–3·04)	0·74
Safety endpoints				
STEEPLE major bleed	7 (1%)	1 (<0·5%)	0·15 (0·02–1·20)	0·07
STEEPLE minor bleed	5 (1%)	2 (<0·5%)	0·41 (0·08–2·13)	0·29
STEEPLE major or minor bleed	12 (2%)	3 (1%)	0·26 (0·07–0·91)	0·04

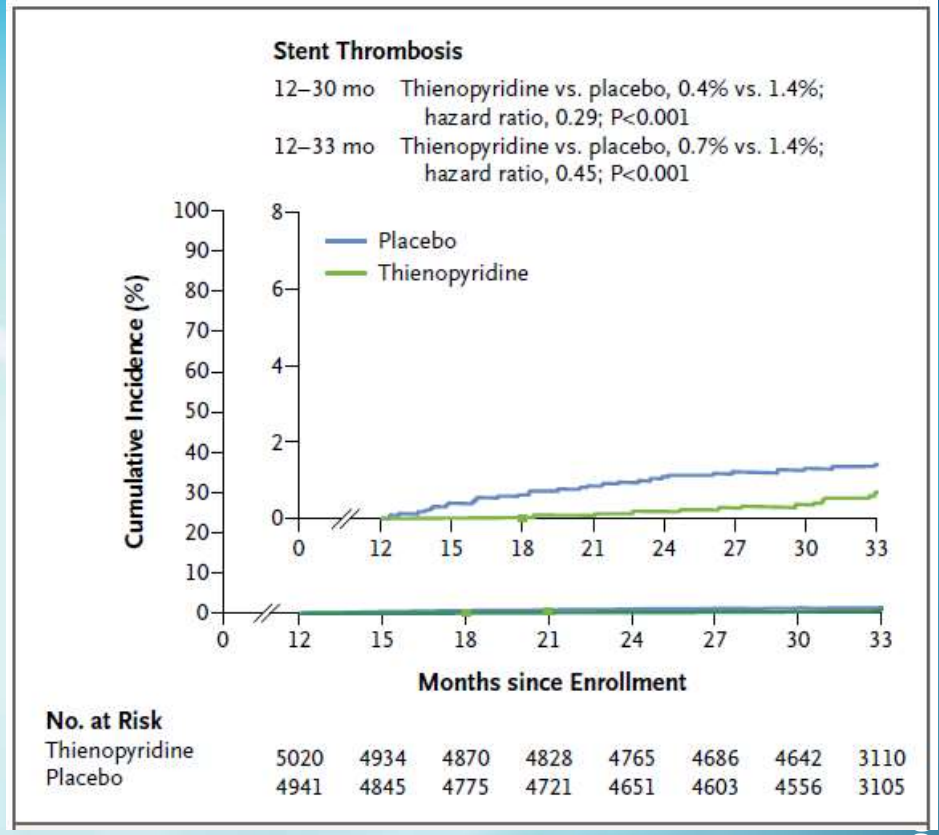
Data are n (%) unless otherwise stated. *All three stent thromboses were definite. TIA=transient ischaemic attack. TIMI=thrombolysis in myocardial infarction.

Collet JP. Lancet 2014;384:1577-85.

DAPT : Co-Primary Effectiveness Endpoint

- 9961 patients were randomized to continued P2Y12 blocker (clopid/prasu) vs PCB on aspirin after 12 months of DAPT (12 vs 30 months)
- SA/UA/NSTEMI/STEMI = 37.8/16.7/15.5/10.5%, EES = 46.7%





6[2015.02]

SANOFI

Mauri L. N Engl J Med 2014;371:2155-66.

Plavix

DAPT : Co-Primary Effectiveness Endpoint

- 9961 patients were randomized to continued P2Y12 blocker (clop/prasu) vs PVB on aspirin after 12 months of DAPT.

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

DAPT : Co-Primary Effectiveness Endpoint

- 9961 patients were randomized to continued P2Y12 blocker (clop/prasu) vs PVB on aspirin after 12 months of DAPT.

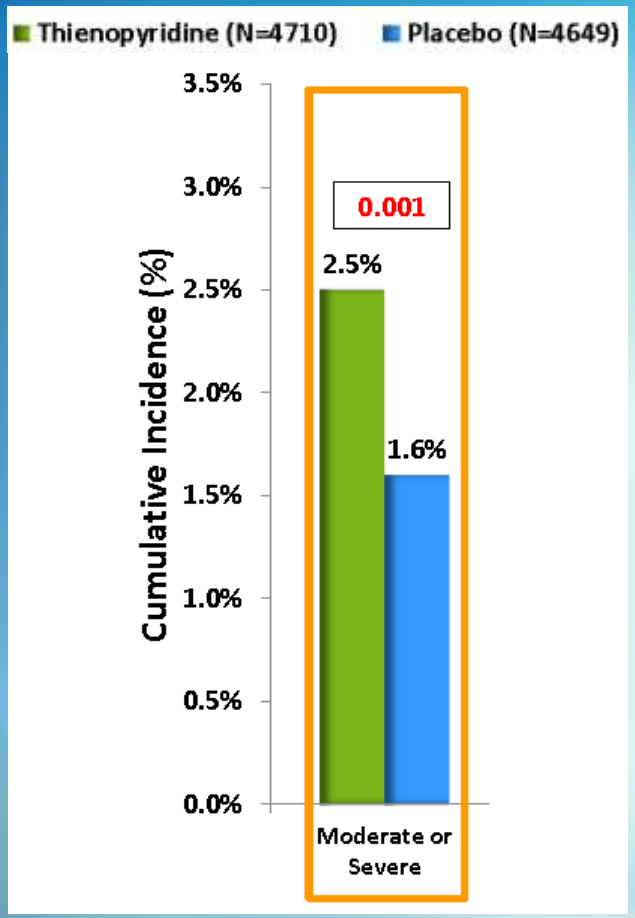
Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N=5020)	Placebo (N=4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

Mauri L. N Engl J Med 2014;371:2155-66.

DAPT : Safety Profile

co-1° EP: Moderate or severe bleeding



All-Cause Mortality

12-30 Months	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	98 (2.0%)	74 (1.5%)	0.052	24 (0.5%)
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

Mortality data in additional blinded adjudication and meta-analysis

Non-Cardiovascular Deaths, 12-33 Months			
Relatedness for Deaths*	Thienopyridine N=5020	Placebo N=4941	P-value
Bleeding-Related Death	11 (0.22%)	3 (0.06%)	0.057
Trauma-Related Death	9 (0.18%)	2 (0.04%)	0.07
Cancer-Related Death	31 (0.62%)	14 (0.28%)	0.02

SANOFI

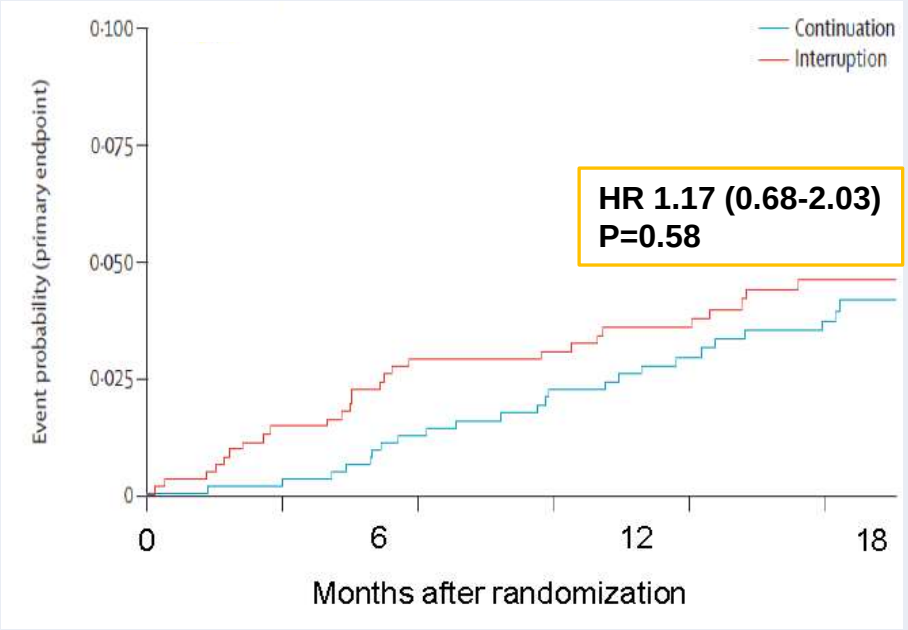
Mauri L. N Engl J Med 2014;371:2155-66.

Plavix

Is longer better?

ARCTIC-INTERRUPTION

MACCE

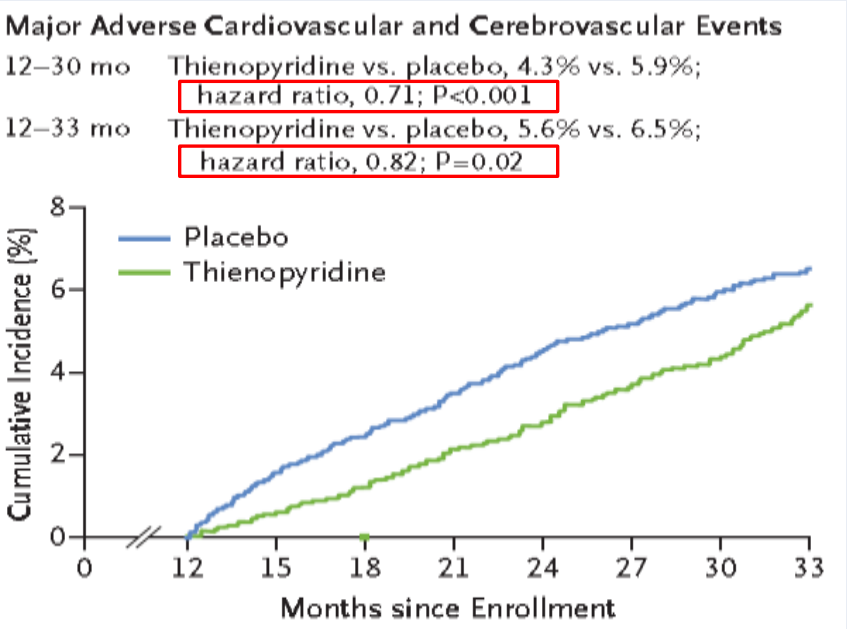


Bleeding

Major or minor bleeding (STEEPLE definition)
1.9% vs. 0.5%, p=0.04

DAPT

MACCE



Bleeding

Moderate or severe bleeding (GUSTO definition)
2.5% vs. 1.6%, p=0.001

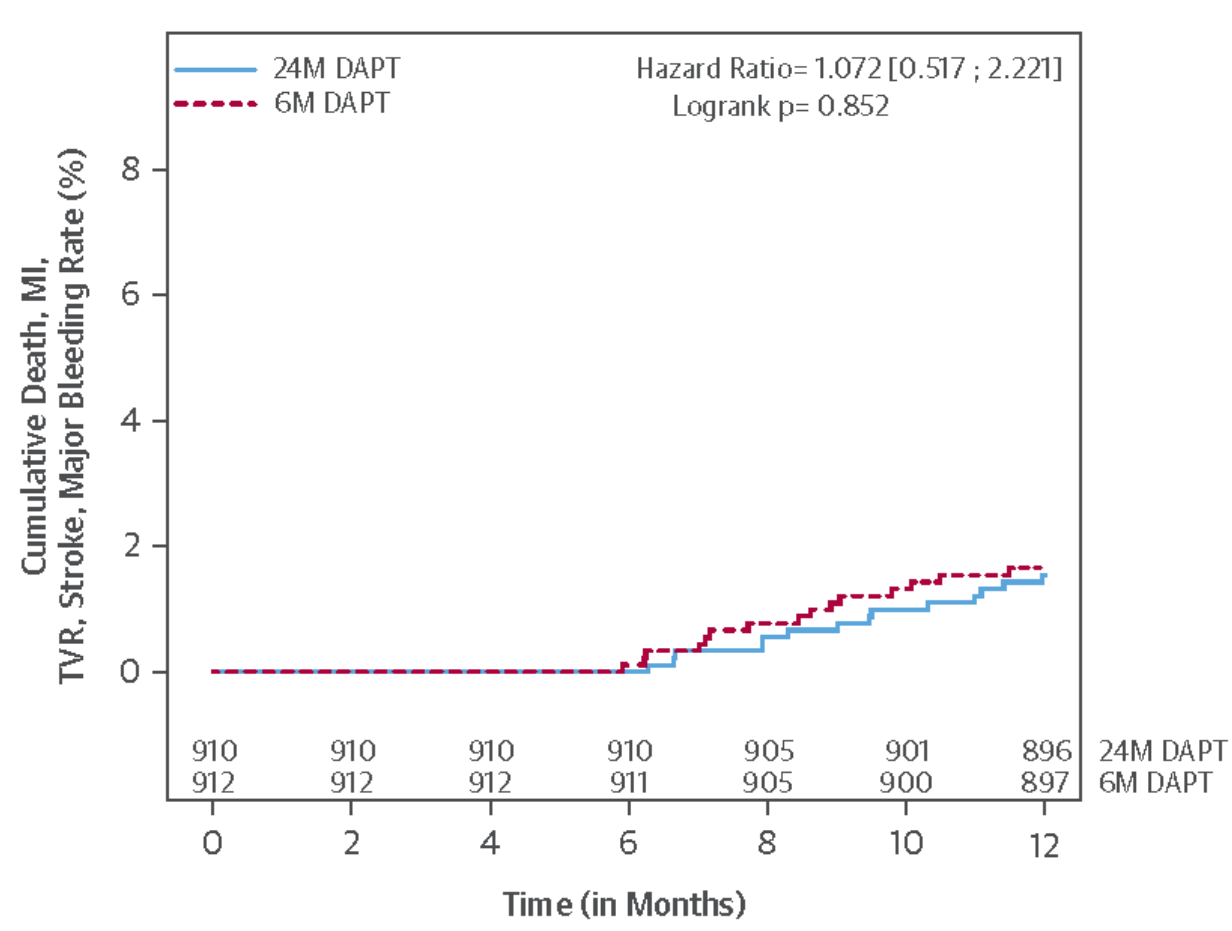
Collet JP. Lancet. 2014;384:1577-85.
Mauri L. N Engl J Med 2014;371:2155-66.

6 or even 3 months for non-ACS patients ??

ITALIC : Primary Endpoint on 1 yr

New generation DES followed by 6- vs 24-months DAPT in ACS

- Prospective, open-label randomized trial conducted at 70 sites in Europe and the Middle East. (941 in 24 Mo and 953 in 6 Mo DAPT, SA+SI=60%, all Xience-V)
- Patients undergoing implantation of everolimus-eluting stents with confirmed nonresistance to aspirin to receive 6- or 24-month DAPT (n=2,031)



Gilard M J Am Coll Cardiol. 2015;65:777-86.

ITALIC : Primary Endpoint on 1 yr

New generation DES followed by 6- vs 24-months DAPT

Total Population

	Resistant Group (n – 131)	24-Month DAPT (n – 910)	6-Month DAPT (n – 912)	Hazard Ratio (95% CI)	p Value
Primary endpoint: death from any cause, MI, stroke, TVR, or major bleeding	2 (1.5)	14 (1.5)	15 (1.6)	1.072 (0.517–2.221)	0.85
Secondary endpoints					
Minor bleeding	0	4 (0.4)	5 (0.5)	1.247 (0.335–4.643)	0.74
Minimal bleeding	1 (0.8)	6 (0.7)	6 (0.7)	0.997 (0.321–3.090)	0.99
Death					
All deaths	1 (0.8)	7 (0.8)	8 (0.9)	1.143 (0.414–3.152)	0.80
Cardiac death	0	3 (0.3)	5 (0.5)	1.667 (0.398–6.974)	0.48
Myocardial infarction	0	4 (0.4)	6 (0.7)	1.500 (0.423–5.317)	0.53
Stroke	0	4 (0.4)	0	N/A	
TVR	1 (0.8)	2 (0.2)	5 (0.5)	2.499 (0.485–12.882)	0.27
Stent thrombosis	0	0	3 (0.3)	N/A	
Major bleeding	0	3 (0.3)	0	N/A	

High-Risk ACS Population

	Resistant Group (n – 50)	24-Month DAPT (n – 397)	6-Month DAPT (n – 395)	Hazard Ratio (95% CI)	p Value
Primary endpoint: death from any cause, MI, stroke, TVR, or major bleeding	0	4 (1.0)	7 (1.8)	1.773 (0.519–6.057)	0.361
Secondary endpoints					
Minor bleeding	0	3 (0.8)	1 (0.3)	0.334 (0.035–3.211)	0.34
Minimal bleeding	0	3 (0.8)	2 (0.5)	0.669 (0.112–4.002)	0.66
Death					
All deaths	0	1 (0.3)	4 (1.0)	4.041 (0.452–36.151)	0.21
Cardiac death	0	0	3 (0.8)	N/A	
MI	0	2 (0.5)	2 (0.5)	1.006 (0.142–7.144)	0.99
Stroke	0	1 (0.3)	0	N/A	
TVR	0	0	3 (0.8)	N/A	0
Stent thrombosis	0	0	2 (0.5)	N/A	
Major bleeding	0	1 (0.3)	0	N/A	

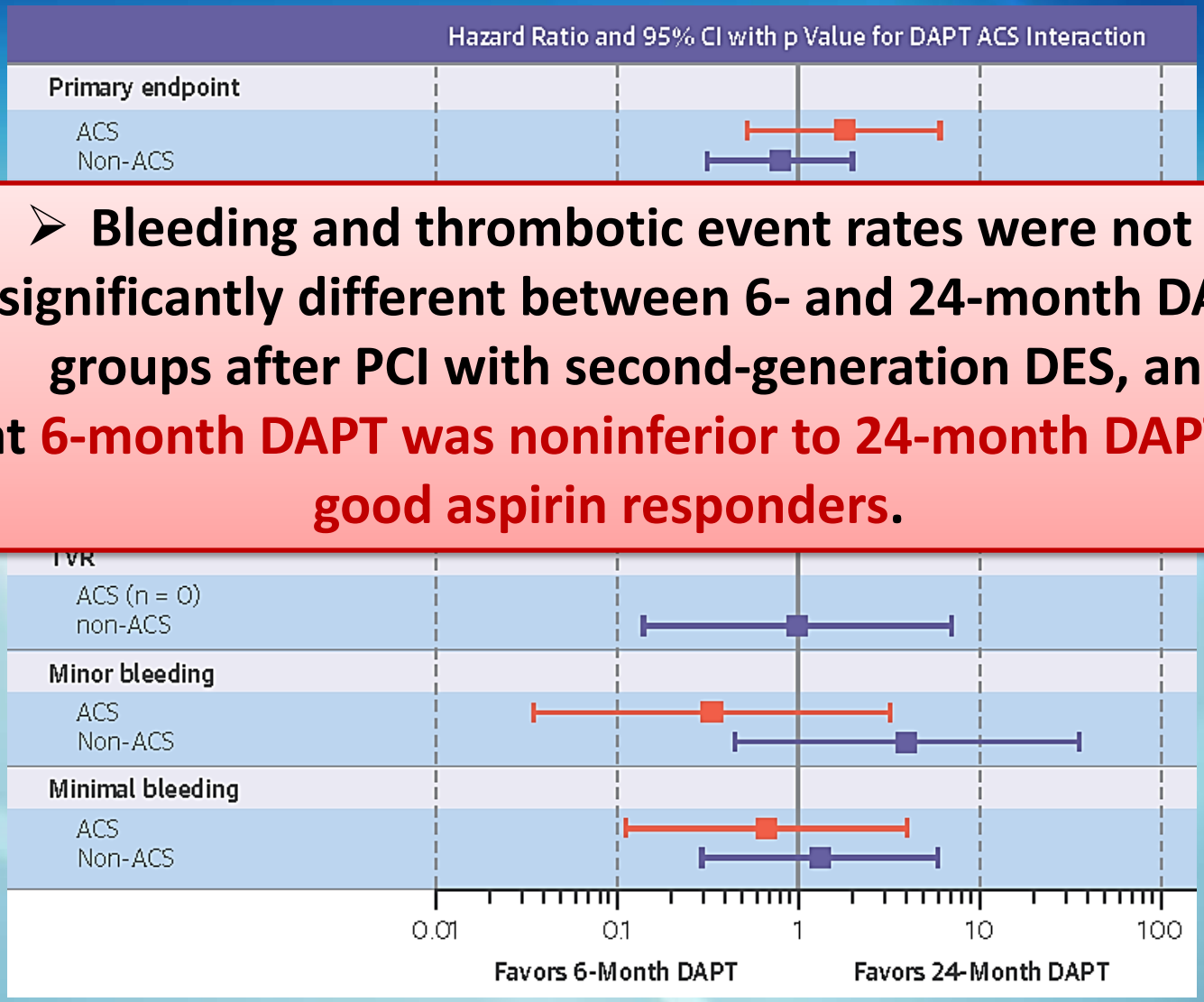
Values are n (%) unless otherwise indicated.
TVR = urgent target vessel revascularization

SANOFI

Gilard M J Am Coll Cardiol. 2015;65:777-86.

ITALIC : 1 year outcome in ACS and non-ACS patients

New generation DES followed by 6- vs 24-months DAPT



- **Bleeding and thrombotic event rates were not significantly different between 6- and 24-month DAPT groups after PCI with second-generation DES, and that 6-month DAPT was noninferior to 24-month DAPT in good aspirin responders.**

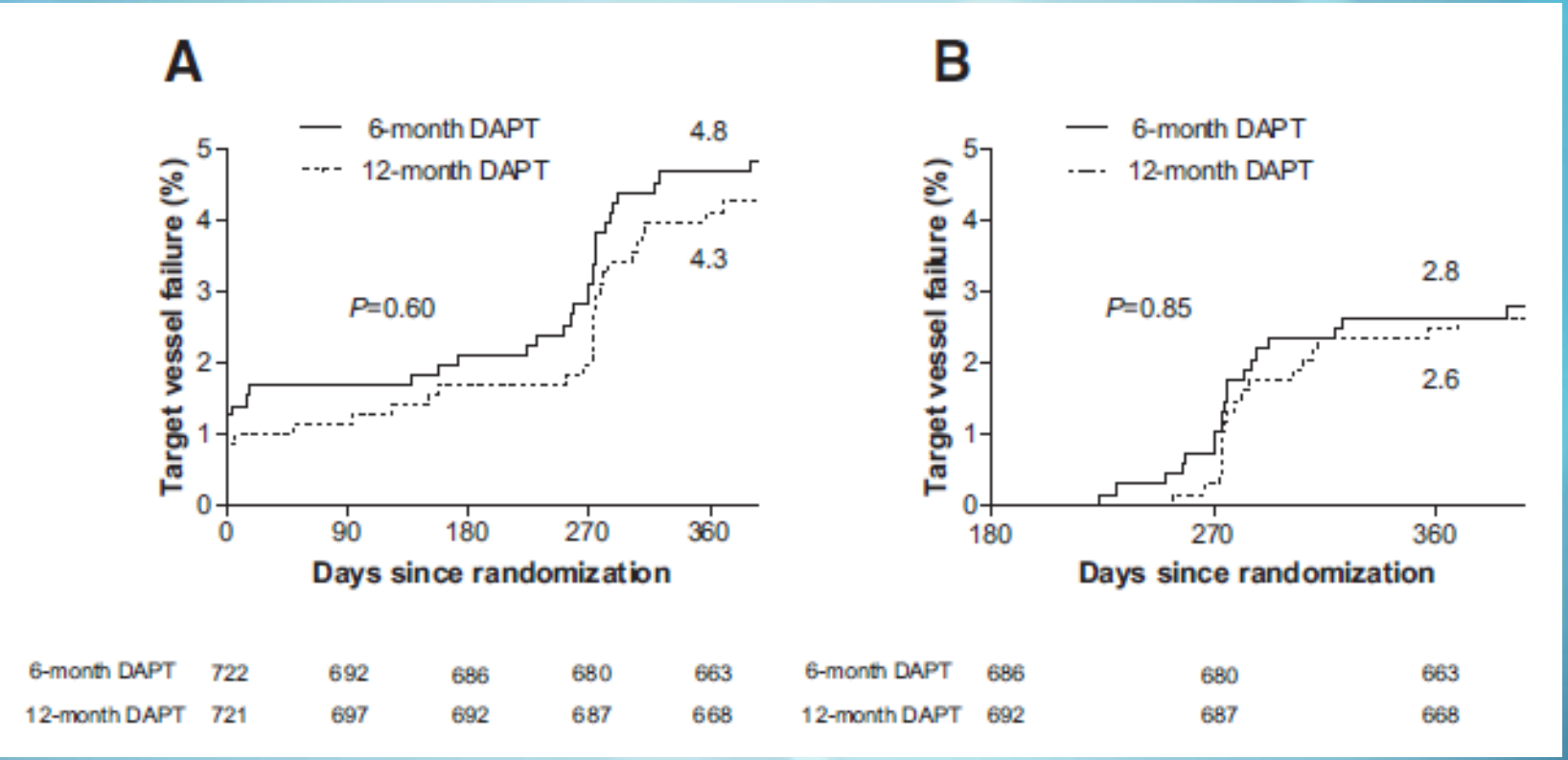
SANOFI

Gilard M J Am Coll Cardiol. 2015;65:777-86.

Plavix

EXCELLENT 6- vs 12 Mo DAPT in DES (n=1,399)

- 1:1 randomized, multicenter, investigator-designed, non-inferiority study
- **Patients with a stable or unstable angina diagnosis, excluded MI within 3 days undergoing revascularization with at least 1 DES (n=1,443, EES 75%, SES 25%), SA/SI (48%), UA/NSTEMI (49%)**
- Primary Endpoint: TVF including cardiac death, MI, or TVR within 12 months.
- Secondary endpoint: all cause death, CV death, MI, ST, major bleeding with TIMI, CVA, revascularization



Gwon HC. Circulation 2012;125:505-13.

EXCELLENT 6- vs 12 Mo DAPT in DES (n=1,399)

Table 4. Detailed Information on Stent Thrombosis

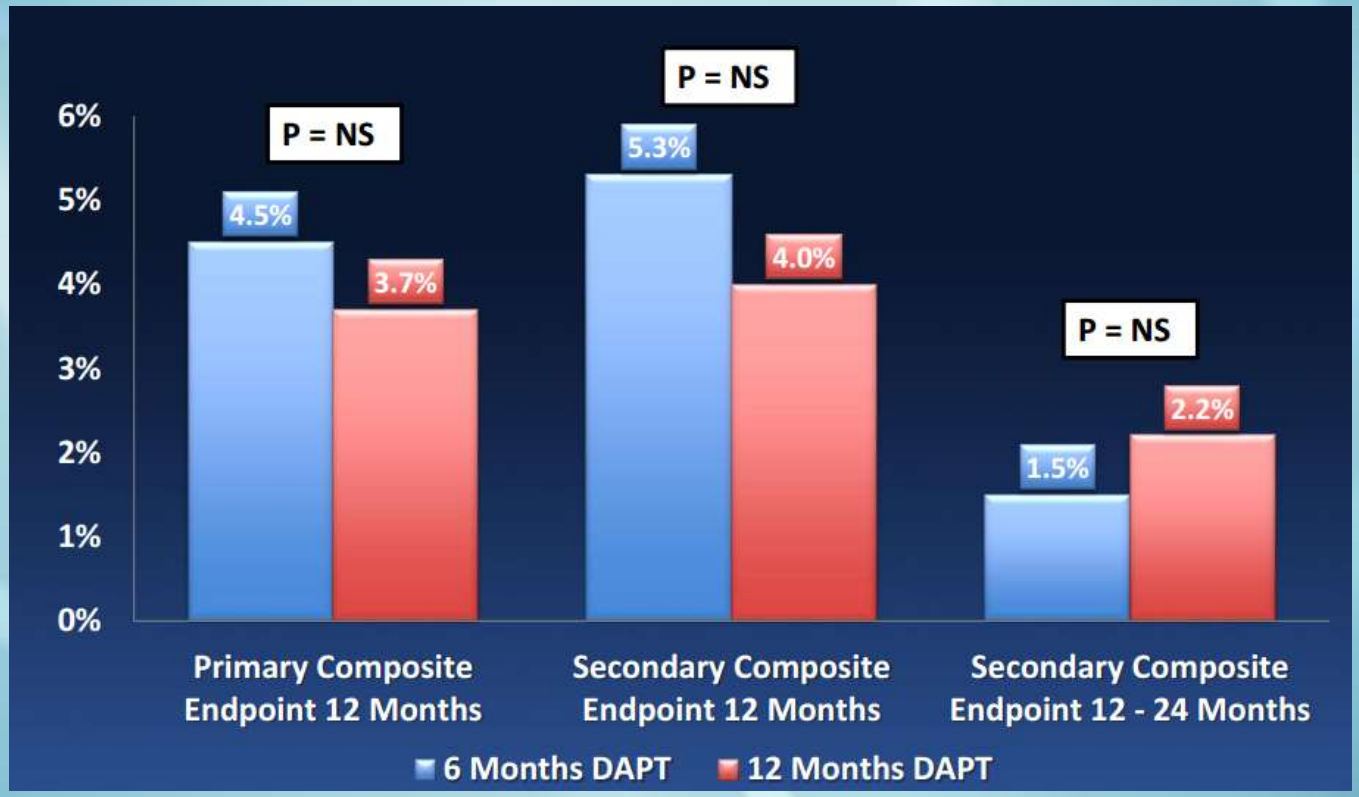
Time to Stent Thrombosis, d	Classification	Group	Clinical Presentation	Diabetic Status	Ejection Fraction, %	Stent Type	Aspirin	Clopidogrel	Outcome
0	Definite	6-mo DAPT	ST-segment–elevation myocardial infarction	No	55	EES	Continued	Continued	TLR
4	Definite	6-mo DAPT	Stable angina	Yes (OHA treated)	58	SES	Continued	Continued	Myocardial infarction
7	Probable	12-mo DAPT	Unstable angina	No	74	EES	Continued	Continued	Death
15	Definite	6-mo DAPT	Non–ST-segment–elevation myocardial infarction	Yes (OHA treated)	62	EES	Continued	Continued	Myocardial infarction
17	Definite	6-mo DAPT	Stable angina	Yes (OHA treated)	70	SES	Continued	Continued	Myocardial infarction
173	Definite	6-mo DAPT	Stable angina	Yes (OHA treated)	Not available	EES	Continued	Continued	TLR
273	Definite	6-mo DAPT	Stable angina	No	70	SES	Continued	Discontinued at day 184	TLR

DAPT indicates dual antiplatelet therapy; EES, everolimus-eluting stent; TLR, target lesion revascularization; OHA, oral hypoglycemic agents; and SES, sirolimus-eluting stent.

Gwon HC. Circulation 2012;125:505-13.

SECURITY 6- vs 12 Mo DAPT in 2nd G DES (n=1,399)

- 1:1 randomized, multicenter, international, investigator-driven, non-inferiority study
- **Patients with a stable or unstable angina diagnosis or documented silent ischemia undergoing revascularization with at least 1 2nd generation DES**
- Primary Endpoint: Composite of cardiac death, MI, stroke, definite or probable stent thrombosis or BARC type 3 or 5 bleeding at 12 months.
- Secondary endpoint: Composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months.

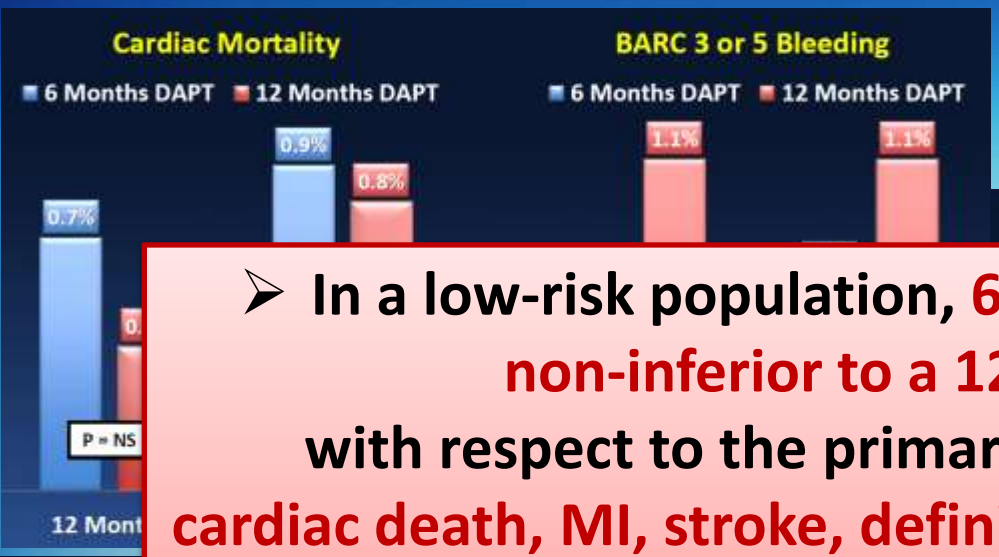


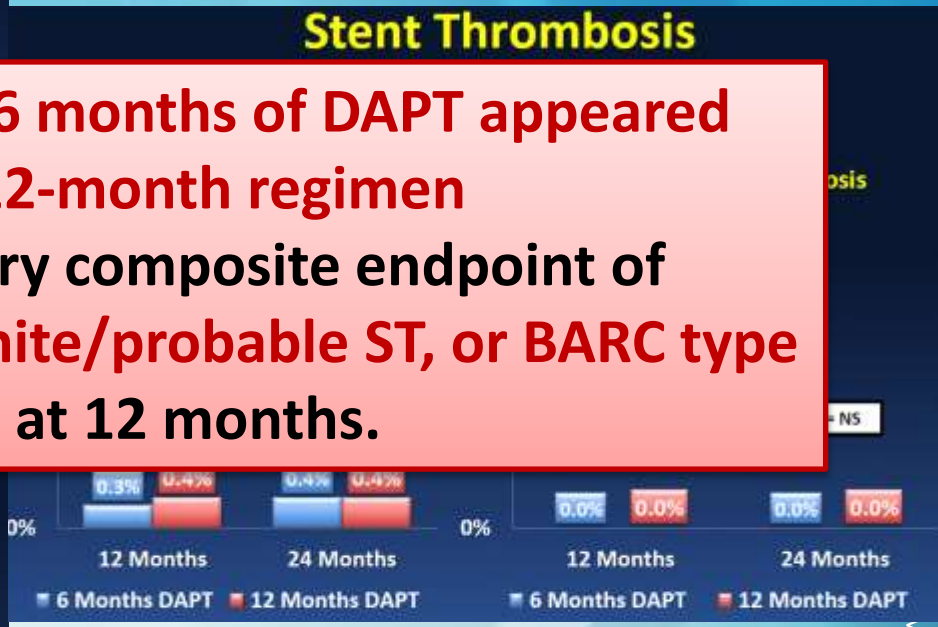
SANOFI

Colombo A. J Am Coll Cardiol 2014;64:2086-97.

Plavix

SECURITY 6- vs 12-months DAPT (n=1,399)





- In a low-risk population, **6 months of DAPT appeared non-inferior to a 12-month regimen** with respect to the primary composite endpoint of **cardiac death, MI, stroke, definite/probable ST, or BARC type 3 or 5 bleeding** at 12 months.

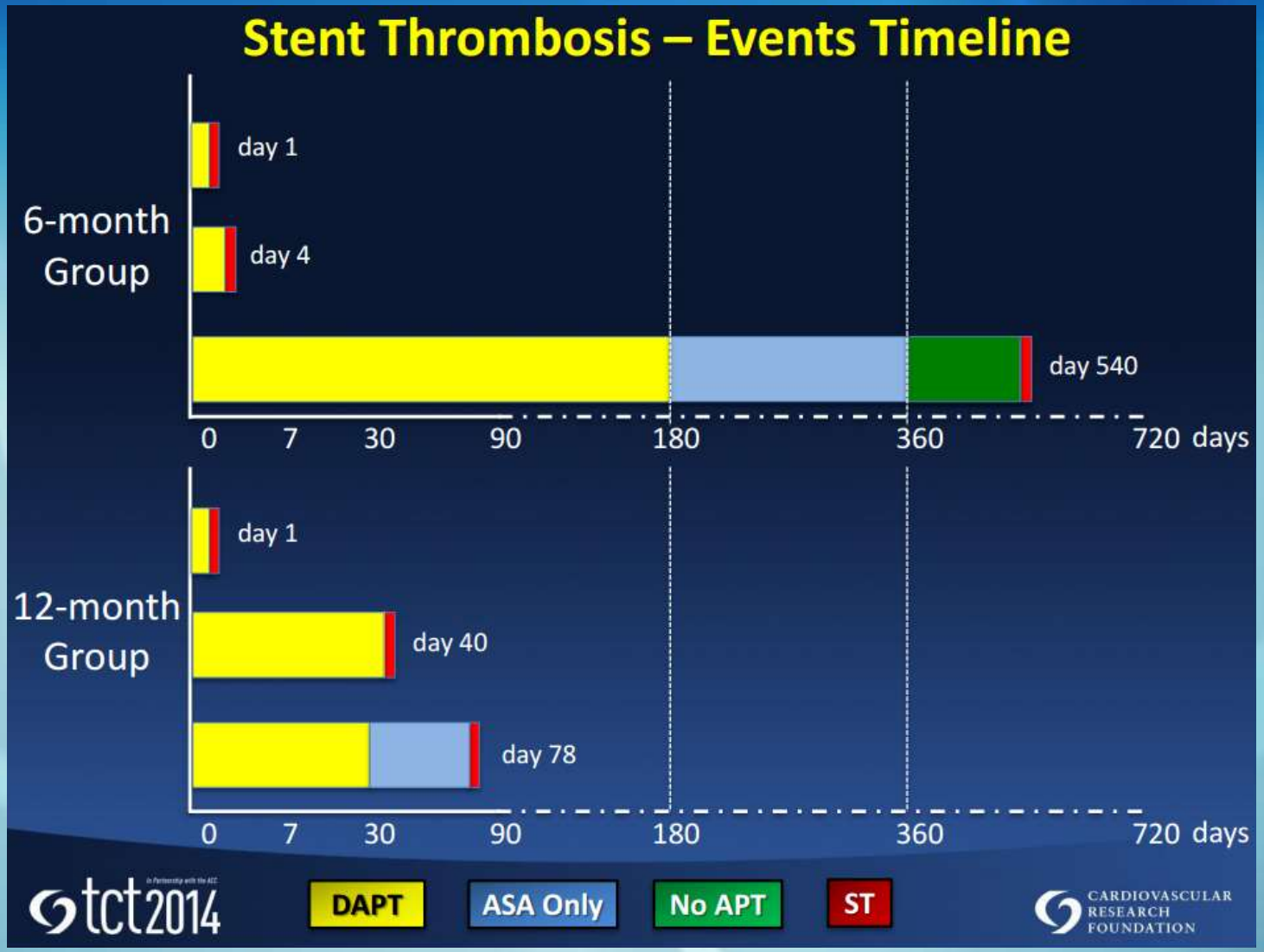
M.CLO.14.02.06[2015.02]

SANOFI

Colombo A. J Am Coll Cardiol 2014;64:2086-97.

Plavix
Clopidogrel 75mg
Take Protection Further. Today.

SECURITY 6- vs 12-months DAPT (n=1,399)



Colombo A. J Am Coll Cardiol 2014;64:2086-97.

SECURITY predictors for PEP

TABLE 6 Predictors of the Primary Endpoint at Multivariable Analysis

Variables in the Model*	HR	95% CI	p Value
Age ≥75 yrs	2.211	1.234-3.962	0.007
Endeavor Resolute vs. Biomatrix/Xience/Promus	2.336	1.051-5.190	0.019
Mean number of stents (for each unit increase)	1.410	1.128-1.741	0.002
Mean stent length (for each 5-U increase)	1.383	1.135-1.685	0.001
Mean stent size (for each 2.5-U increase)	1.326	1.106-1.590	0.002
Diabetes mellitus			0.069
NIDDM vs. none	0.895	0.464-1.729	
IDDM vs. none	2.349	1.080-5.106	
DAPT 6- vs. 12-month	1.272	0.754-2.145	0.367
Female	1.596	0.897-2.838	0.111

*Cox model fitted on 1,360 patients with 57 primary events because of missing values.

HR = hazard ratio; other abbreviations as in Tables 1 and 5.

KR.PM.CLO.14.02.06[2015.02]

SANOFI

Colombo A. J Am Coll Cardiol 2014;64:2086-97.

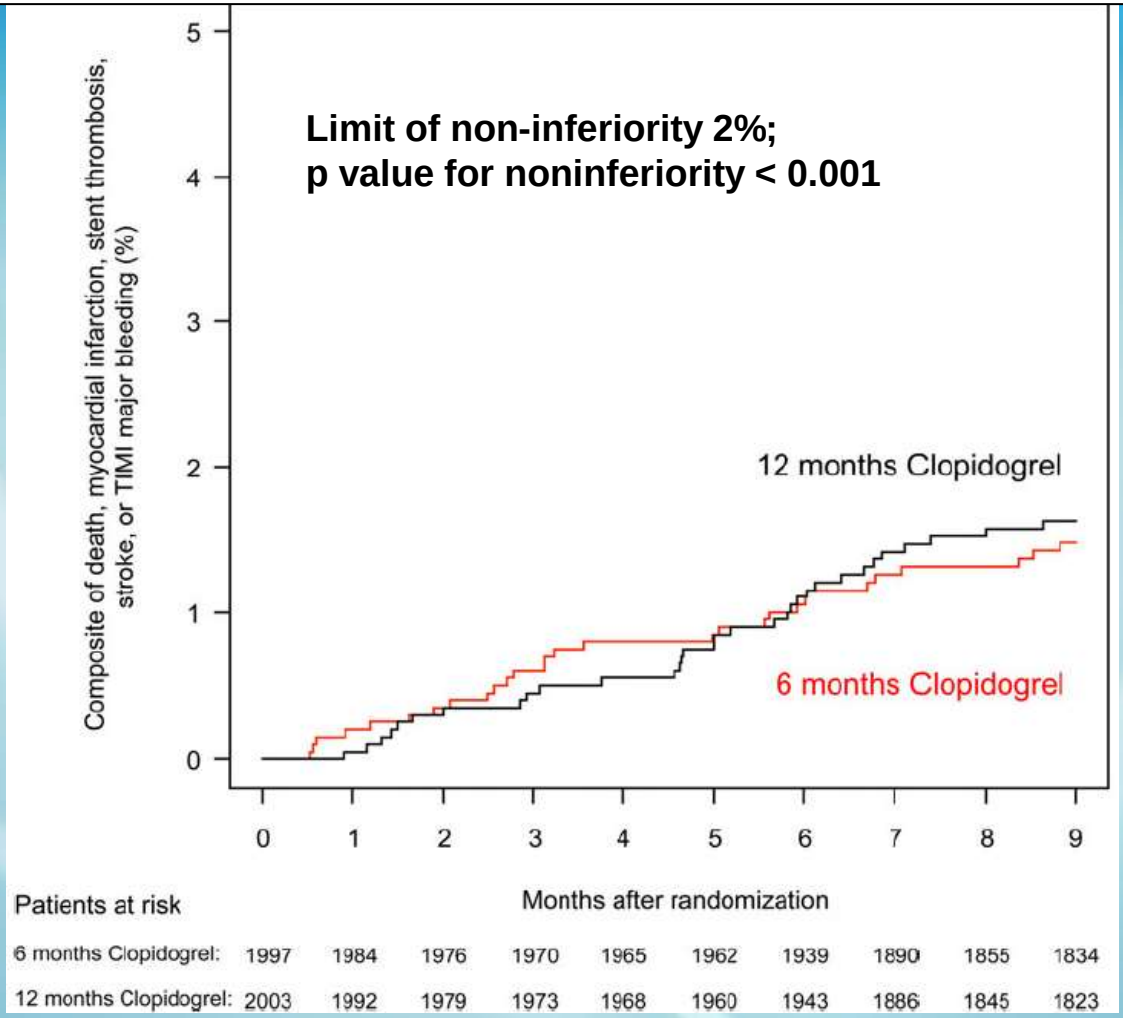
Plavix
Clopidogrel 75mg
Take Protection Further. Today.

ISAR-SAFE : Primary composite endpoint

New generation DES followed by 6- vs 12-months DAPT

- SA/UA/NSTEMI/STEMI = 49/21/10/8%, N=4,000

Death, MI, stent thrombosis, stroke or thrombolysis in MI major bleeding



32/2,003 patients (1.6%)

29/1,997 patients (1.5%)

KR.PM.CLO.14.02.06[2015.02]

Schulz-Schüpke S. Eur Heart J. 2015 Jan 23.

ISAR-SAFE : Primary composite endpoint on 9 Mo

New generation DES followed by 6- vs 12-months DAPT

Table 4 Clinical outcomes at 9 months

	Six months clopidogrel (n = 1997)	Twelve months clopidogrel (n = 2003)	HR (95% CI)	P-value
stent thrombosis or stroke)	26 1.3% (0.8–1.8%)	30 1.5% (1.0–2.1%)	0.87 (0.51–1.47)	0.59
Definite stent thrombosis	5 0.3% (0–0.5%)	3 0.2% (0–0.3%)	1.66 (0.40–6.96)	0.49
TIMI[a] minor bleeding	2 0.1% (0–0.2%)	8 0.4% (0.1–0.7%)	0.25 (0.05–1.17)	0.08
TIMI[a] major or minor bleeding	6 0.3% (0.1–0.5%)	13 0.7% (0.3–1.0%)	0.46 (0.18–1.21)	0.12
BARC[b] bleeding	27 1.4% (0.9–1.9%)	55 2.8% (2.1–3.5%)	0.49 (0.31–0.77)	0.002
Class 1	11	20		
Class 2	15	24		
Class 3a	1	11		
Class 3b	4	8		
Class 3c	1	3		
Class 5	0	1		
Blood transfusion	3	9		

- **No significant difference in net clinical outcome between 6 and 12 months of clopidogrel therapy after DES. However, the results of the trial must be considered in view of its premature termination and lower than expected event rates.**

KR.PM.CLO.14.02.06[2015.02]

SANOFI

Schulz-Schüpke S. Eur Heart J. 2015 Jan 23. [epub]

Plavix

Benefits with longer DAPT duration?

Similar ischemic risk, but increased stroke and bleeding risk

- Meta-REAL/ZEST-LATE (24/12), EXCELLENT (12/6), and PRODIGY (24/6)

Table 1
Main clinical, angiographic and procedural characteristics of the included studies.

	Excellent		Prodigy[a]		Real-late/zest-late	
	Long	Short	Long	Short	Long	Short
Study characteristics						
Duration of Tx, (months)	12	6	24	6	24	12
No. of patients	721	722	741	737	1357	1344
No. of sites	19		3		26	
Primary endpoint	Cardiac death, MI, or TVR		Overall death, MI, CVA		Cardiac death or MI	
Study design	Non-inferiority		Superiority		Superiority	
Follow up duration, (months)	12.0		24		19.2	
Loss at follow-up, %	1.2	0.9	0.3	0.4	0.6	0.7
Pts characteristics						
Age, mean (SD)	62.4 (10.4)	63.0 (9.6)	67.4 (11.2)	67.8 (11.2)	62.0 (9.8)	61.9 (9.9)
Males, no. (%)	461 (63.9)	470 (65.1)	583 (78.7)	573 (77.8)	950 (70.0)	933 (69.4)
Diabetes, no. (%)	278 (38.6)	272 (37.7)	182 (24.6)	185 (25.0)	340 (25.1)	364 (27.1)
Stable CAD, no. (%)	346 (48.0)	353 (48.9)	195 (26.3)	193 (26.2)	514 (37.9)	500 (37.2)
NSTEACS, no. (%)	349 (48.4)	350 (48.5)	308 (41.6)	306 (41.5)	688 (50.1)	703 (52.3)
STEMI, no. (%)	26 (3.6)	19 (2.6)	238 (32.1)	238 (32.3)	155 (11.4)	141 (10.5)
1-vessel disease	346 (48)	347 (48.1)	205 (27.7)	216 (29.3)	690 (50.8)	711 (52.9)
Multi-vessel disease, no. (%)	375 (52)	375 (51.9)	536 (72.3)	521 (70.7)	667 (49.2)	633 (47.1)
No. of implanted stents, mean (SD)	1.6 (0.9)	1.6 (1.0)	1.83 (1.23)	1.94 (1.30)	1.3 (0.5)	1.2 (0.5)
Everolimus-ES, no. (%)	539 (74.8)	540 (74.8)	248 (33.5)	247 (33.5)	–	–
Sirolimus-ES, no. (%)	182 (25.2)	182 (25.2)	–	–	1057 (56.5)	1052 (57)
Paclitaxel-ES, no. (%)	–	–	245 (33.1)	245 (33.2)	456 (24.4)	439 (23.8)
Zotarolimus-ES, no. (%)	-	-	248 (33.4)	245 (33.2)	350 (18.7)	347 (18.8)

CAD: coronary artery disease; ES: eluting stent; MI: myocardial infarction; NSTEACS: non-ST segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; Tx: therapy.

[a] Patients in the PRODIGY trial who were randomized to bare metal stenting were excluded to comply with inclusion criteria consisting of only patients who received DES implantation at the time of intervention.

Valgimigli M, Int J Cardiol 2013;168:2579

Benefits with longer DAPT duration?

Similar ischemic risk, but increased stroke and bleeding risk

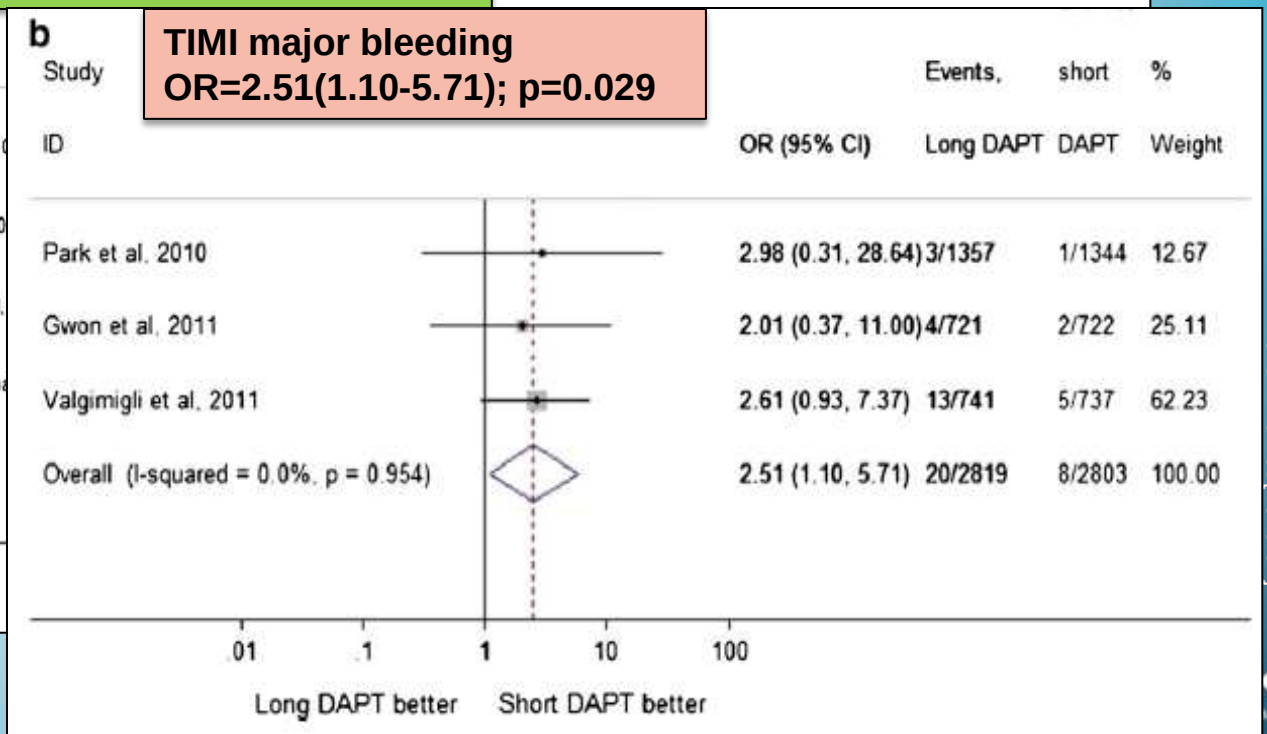
- Meta-REAL/ZEST-LATE (24/12), EXCELLENT (12/6), and PRODIGY (24/6)

Cardiac death/MI/stroke
OR=1.26 (0.88-1.80); p=0.21

Definite or probable stent thrombosis
OR=0.73 (0.31-1.72); p=0.47

Stroke
OR=1.93 (1.01-3.69); p=0.047

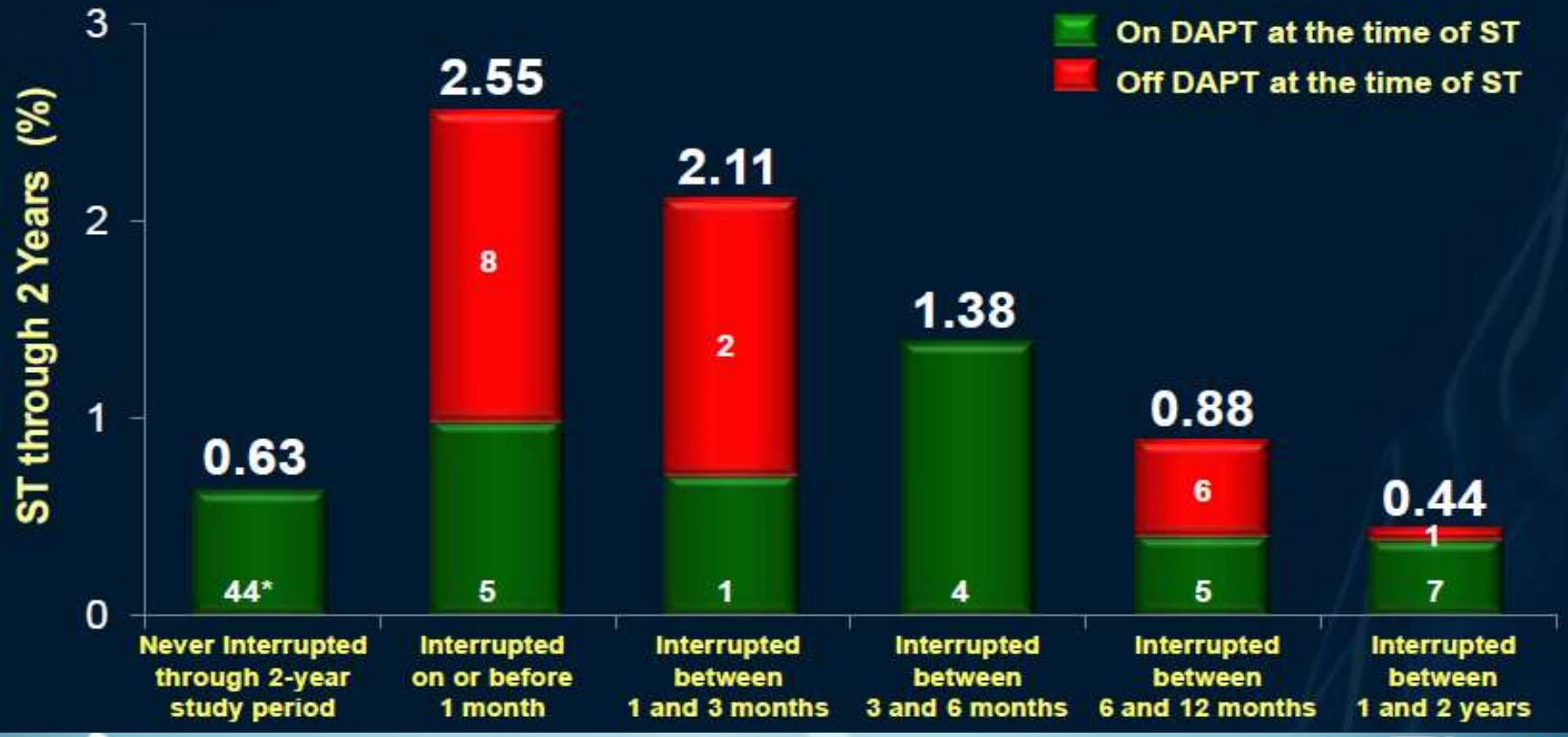
TIMI major bleeding
OR=2.51(1.10-5.71); p=0.029



Valgimigli M, Int J Cardiol 2013;168:2579

Most of stent thrombosis occurs in the period of DAPT continuation.

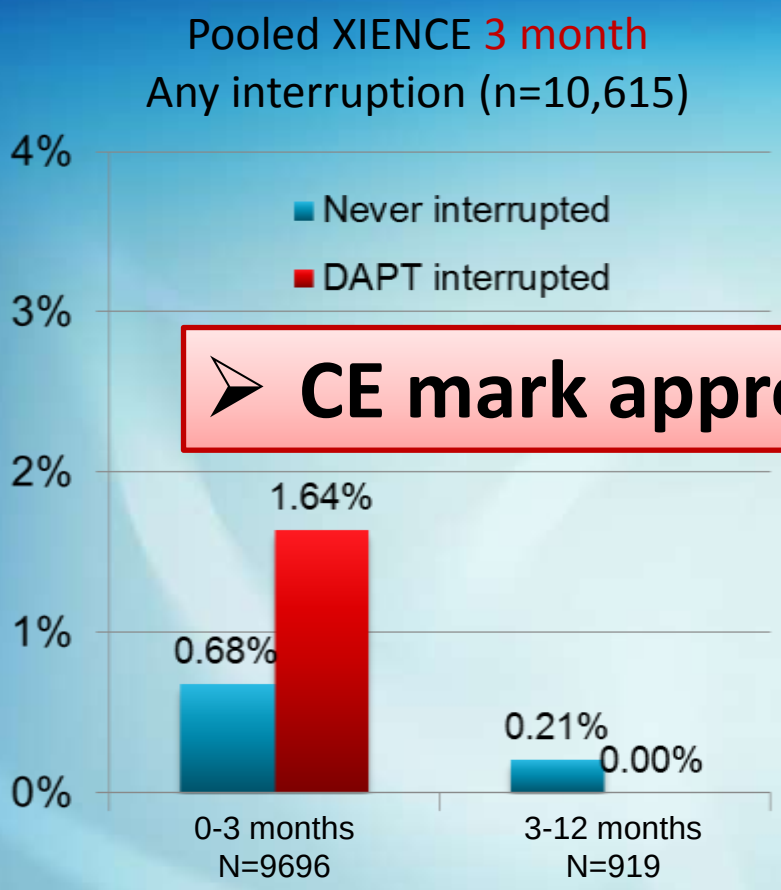
- Pooled analysis of 7 EES trial (N=11,219)
- 70% of stent thrombosis episodes occur on DAPT
- DAPT interruption did not result in ST in 99.4% of patients.

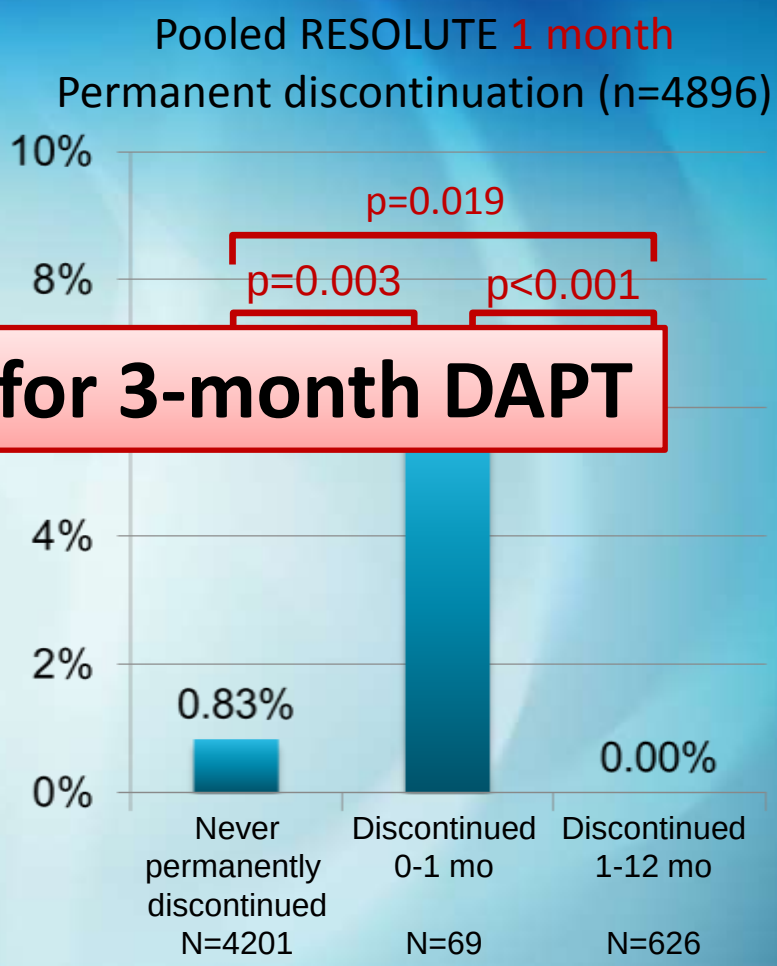


Stone G, TCT 2011

Short DAPT Duration for Current DES?

3-month DAPT for EES and 1-month for R-ZES





➢ **CE mark approval for 3-month DAPT**

* Pooled analysis of XIENCE V USA, SPIRIT V, SPRIT Women SAS, and XIENCE V India

Modified from Stone G, TCT 2012, and Kirtane AJ, ESC 2012

2014 ESC/EACTS guideline for myocardial revascularization

DAPT for SCAD			
BMS	at least 1 month	1A	
DES	6 months	1B	EXCELLENT
DES with high risk of bleeding	< 6 months	IIbA	OPTIMIZE
P2Y12 inhibitor for NSTEMI			
DAPT	12 months if not contraindicated	1A	PCI-CURE
DAPT option	Prasugrel, Ticagrelor, Clopidogrel	1B	CURRENT-OASIS7 PCI-CURE
DAPT for STEMI			
DAPT	12 months if not contraindicated	1A	
DAPT option	Prasugrel, Ticagrelor, Clopidogrel	1B	TRIOTON, PLATO, CURRENT-OASIS7

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

Tullio Palmerini, Umberto Benedetto, Letizia Bacchi-Reggiani, Diego Della Riva, Giuseppe Biondi-Zoccai, Fausto Feres, Alexandre Abizaid, Myeong-Ki Hong, Byeong-Keuk Kim, Yangsoo Jang, Hyo-Soo Kim, Kyung Woo Park, Philippe Genereux, Deepak L Bhatt, Carlotta Orlandi, Stefano De Servi, Mario Petrou, Claudio Rapezzi, Gregg W Stone

- **Longer DAPT was associated with a 22% increased rate of all-cause mortality due to a 49% increased rate in non-cardiac mortality, with no significant difference in cardiac mortality (HR=0.93, 95% CI 0.73-1.17, p=0.52). No significant heterogeneity across trials or between pooled trials stratified by DAPT duration was apparent.**

- **These results support either a short-term (3 or 6 months) DAPT strategy in most patients, especially those at low risk of recurrent coronary events and stent thrombosis, and at high risk of bleeding.**

- **Extended DAPT strategy (longer than 1 year) may still be appropriate in selected patients in whom prevention of stent and non-stent related coronary events are likely to offset the adverse events associated with extended duration antiplatelet therapy.**

SANOFI

Palmerini T, et al. Lancet. 2015 Mar 13.

Plavix

Main characteristics

	Number of patients in each treatment group	Primary endpoint	Design and randomisation	Follow-up duration after randomisation	Results of the primary endpoint
ARCTIC-Interruption, 2014[25]	12 months (n=624); 18–24 months (n=635)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or target vessel revascularisation	Superiority, randomisation at discontinuation of dual antiplatelet therapy	Median of 17 months	Superiority of >12-month dual antiplatelet therapy not shown
DAPT, 2014[18]	12 months (n=4941); 30 months (n=5020)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or bleeding	Superiority, randomisation at discontinuation of dual antiplatelet therapy	18 months	Superiority of 30-month dual antiplatelet therapy shown
DES-LATE, 2013[11]	12 months (n=2514); 36 months (n=2531)	Cardiac death, myocardial infarction, or cerebrovascular accident	Superiority, randomisation at discontinuation of dual antiplatelet therapy	24 months	Superiority of 24-month dual antiplatelet therapy not shown
EXCELLENT, 2012[8]	6 months (n=722); 12 months (n=721)	Cardiac death, myocardial infarction, and ischaemia-driven target vessel revascularisation	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
ISAR-SAFE, 2014[26]	6 months (n=1997); 12 months (n=2003)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or bleeding	Non-inferiority, randomisation at discontinuation of dual antiplatelet therapy	9 months	Non-inferiority shown
ITALIC, 2014[17]	6 months (n=953); 24 months (n=941)	Death, myocardial infarction cerebrovascular accident, target vessel revascularisation, or bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
OPTIMIZE, 2013[7]	3 months (n=1563); 12 months (n=1556)	Death, myocardial infarction, cerebrovascular accident, or major bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
PRODIGY, 2012[10]	6 months (n=751); 24 months (n=750)	Death, myocardial infarction, or cerebrovascular accident	Superiority, randomisation 1 month after percutaneous coronary intervention	24 months	Superiority of 24-month dual antiplatelet therapy not shown
RESET, 2012[9]	3 months (n=1059); 12 months (n=1058)	Cardiac death, myocardial infarction, stent thrombosis, target vessel revascularisation, or major bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
SECURITY, 2014[16]	6 months (n=682); 12 months (n=717)	Cardiac death, myocardial infarction cerebrovascular accident, stent thrombosis, bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown

Palmerini T, et al. Lancet. 2015 Mar 13.

Palmerini T, et al. Lancet. 2015 Mar 13.

Survival comparison with ITT;
shorter vs longer

	Event in shorter DAPT group	Event in longer DAPT group	HR 95% CI
Total death	236/15,765	287/15,901	0.82 (0.69-0.98)
Cardiac death	139/13,144	150/13,236	0.93 (0.73-1.17)
Non-cardiac death	80/13,144	119/13,236	0.67 (0.51-0.89)
Major bleeding	124/15,756	221/15,901	0.58 (0.42-0.72)
Any bleeding	219/13,251	395/13,370	0.56 (0.48-0.66)
Myocardial infarction	359/15,765	238/15,901	1.34 (1.07-1.69)

SANOFI

Palmerini T, et al. Lancet. 2015 Mar 13.

Plavix

Survival comparison with ITT;
shorter vs longer

	≤6-month vs 1-year DAPT	≤6-month vs >1-year DAPT	1-year vs >1-year DAPT
All-cause death	0·95 (0·76–1·20)	0·78 (0·59–1·00)	0·82 (0·65–1·00)
Cardiac death	0·96 (0·68–1·40)	0·90 (0·62–1·30)	0·93 (0·69–1·20)
Non-cardiac death	1·00 (0·69–1·60)	0·65 (0·41–1·00)	0·61 (0·42–0·87)
Myocardial infarction	1·00 (0·75–1·30)	1·70 (1·30–2·40)	1·70 (1·40–2·10)
Definite or probable stent thrombosis	1·10 (0·66–1·70)	2·70 (1·50–5·00)	2·50 (1·70–4·00)
Major bleeding	0·59 (0·36–0·95)	0·34 (0·20–0·55)	0·58 (0·45–0·74)

Data are HR (95% CrI). DAPT=dual antiplatelet therapy. HR=hazard ratio. CrI=credible intervals.

Table 3: **Clinical outcomes stratified by different durations of dual antiplatelet therapy established by network meta-analysis**

SANOFI

Palmerini T, et al. Lancet. 2015 Mar 13.

Plavix

Longer than 12 months for ACS patients ??

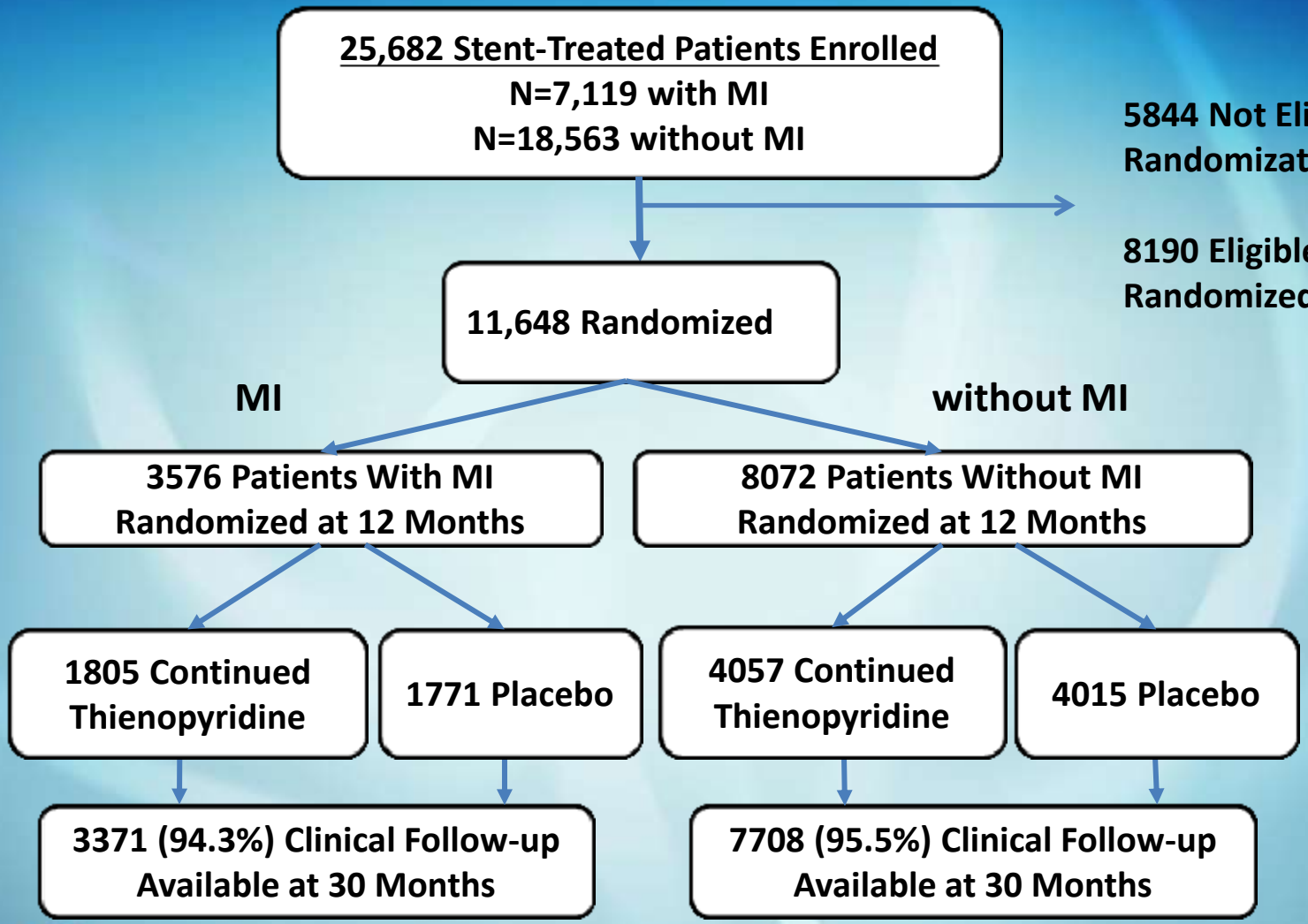
ACC/AHA Guideline Focused Update 2011

Duration of Dual Antiplatelet Therapy (DAPT) for ACS

- **Class I**
  - In patients receiving a stent (BMS or DES) during **PCI for ACS**, $P2Y_{12}$ inhibitor therapy should be given **for at least 12 months**. (Level of Evidence: B)
  - In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. (Level of Evidence: B)
- **Class IIa**
  - If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., 12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. (Level of Evidence: C)
- **Class IIb**
  - Continuation of DAPT beyond 12 months may be considered in patients undergoing DES implantation. (Level of Evidence: C)

DAPT post-hoc analysis

patients with vs. without AMI



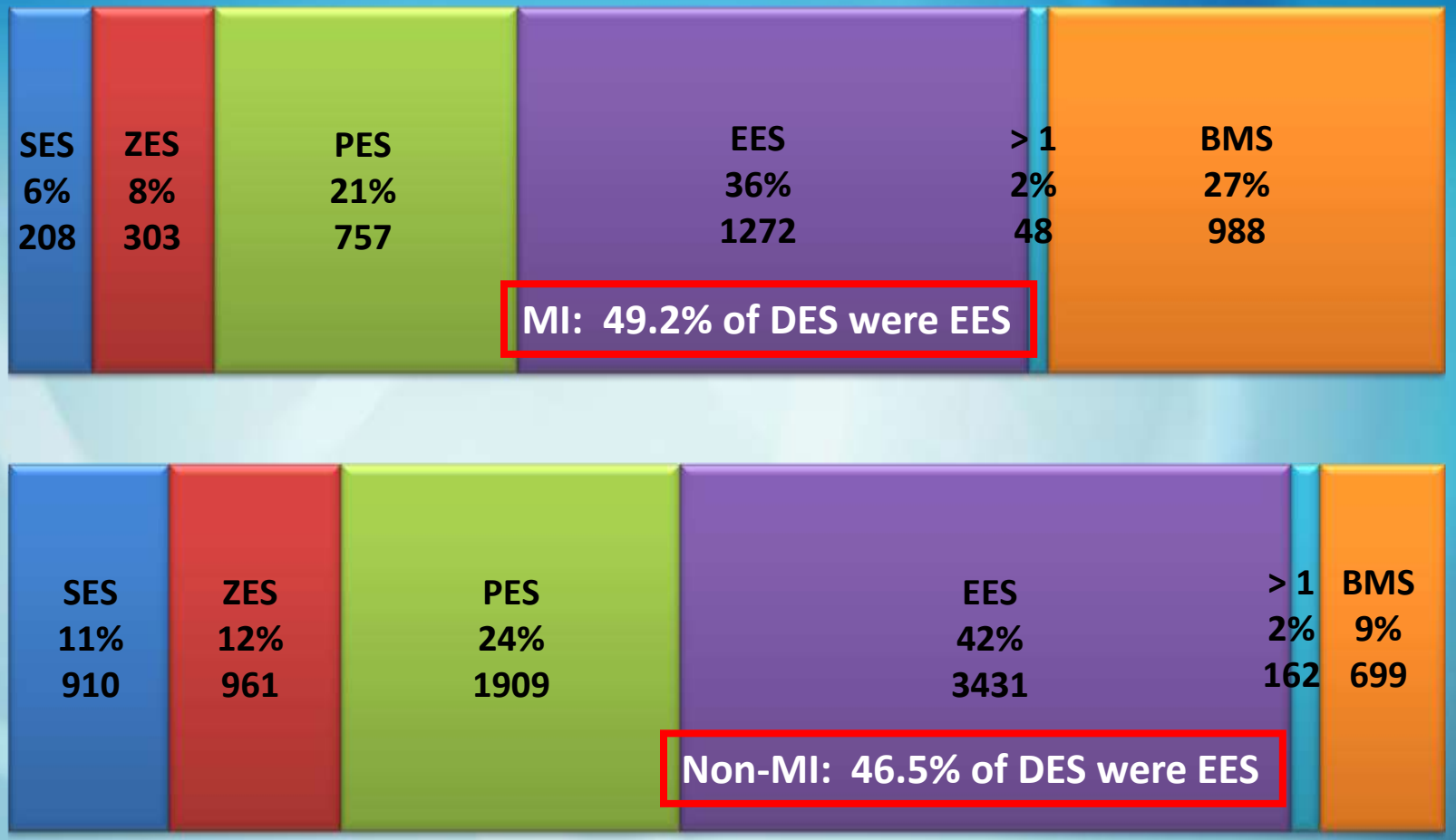
SANOFI

Yeh RW J Am Coll Cardiol 2015;Mar

Plavix

DAPT post-hoc analysis

Stent type at the index procedure

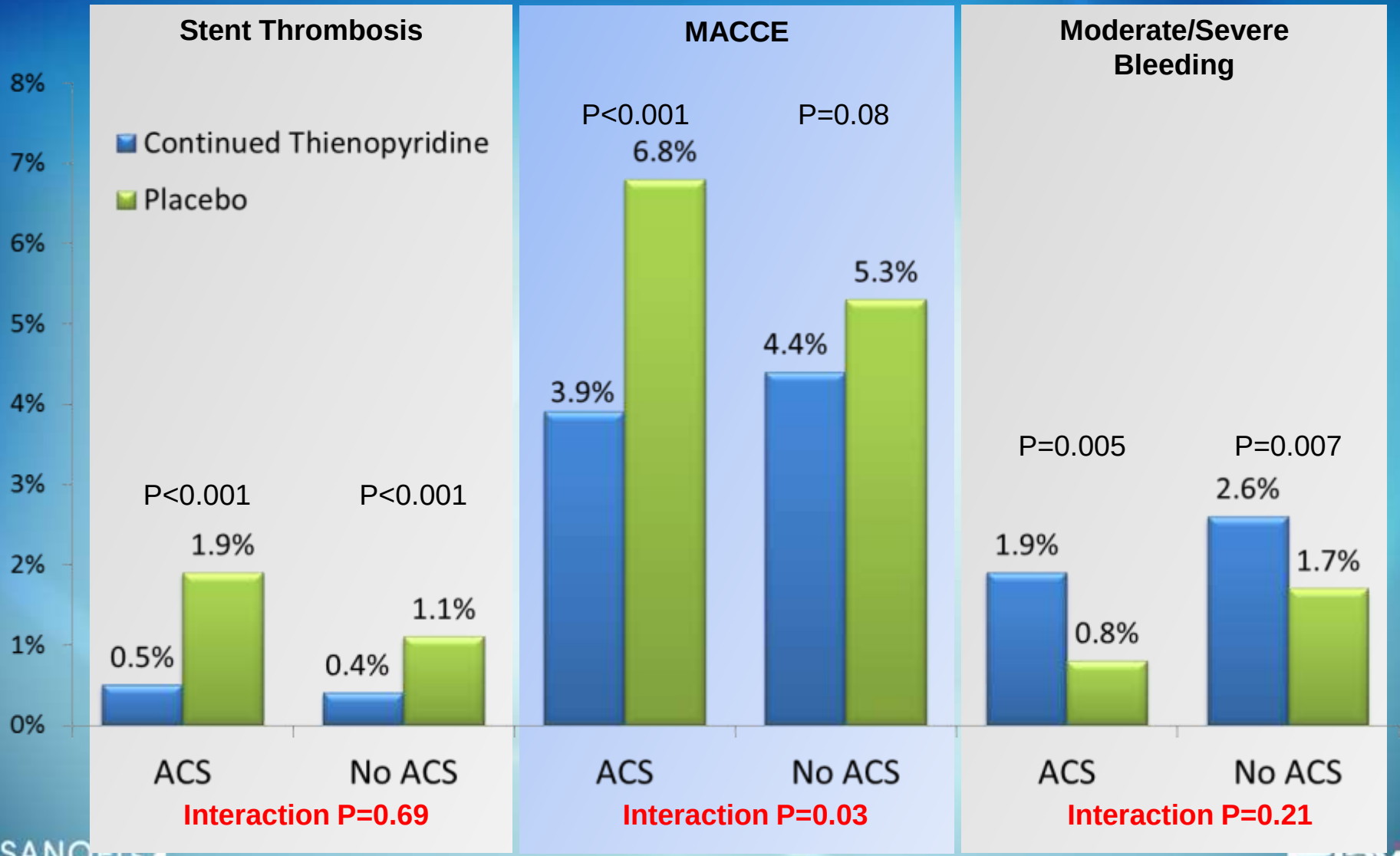


KR.PM.CLO.14.02.06[2015.02]

Yeh RW J Am Coll Cardiol 2015;Mar

DAPT post-hoc analysis

PEP in all randomized population (n=11,648)

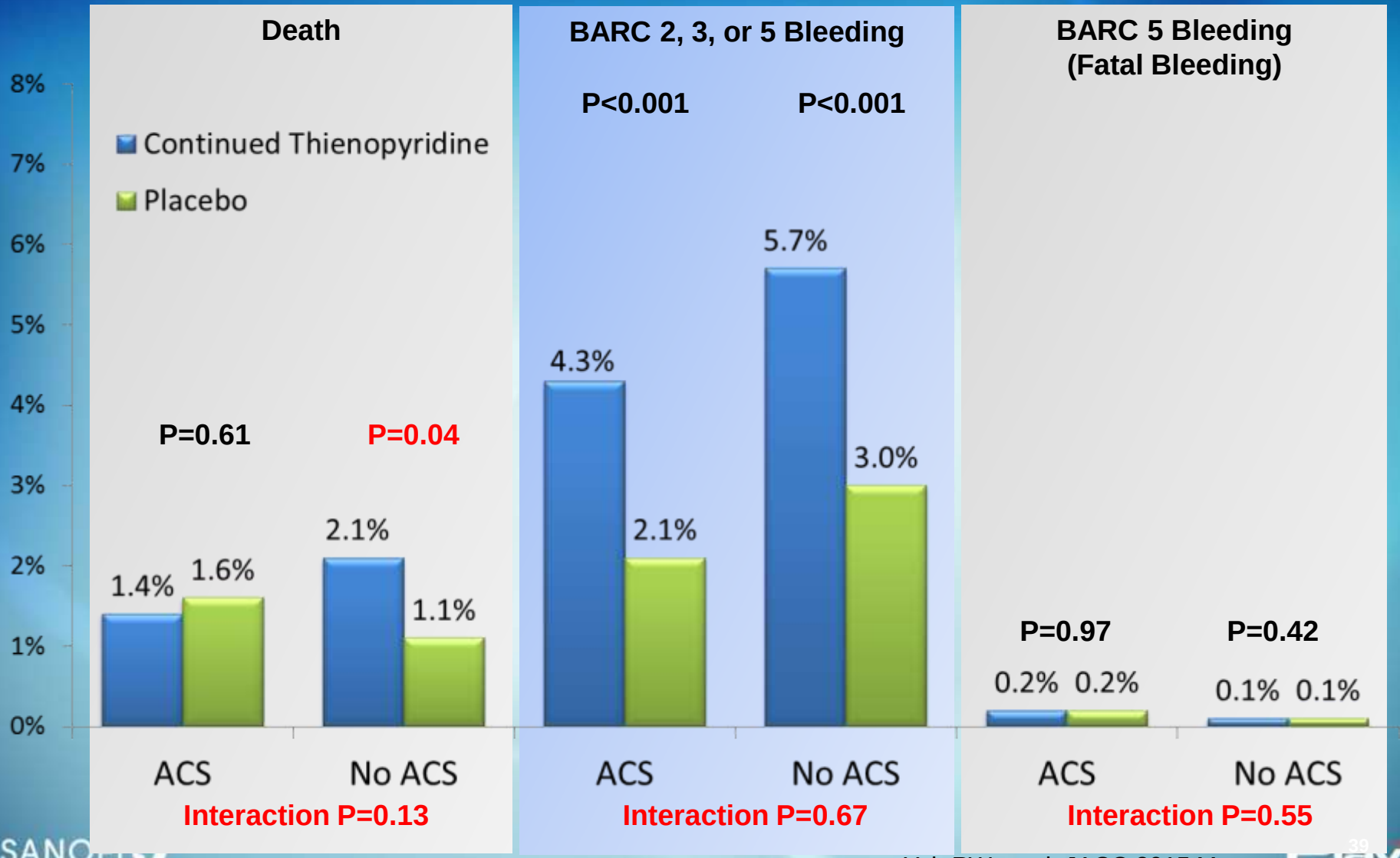


Yeh RW, et al. JACC 2015 Mar

KR.PM.CLO.14.02.06[2015.02]

DAPT post-hoc analysis

SEP in all randomized population (n=11,648)



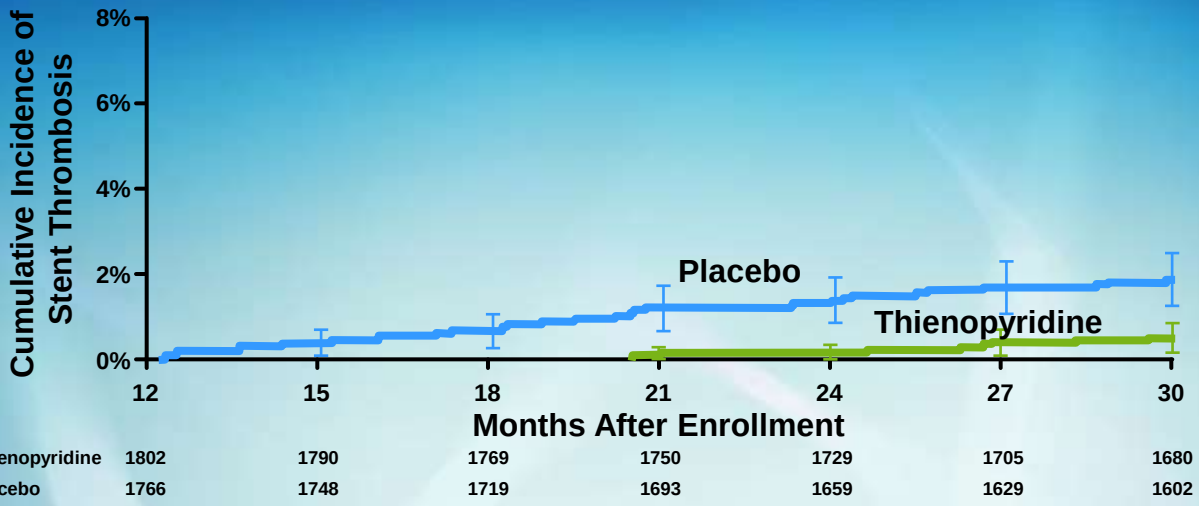
Yeh RW, et al. JACC 2015 Mar

DAPT post-hoc analysis

Stent thrombosis

A. MI Patients

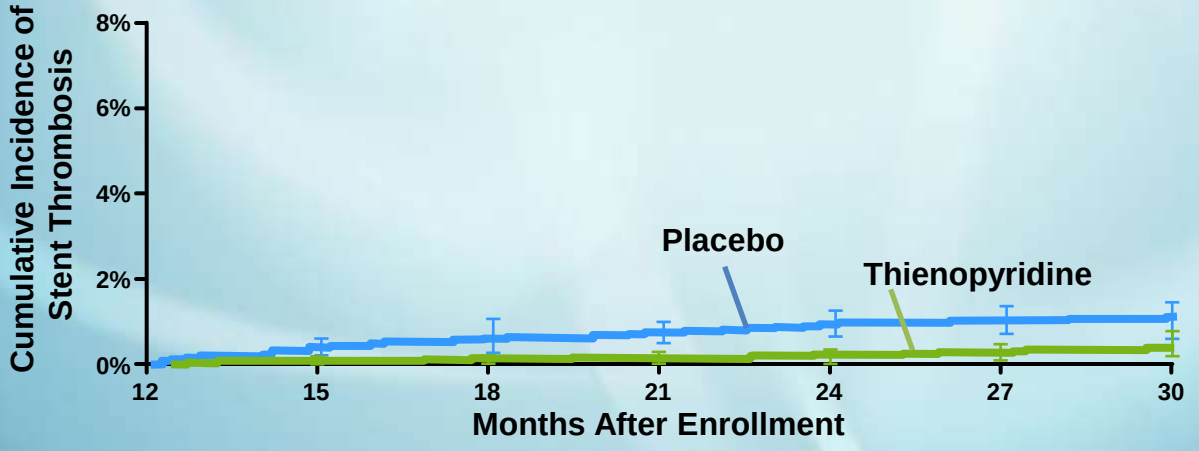
All DES and BMS randomized patients



Thienopyridine	1802	1790	1769	1750	1729	1705	1680
Placebo	1766	1748	1719	1693	1659	1629	1602

HR 0.27 (0.13-0.57)
p<0.001

B. Non-MI Patients



Thienopyridine	4050	4015	3959	3918	3881	3822	3771
Placebo	4008	3979	3918	3873	3833	3785	3747

HR 0.33 (0.18-0.60)
p<0.001

Interaction
P = 0.69

KR.PM.CLO.14.02.06[2015.02]

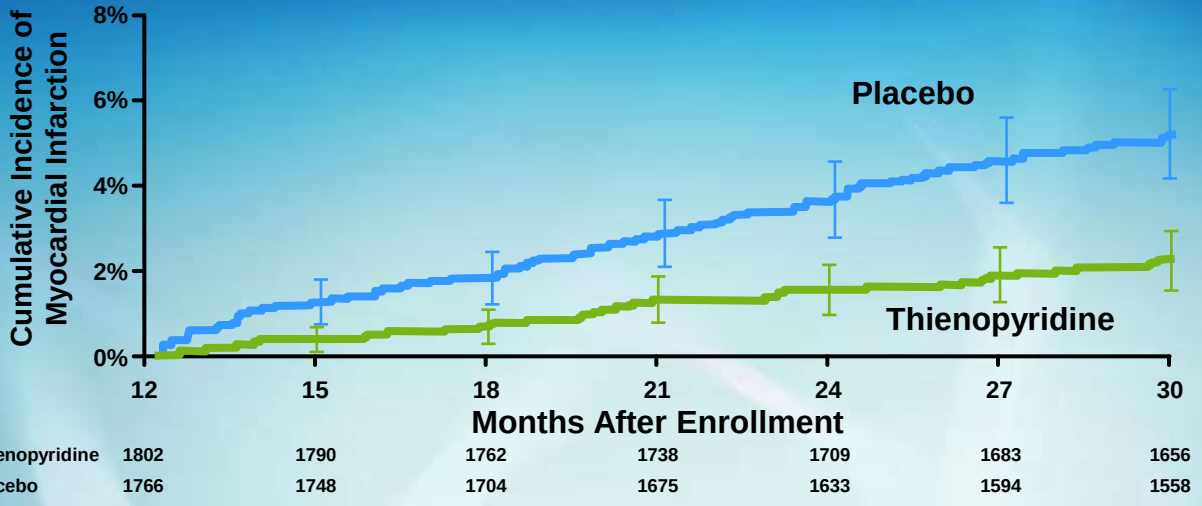
Yeh RW, et al. JACC 2015 Mar

DAPT post-hoc analysis

Myocardial infarction

A. MI Patients

All DES and BMS randomized patients

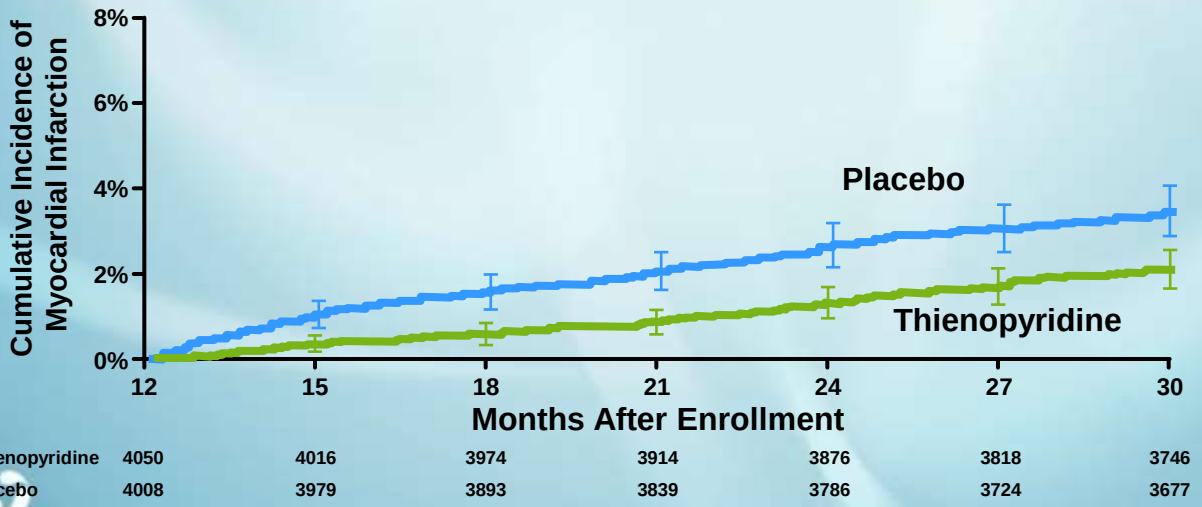


Thienopyridine	1802	1790	1762	1738	1709	1683	1656
Placebo	1766	1748	1704	1675	1633	1594	1558

HR 0.42 (0.29-0.62)
p<0.001

Interaction
P = 0.15

B. Non-MI Patients



Thienopyridine	4050	4016	3974	3914	3876	3818	3746
Placebo	4008	3979	3893	3839	3786	3724	3677

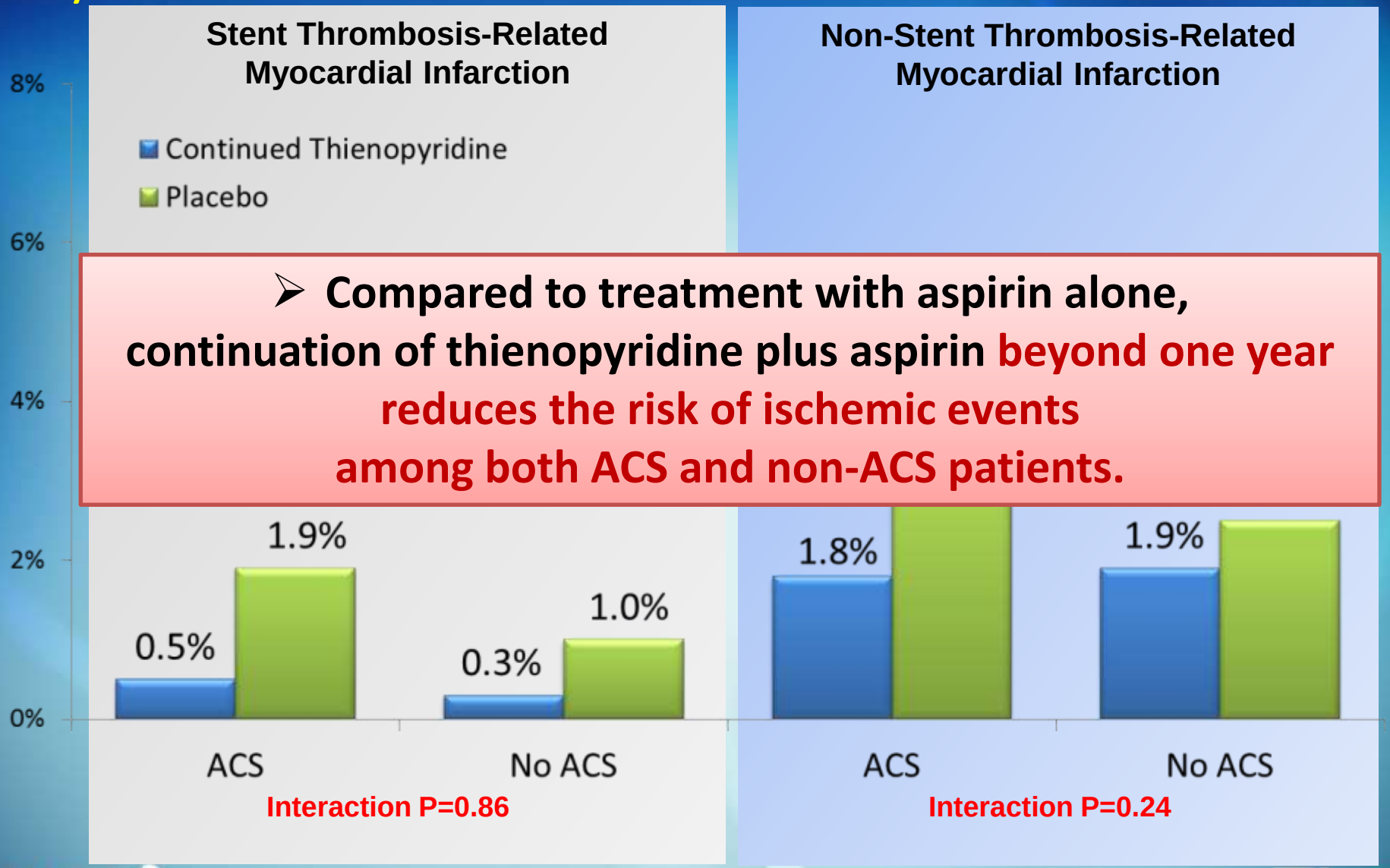
HR 0.60 (0.45-0.79)
p<0.001

KR.PM.CLO.14.02.06[2015.02]

Yeh RW, et al. JACC 2015 Mar

DAPT post-hoc analysis

Myocardial infarction



➢ **Compared to treatment with aspirin alone, continuation of thienopyridine plus aspirin beyond one year reduces the risk of ischemic events among both ACS and non-ACS patients.**

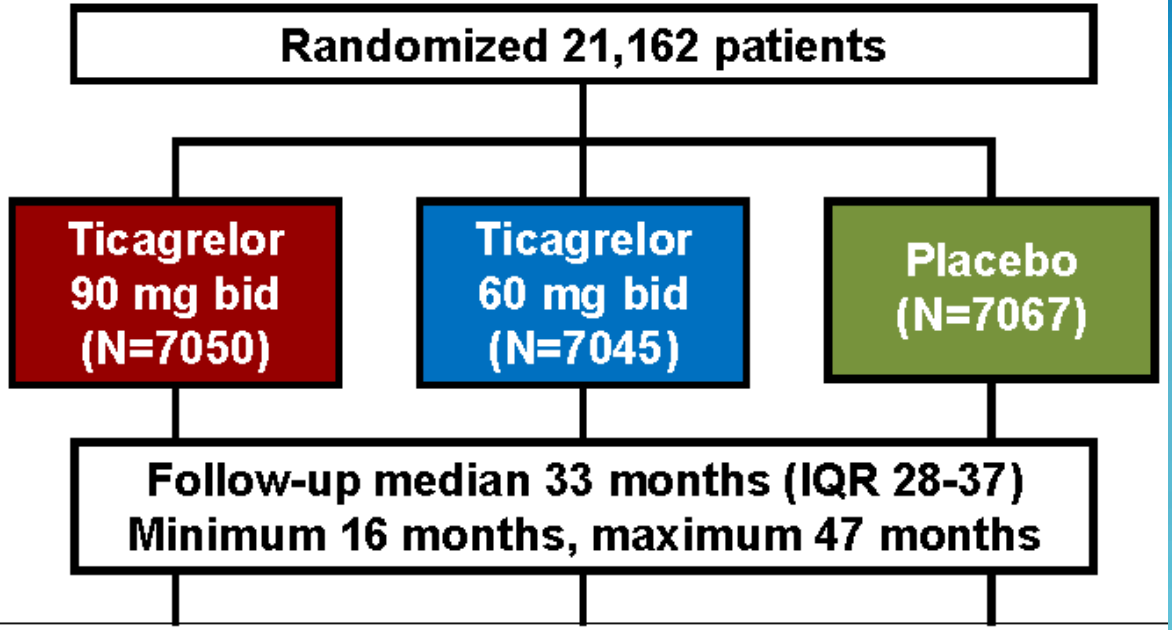
Yeh RW, et al. JACC 2015 Mar

PEGASUS-TIMI 54 : Study flow

Long-term use of Ticagrelor vs placebo in patients with Prior Myocardial Infarction on the background use of Aspirin (after 1 year use of DAPT)

KEY INCLUSION

- Age ≥50 years
- At least 1 of the following:
  - ✓ Age ≥65 years
  - ✓ Diabetes requiring medication
  - ✓ 2nd prior MI (>1 year ago)
  - ✓ Multivessel CAD
  - ✓ CrCl <60 mL/min
- Tolerating ASA and able to be dosed at 75-150 mg/d



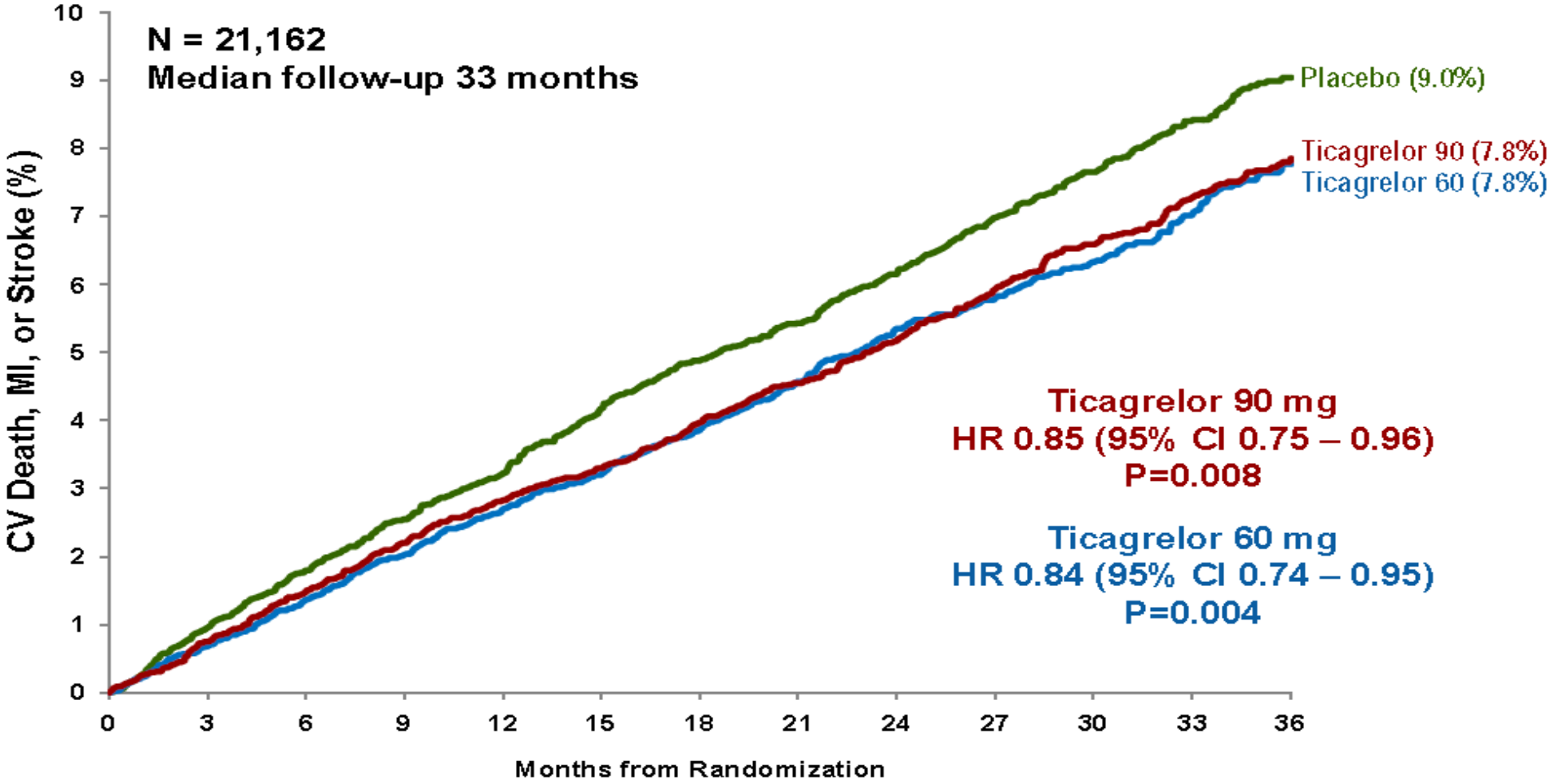
Premature perm. drug discontinuation	12%/yr	11%/yr	8%/yr
Withdrew consent	0.7% total	0.7% total	0.7% total
Lost to follow-up	3 patients	6 patients	1 patient

Ascertainment for primary endpoint was complete for 99% of potential patient-years of follow up.

Bonaca MP. N Engl J Med 2015 Mar [epub]

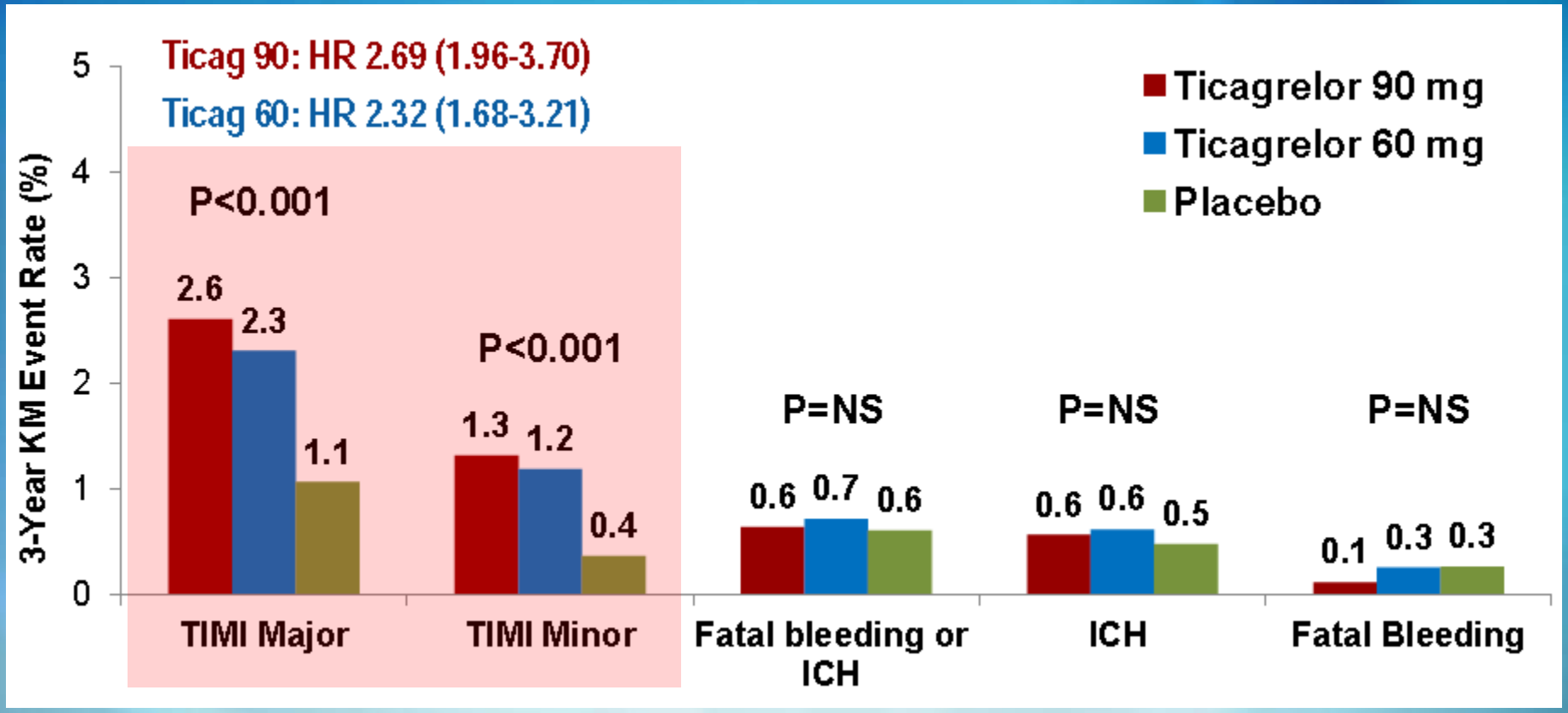
PEGASUS-TIMI 54 : PEP

Cardiovascular (CV) death, MI, or stroke



Bonaca MP, et al. NEJM 2015 Mar 14.

PEGASUS-TIMI 54 : bleeding



KR.PM.CLO.14.02.06[2015.02]

SANOFI

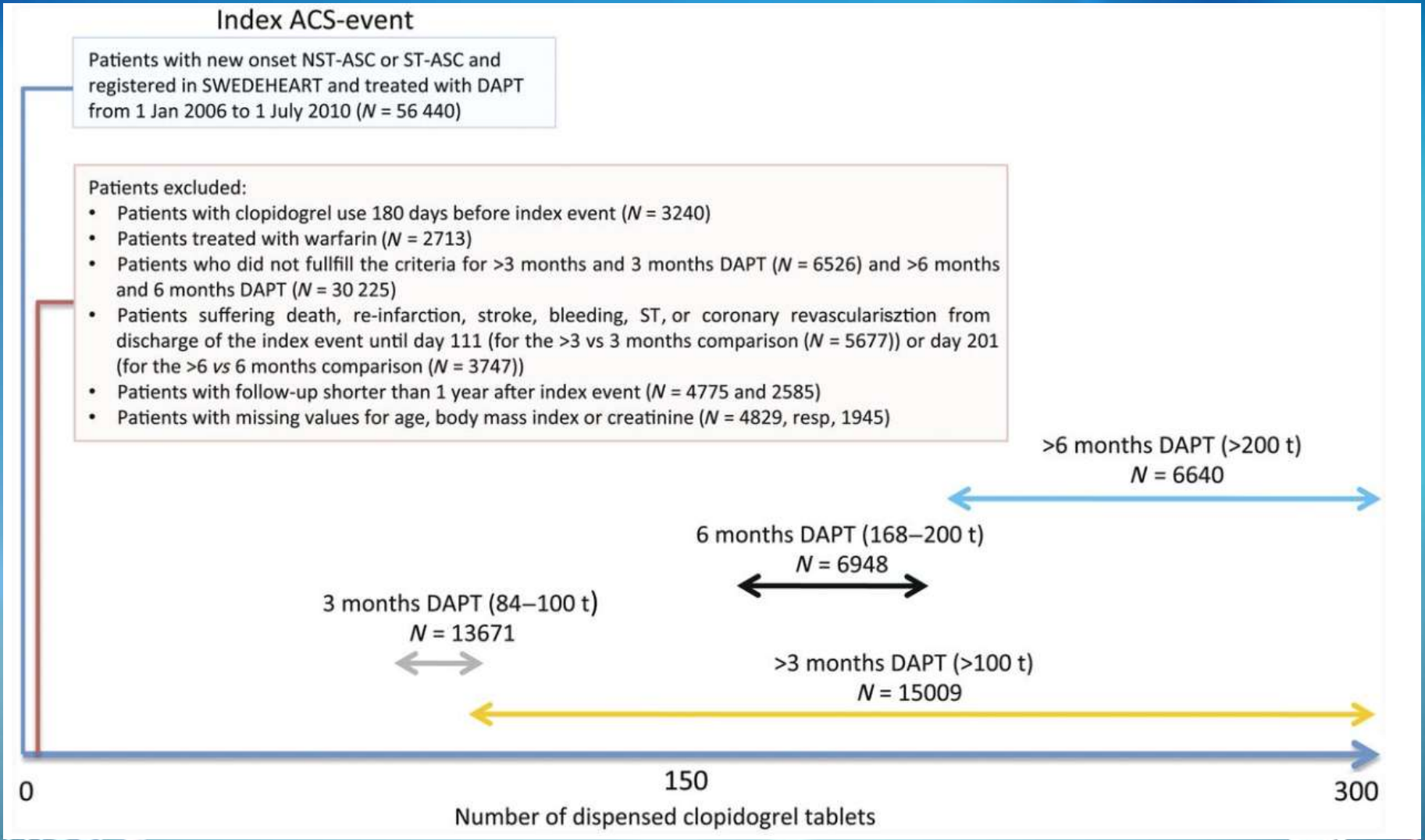
Bonaca MP, et al. NEJM 2015 Mar 14.

Plavix

3 or 6 months
for ACS patients ??

SWEDEHEART Registry

DAPT duration in ACS patients (n=56,440; Stent 74.5%, DES 21.6%)

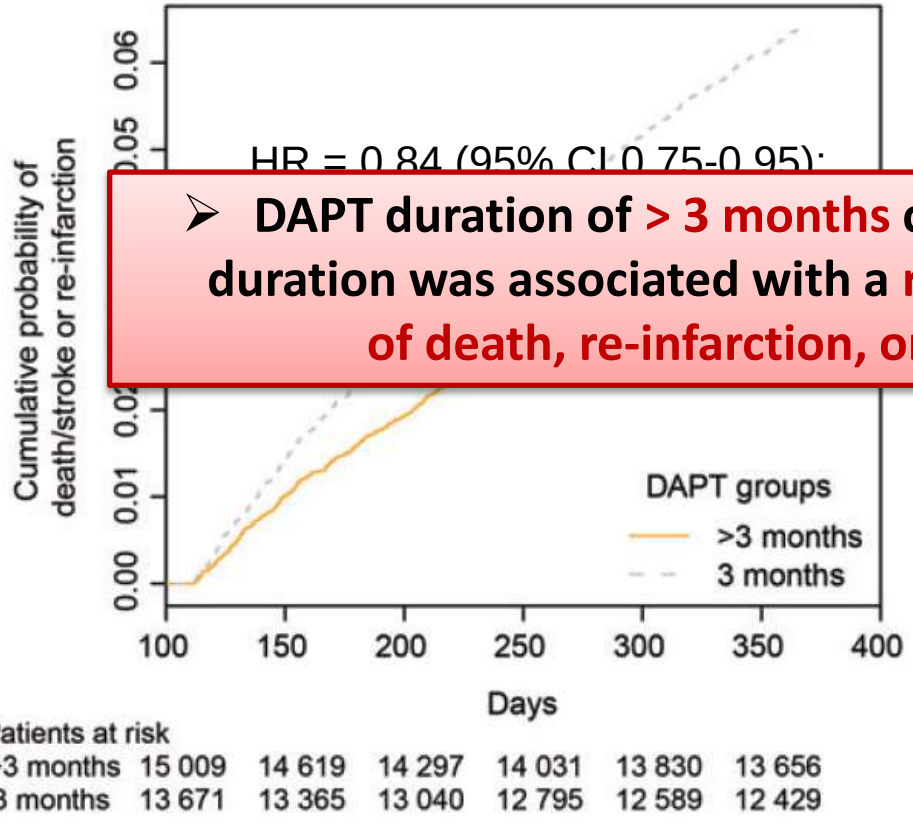


Varenhorst C. Eur Heart J 2014;35:969-78.

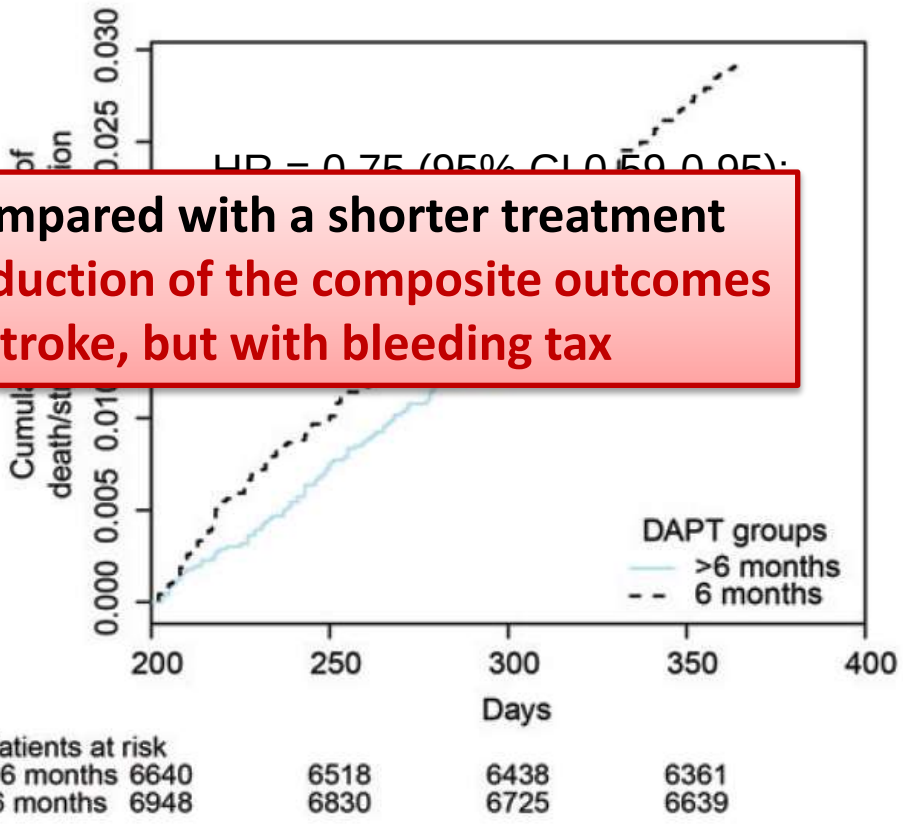
SWEDEHEART Registry

End-points analysis

Death, MI, or stroke (3 mo vs. > 3 mo)



Death, MI, or stroke (6 mo vs. > 6 mo)



- **DAPT duration of > 3 months compared with a shorter treatment duration was associated with a reduction of the composite outcomes of death, re-infarction, or stroke, but with bleeding tax**

* DAPT duration was defined using information on number of dispensed tablets

015.02]

SANOFI

Varenhorst C. Eur Heart J. 2014;35:969-78.

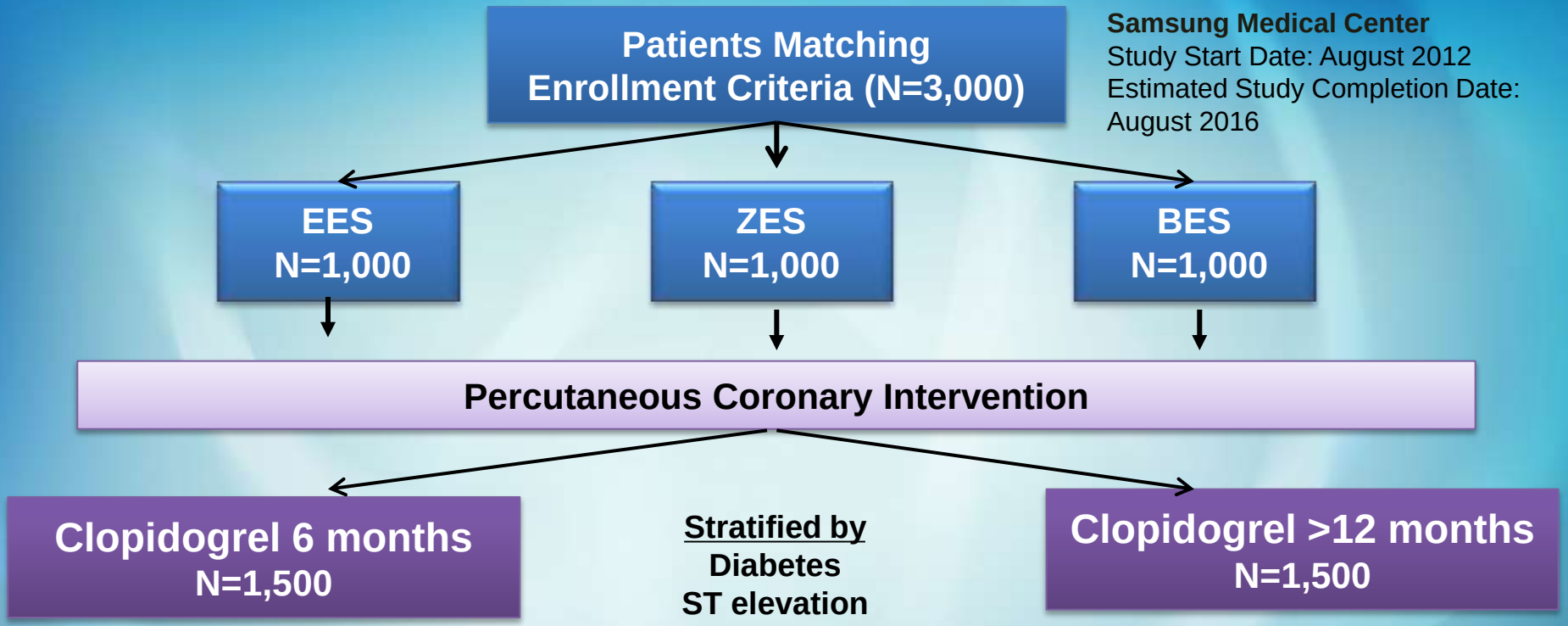
Plavix
Clopidogrel 75mg
Take Protection Further. Today.

Ongoing trials

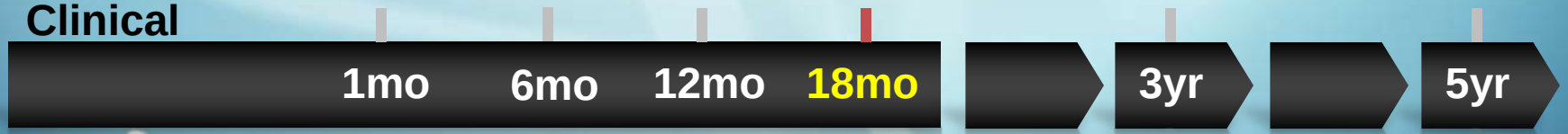
SMART-DATE in ACS

Smart Angioplasty Research Team : Safety of 6-month Duration of Dual Antiplatelet Therapy after PCI in Patients with ACS

P.I.: Gwon HC MD
Samsung Medical Center
Study Start Date: August 2012
Estimated Study Completion Date: August 2016



Primary clinical endpoint evaluation : Composite of death, MI, stent thrombosis, cerebrovascular events or BARC ≥ 3

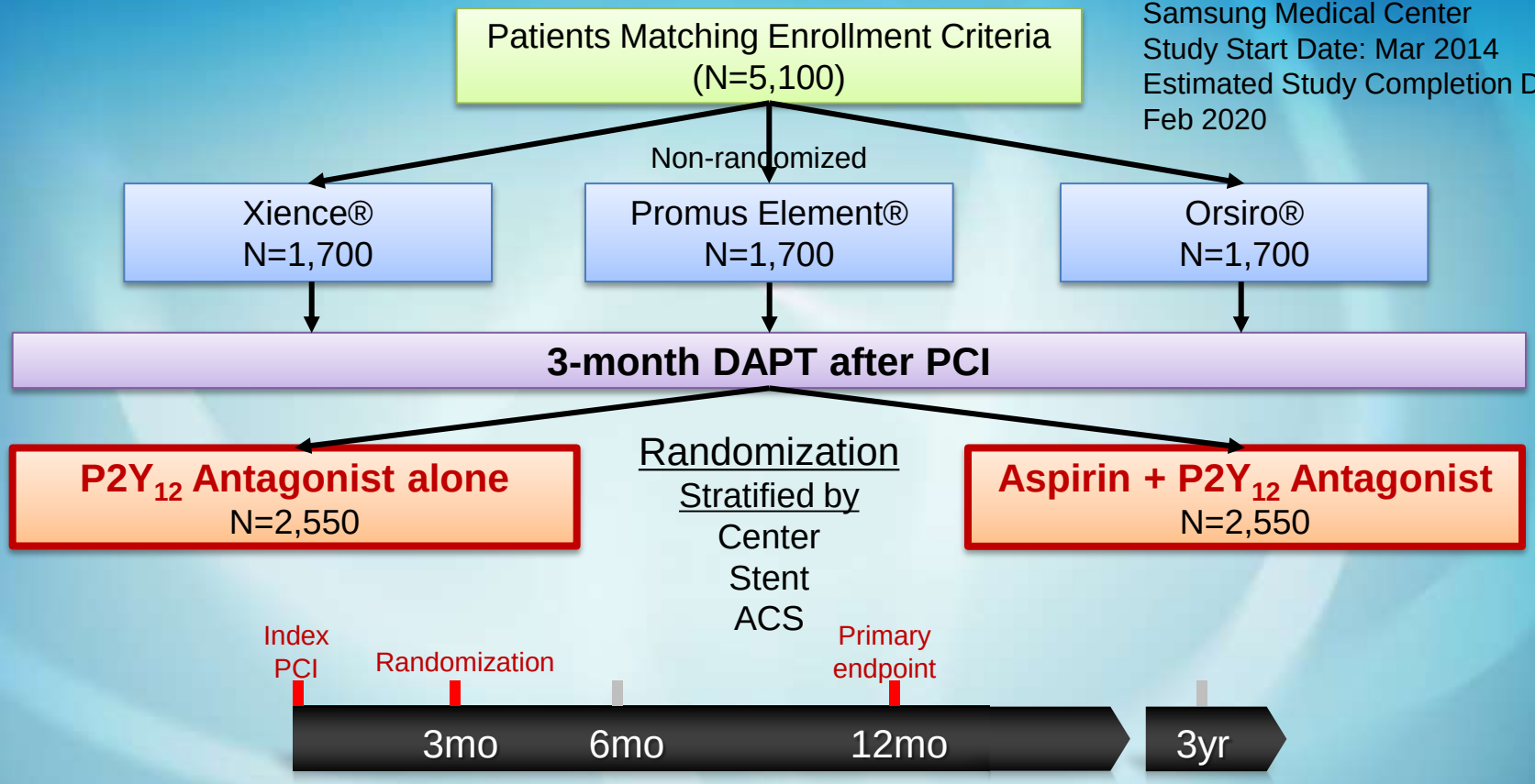


ClinicalTrials.gov Identifier: NCT01701453

SMART-CHOICE

Comparison Between $P2Y_{12}$ Antagonist Monotherapy and Dual Antiplatelet Therapy After DES

P. I.: Gwon HC MD
Samsung Medical Center
Study Start Date: Mar 2014
Estimated Study Completion Date: Feb 2020



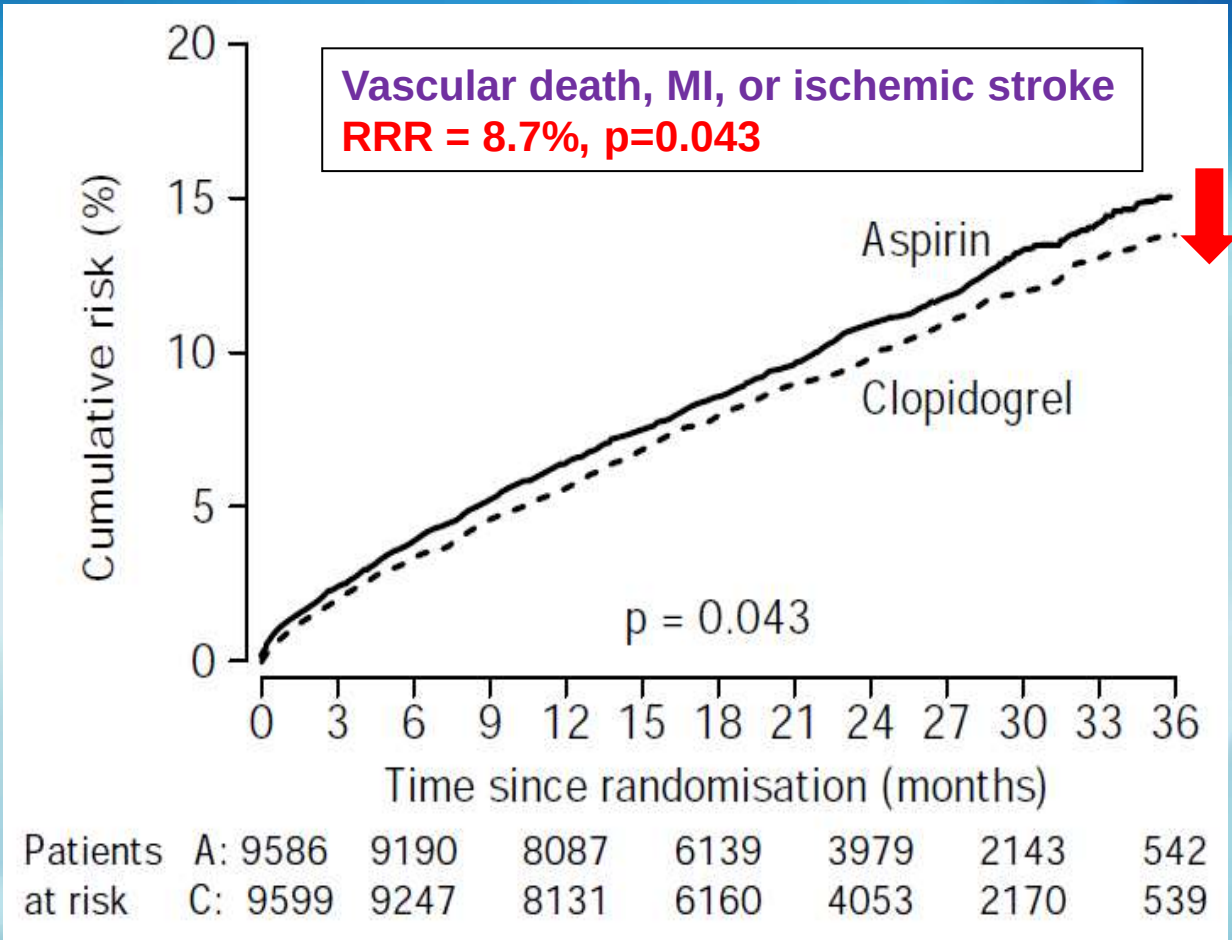
Primary endpoint: Net adverse cardiocerebrovascular event (NACE): A composite of death, MI, CVA, or BARC bleeding

ClinicalTrials.gov Identifier: NCT02079194

Which monotherapy is better following DAPT ??

CAPRIE

Which monotherapy is better after DAPT? (clopidogrel 75 mg vs. aspirin 325 mg in CVD patients)

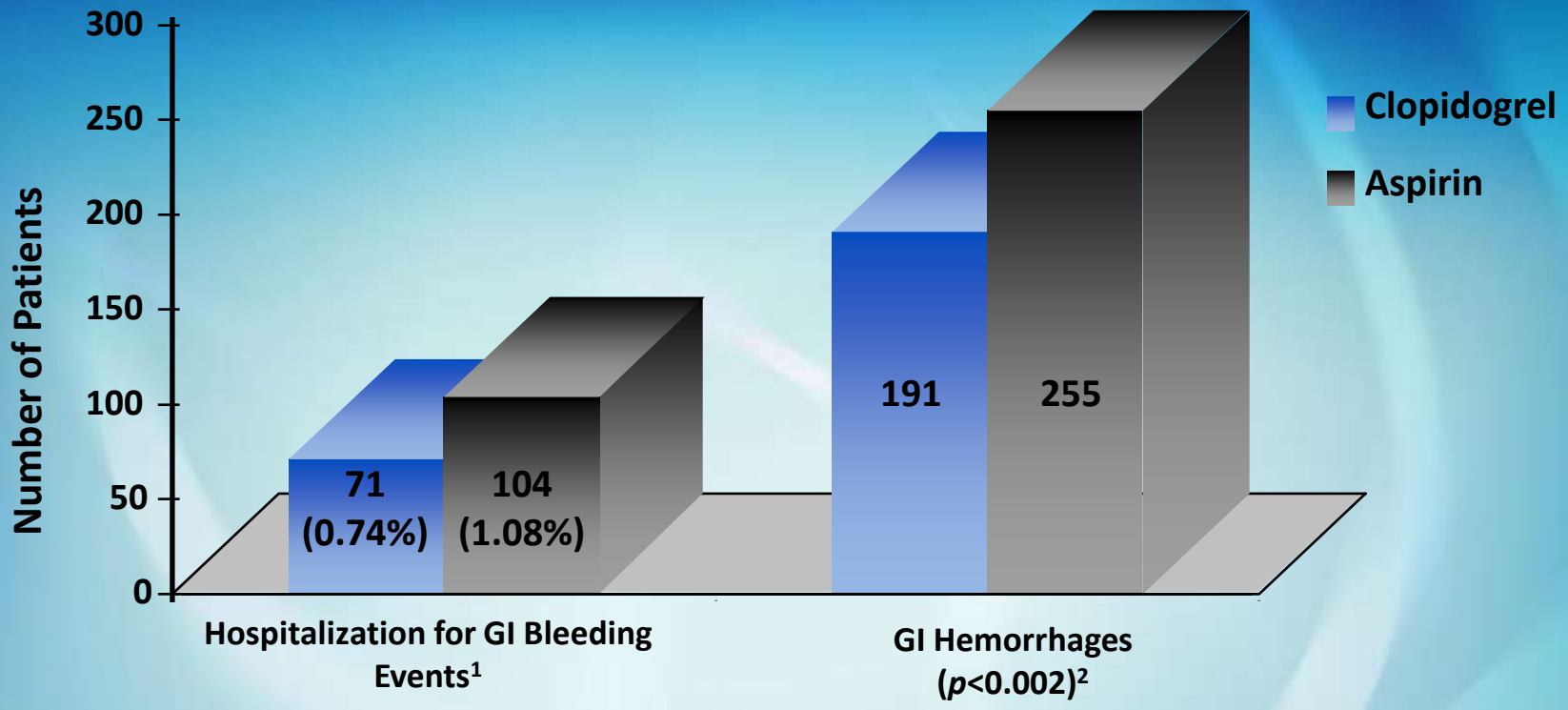


Patients with recent ischemic stroke, recent MI, or symptomatic PAD (N = 19,185)

CAPRIE Steering Committee, Lancet 1996;348:1329-39

CAPRIE

Hemorrhagic events



- Trend to more cerebral hemorrhages, fatal or non-fatal, and more hemorrhagic deaths in aspirin group: 37 versus 51 (0.39% vs. 0.53%)

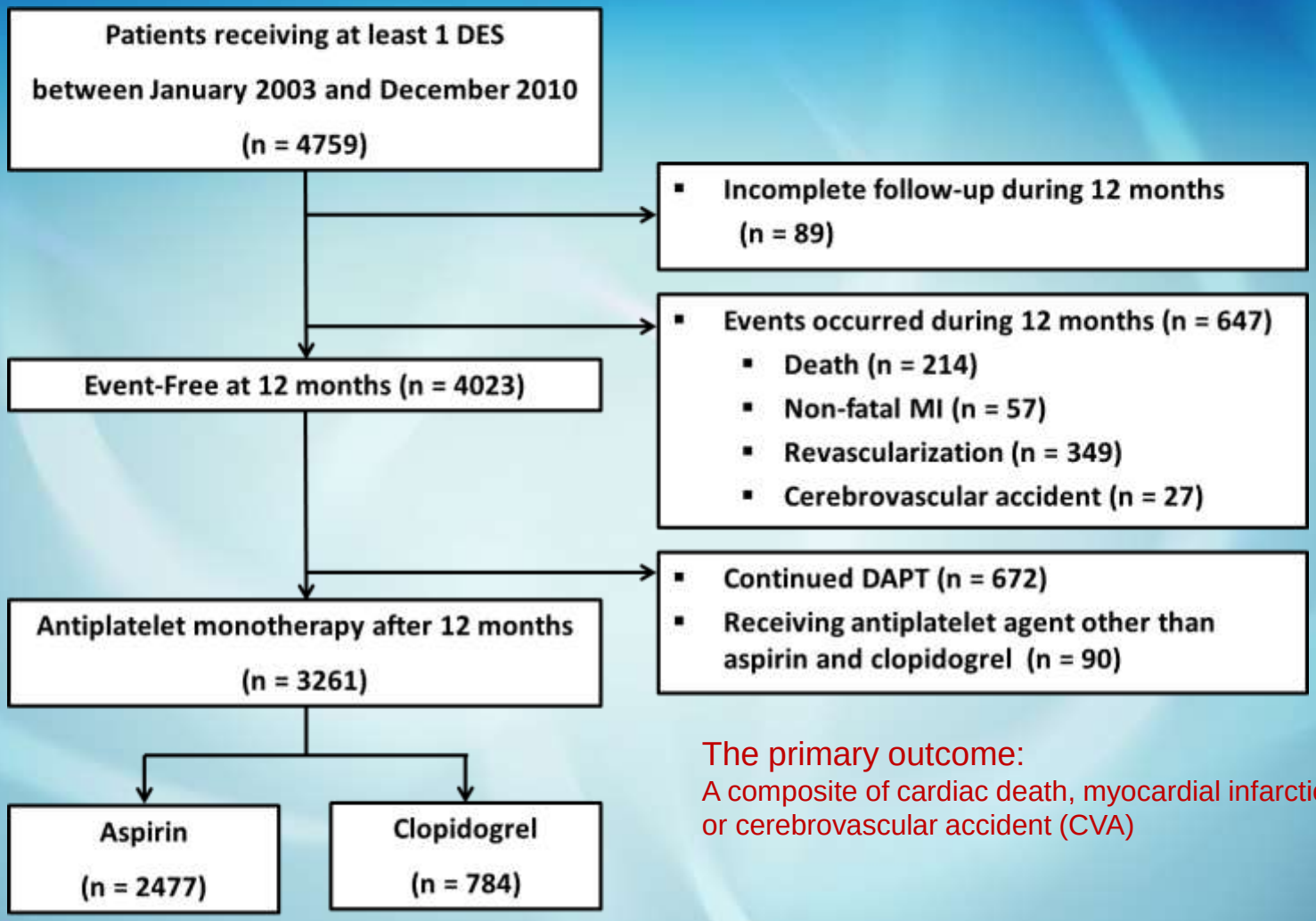
SANOFI

CAPRIE Steering Committee, Lancet 1996;348:1329-39

Plavix
Take Protection Further. Today.

clopidogrel monotherapy after DAPT?

Single center, observational study (Samsung Medical Center in Korea)



The primary outcome:
A composite of cardiac death, myocardial infarction (MI), or cerebrovascular accident (CVA)

TK Park. J Am Coll Cardiol. 2014;63:(12_S)

clopidogrel monotherapy after DAPT?

	Aspirin	Clopidogrel	Univariable + IPTW		Multivariable + IPTW	
	(n=2472)	(n=771)	HR (95% CI)	P value	HR* (95% CI)	P value
Cardiac death, MI, or CVA	90 (3.6)	16 (2.1)	0.51 (0.28-0.92)	0.02	0.46 (0.25-0.84)	0.01
Cardiac death or MI	55 (2.2)	8 (1.0)	0.43 (0.19-0.98)	0.04	0.42 (0.18-0.97)	0.04
Death from any cause	86 (3.5)	18 (2.3)	0.80 (0.48-1.33)	0.38	0.76 (0.45-1.28)	0.30
Cardiac death	30 (1.2)	2 (0.3)	0.29 (0.07-1.13)	0.07	0.26 (0.07-1.03)	0.06
MI	31 (1.3)	7 (0.9)	0.55 (0.21-1.49)	0.24	0.58 (0.21-1.58)	0.29
CVA	41 (1.7)	8 (1.0)	0.54 (0.24-1.22)	0.14	0.44 (0.19-1.04)	0.06
Stent thrombosis	5 (0.2)	1 (0.1)	0.31 (0.02-6.12)	0.44	0.28 (0.01-6.42)	0.42
TIMI major bleeding	23 (0.9)	10 (1.3)	1.16 (0.51-2.62)	0.73	1.14 (0.49-2.64)	0.76
Fatal	1 (0.04)	1 (0.1)	2.15 (0.08-54.35)	0.64	-	-
Intracranial	8 (0.3)	4 (0.5)	0.87 (0.17-4.43)	0.87	0.88 (0.17-4.64)	0.88

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.

Adapted from a presentation of Prof. Young-bin Song, SMC, Jan 2015

Subgroup	Patients	Primary outcome (%)		Adjusted HR (95% CI)	p value	p for Interaction
		Aspirin	Clopidogrel			
Age						
≥ 65 years	1383	50 (4.9)	10 (2.7)	0.57 (0.29 - 1.12)	0.10	0.36
< 65 years	1860	40 (2.7)	6 (1.5)	0.39 (0.12 - 1.25)	0.12	
ACS						
Yes	1341	43 (4.2)	5 (1.5)	0.27 (0.08 - 0.90)	0.03	0.15
No	1902	47 (3.2)	11 (2.5)	0.58 (0.28 - 1.20)	0.14	
DM						
Yes	1159	41 (4.9)	9 (2.8)	0.72 (0.35 - 1.49)	0.38	0.55
No	2084	49 (3.0)	7 (1.6)	0.39 (0.16 - 0.97)	0.04	
Current smoking						
Yes	603	10 (2.3)	1 (0.6)	0.17 (0.02 - 1.77)	0.14	0.45
No	2640	80 (3.9)	15 (2.5)	0.54 (0.29 - 1.02)	0.06	
CVA						
Yes	126	7 (8.9)	1 (2.1)	0.80 (0.19 - 3.39)	0.76	0.71
No	3117	83 (3.5)	15 (2.1)	0.52 (0.28 - 0.97)	0.04	
Type of stent						
SES/PES	1835	69 (4.3)	6 (2.5)	0.35 (0.12 - 1.08)	0.07	0.52
EES/ZES/BES	1408	21 (2.4)	10 (1.9)	0.72 (0.31 - 1.66)	0.44	
Multi-vessel disease						
Yes	1833	61 (4.5)	11 (2.3)	0.60 (0.31 - 1.17)	0.13	0.52
No	1410	29 (2.6)	5 (1.7)	0.31 (0.09 - 1.15)	0.08	

Adapted from a presentation of Prof. Young-bin Song, SMC, Jan 2015

KR.PM.CLO.14.02.06[2015.02]

SANOFI

Plavix
Clopidogrel 75mg
Take Protection Further. Today.

Still in Aspirin ?

- Marginally statistically significant inferiority
  - Annual event rate 5.32% versus 5.83%, p = 0.043
  - About 200 patients would need to use clopidogrel rather than aspirin for 1 year to prevent just one vascular event.

- Cost-effectiveness
  - Clopidogrel has recently become available in a generic formation
  - The high cost of clopidogrel could be mitigated in current clinical settings

HOST-EXAM : Aspirin vs. Clopidogrel

Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis - EXtended Antiplatelet Monotherapy

- Study design: Phase 4, Interventional , randomized, open-label, multicenter trial
- Objectives :
  To compare the efficacy and safety of **clopidogrel monotherapy** with **aspirin monotherapy** in patients **who received dual or triple antiplatelet therapy for 1 year (± 6 months) after drug-eluting stent implantation** for coronary artery disease
- Patient Enrollment : 5,500 patients enrolled at 55 centers in Korea
- Patient Follow-up : Clinical follow-up will occur at 1, 12 and 24 months

- Primary Endpoint :
  Composite of cardiovascular death, myocardial infarction, stroke, severe/moderate bleeding, readmission due to acute coronary syndrome, urgent revascularization
- Secondary Endpoint :
  - Target vessel/lesion revascularization
  - Stent thrombosis (acute, sub-acute, late, very late)
  - Peripheral vascular intervention

ClinicalTrials.gov Identifier: NCT02044250
Study Chair: Hyo-Soo Kim, MD, PhD Seoul National University Hospital
Study Start Date: Feb 2014/ Estimated Study Completion Date: Feb 2019

GLOBAL LEADERS Study

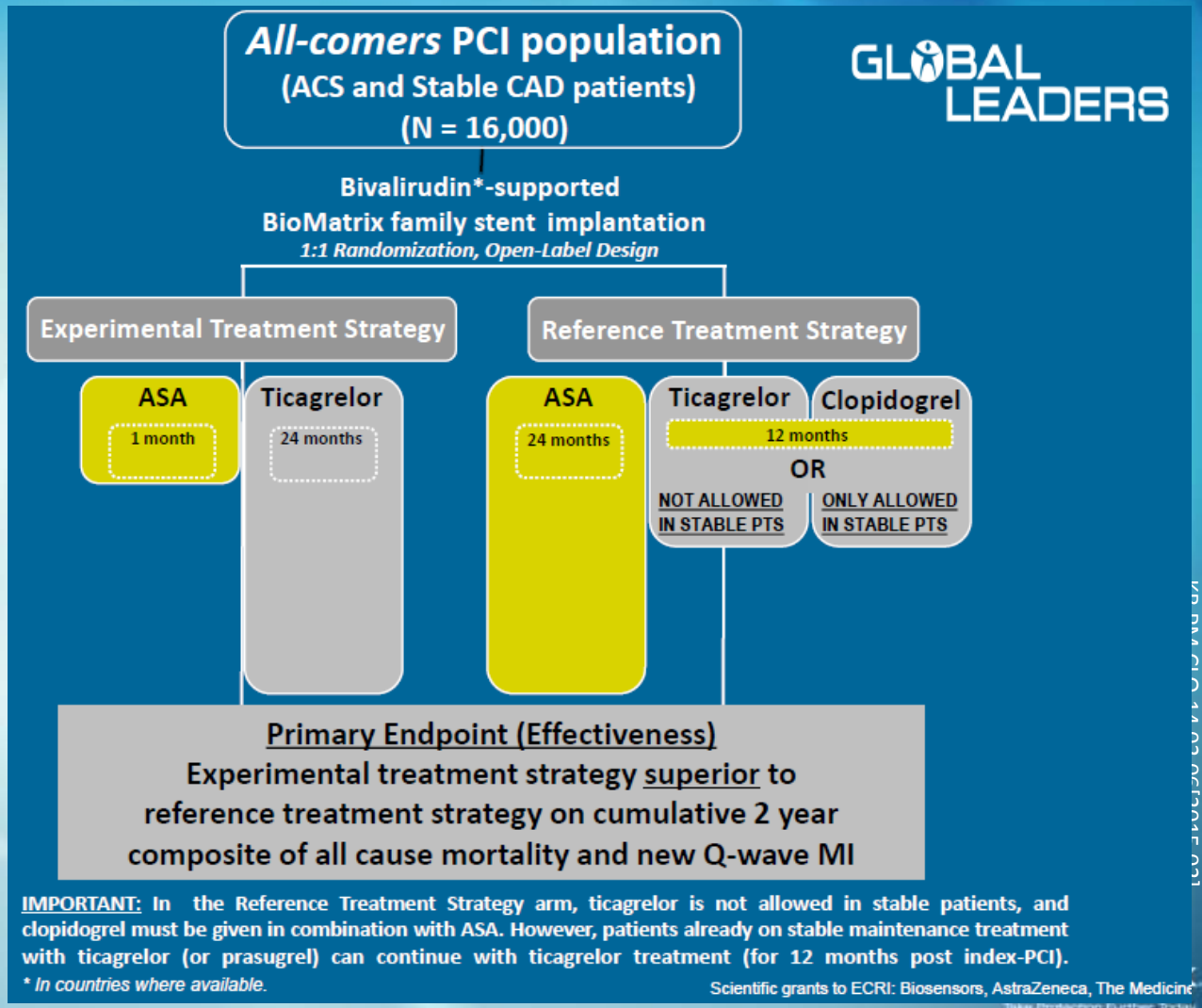
Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy vs. a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing PCI

Ticagrelor monotherapy

vs

DAPT

1 month
after DES implantation



Patrick Surruys, EuroPCR 2012
ClinicalTrials.gov Identifier: NCT01813435

SANOFI

Conclusions & Points for discussion

1. To determine the optimal or minimal necessary duration of DAPT is very important, because prolonged duration of DAPT may increase bleeding risk (more death?) as well as cost and inconvenience.
2. According to recent studies, a shorter course of DAPT recommended by the guidelines may be considered, especially with new-generation DES.
3. Interruption of DAPT 6 months after DES implantation is possible, including in ACS patients.
4. The prolonged DAPT, however, may be considered in specific subsets of high-risk patients, which is to be determined in future studies.
5. There is an ischemic benefit with DAPT continuation beyond 1 year.
6. There is hazard (MI/ST) within 3 months of thienopyridine discontinuation.

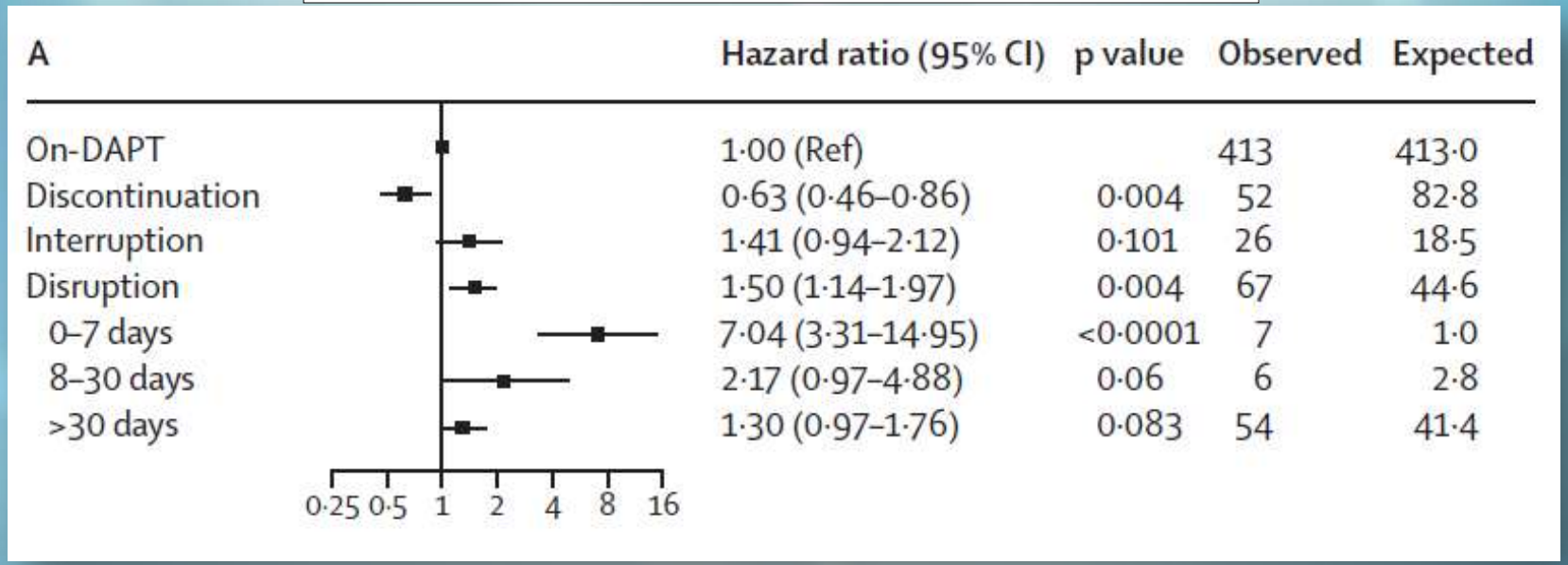
- Difficult to identify the patients who may benefit more from continuation.
- No common rule for duration of DAPT, only individualized decisions.

Carefully Guided Discontinuation is Safe

PARIS study

- Discontinuation: by recommendation of the physician
- Interruption: due to the need for a surgical procedure
- Disruption: due to a bleeding episode or non-compliance.

Cardiac death, def/prob ST, MI, or TLR



Mehran R, Lancet 2013

KR.PM.CLO.14.02.06[2015.02]