Optimal Duration and of Dual Antiplatelet Therapy after PCI

Kyung Woo Park, MD, PhD

Department of Internal Medicine,

Cardiovascular Center,

Seoul National University Hospital

1. Optimal Duration of DAPT
2. Optimal Combination of antiplatelet agents

How long do you maintain DAPT? (for patients receiving DES)

1. 6 months
2. 12 months
3. More than 12 months but not forever
4. Forever
5. Differs according to thrombosis risk

Should the default duration of DAPT be the same for 1st vs 2nd generation DES?

1. Yes
2. No

Background

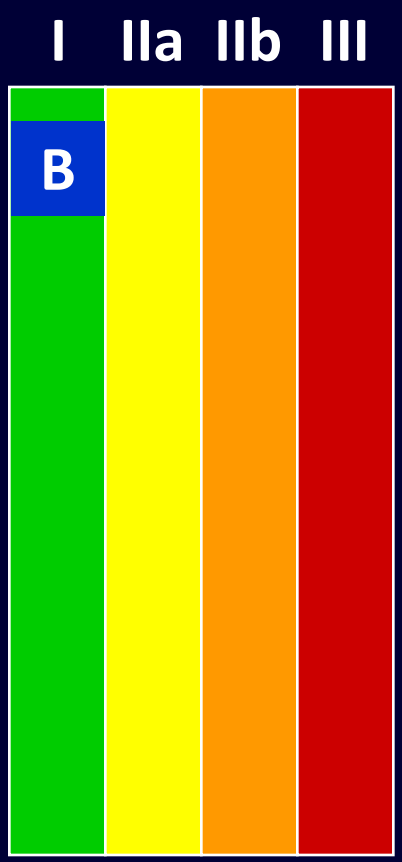
1. DAPT is the backbone of medical therapy post-PCI.
2. Guidelines recommend the use of at least 12 months of DAPT for patients receiving DES.
3. Even longer use is common practice in the ‘real world’.

Questions raised

1. Are the guidelines based on robust randomized trial data?
2. Is the optimal duration of DAPT the same for all patients receiving DES (Does one size fit all)
3. What is the potential benefit of prolonged use of DAPT? Reduction in ST or reduction of global vascular risk
4. Does prolonged DAPT result in a risk reduction of very late ST large enough to negate the bleeding issue and economic costs of prolonged treatment?

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

Oral Antiplatelet Adjunctive Therapies



The duration of P2Y12 inhibitor therapy after stent implantation should generally be as follows:

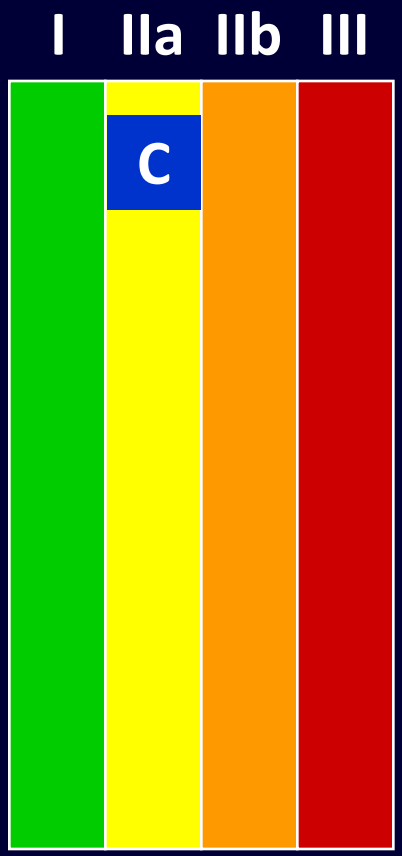
In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for at least 12 months.

In patients receiving a 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.

In patients receiving a BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months.

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

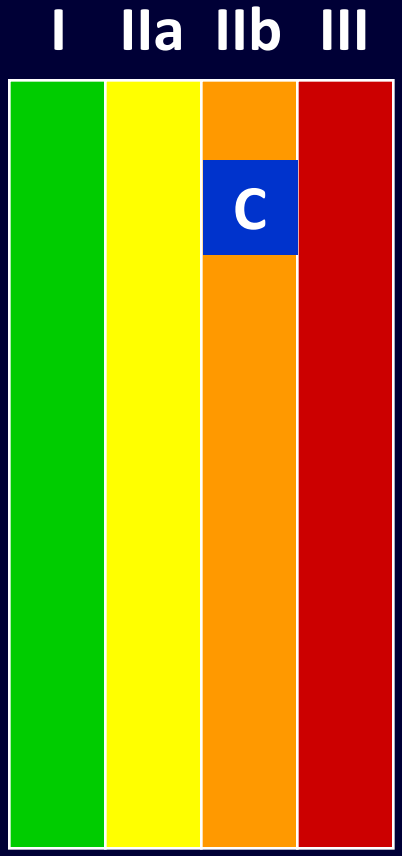
Oral Antiplatelet Adjunctive Therapies



If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of P2Y12 inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of P2Y12 inhibitor therapy is reasonable.

ACC/AHA/SCAI 2007 Focused Update for PCI

Oral Antiplatelet Adjunctive Therapies

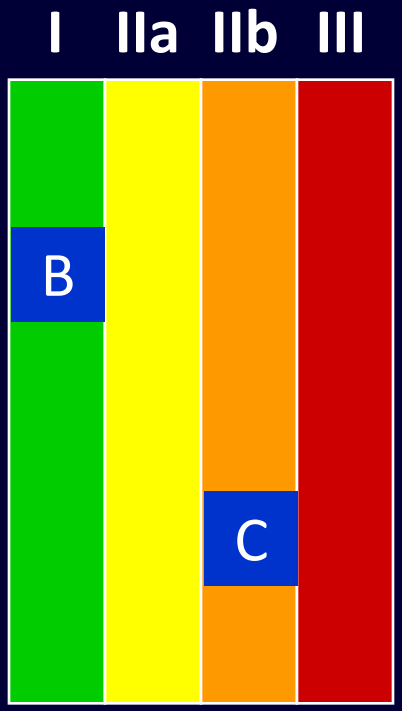


Continuation of clopidogrel therapy beyond 1 year may be considered in patients undergoing DES placement.

(New Recommendation)

2009 Focused Updates: ACC/AHA Guidelines for the Mx of Pts with STEMI and PCI

(Updating the 2004 Guideline and 2007 Focused Update)
(Updating the 2005 Guideline and 2007 Focused Update)
Recommendations for the Thienopyridine



In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily (*B*) or prasugrel 10 mg daily (*B*) should be given for at least 12 months

Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing DES placement (*C*)

Kushner et al., Circulation 2009. 2271-2306

Issues To Be Covered

1. Prolonged use of DAPT

    a. Data that don't support prolonged DAPT

    b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?

Issues To Be Covered

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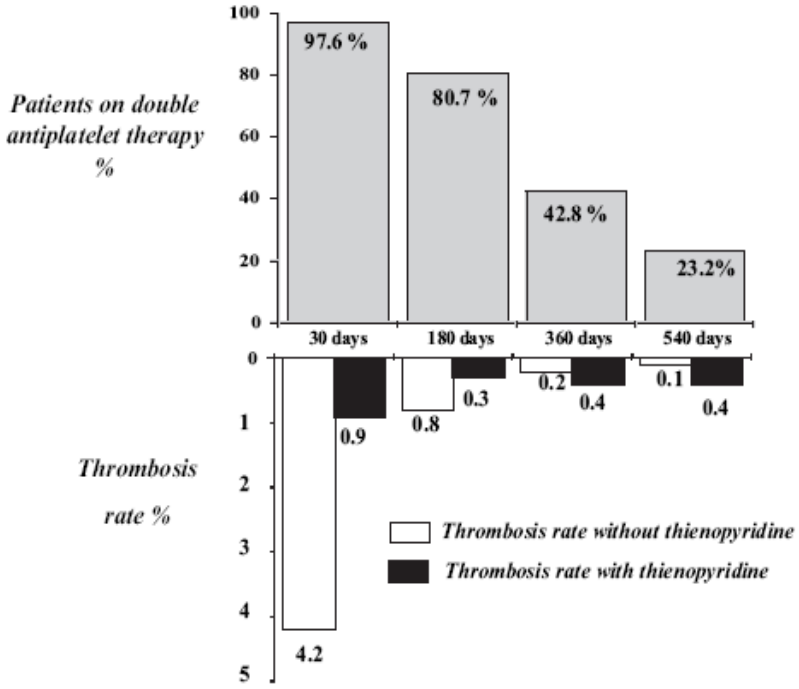
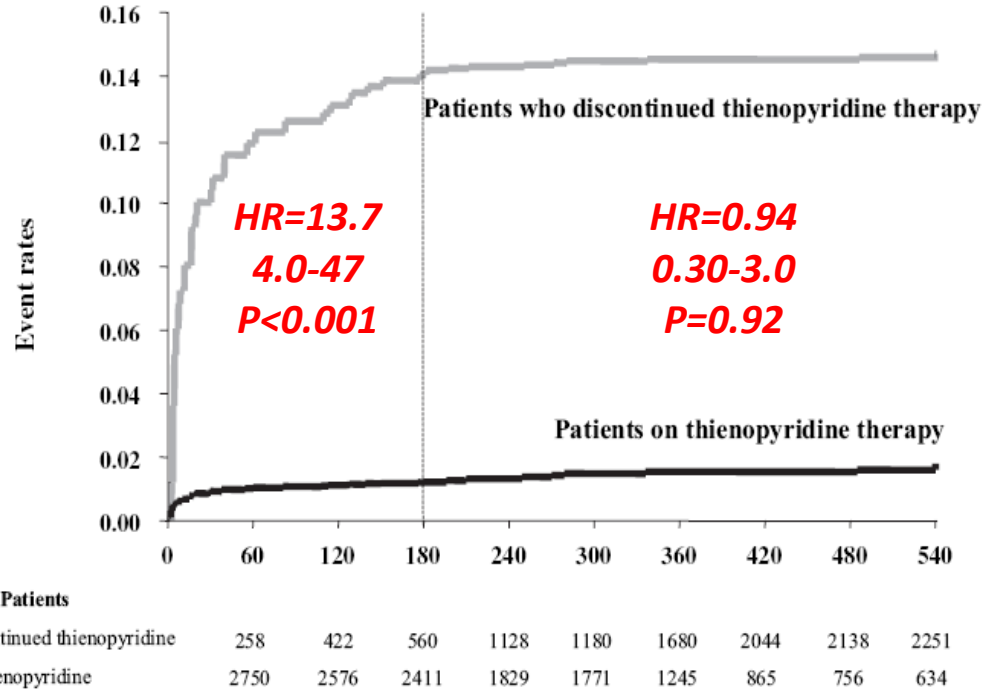
Discontinuation of Thienopyridine and Risk of Stent Thrombosis: Milan-Siegburg Cohort Study

Airoldi F et al. *Circulation* 2007;116:745-54

3,021 patients with 5,389 lesions treated with DES (2002-2004)

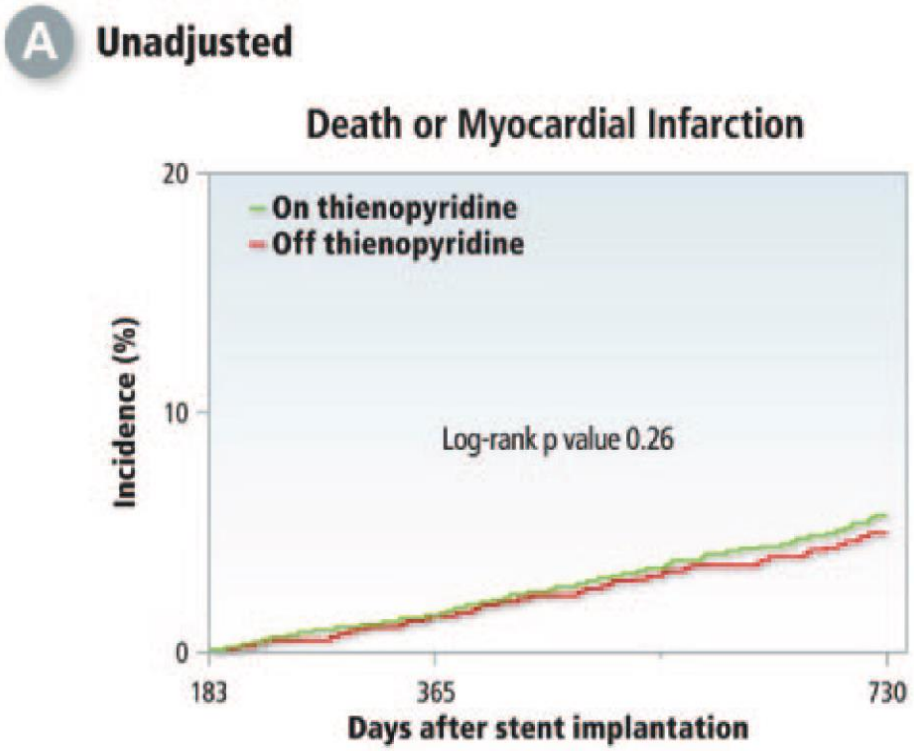


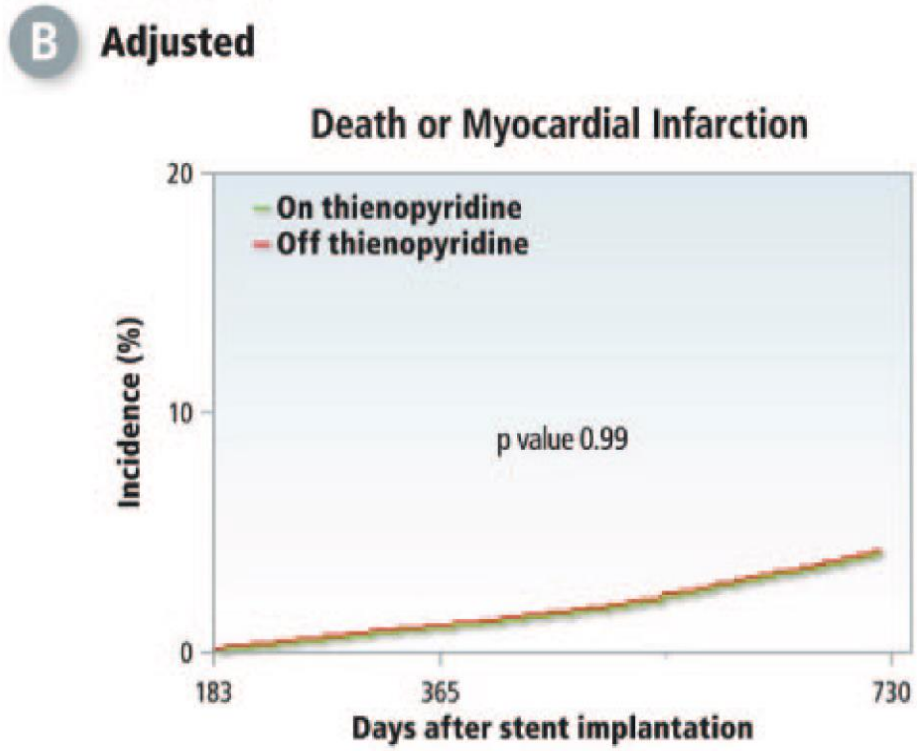


Discontinuation of Thienopyridine and Risk of Stent Thrombosis With Sirolimus-Eluting Stents

Kimura T et al. *Circulation* 2009;119:7987-995

Landmark Analysis on Thienopyridine Use Beyond 6 Months

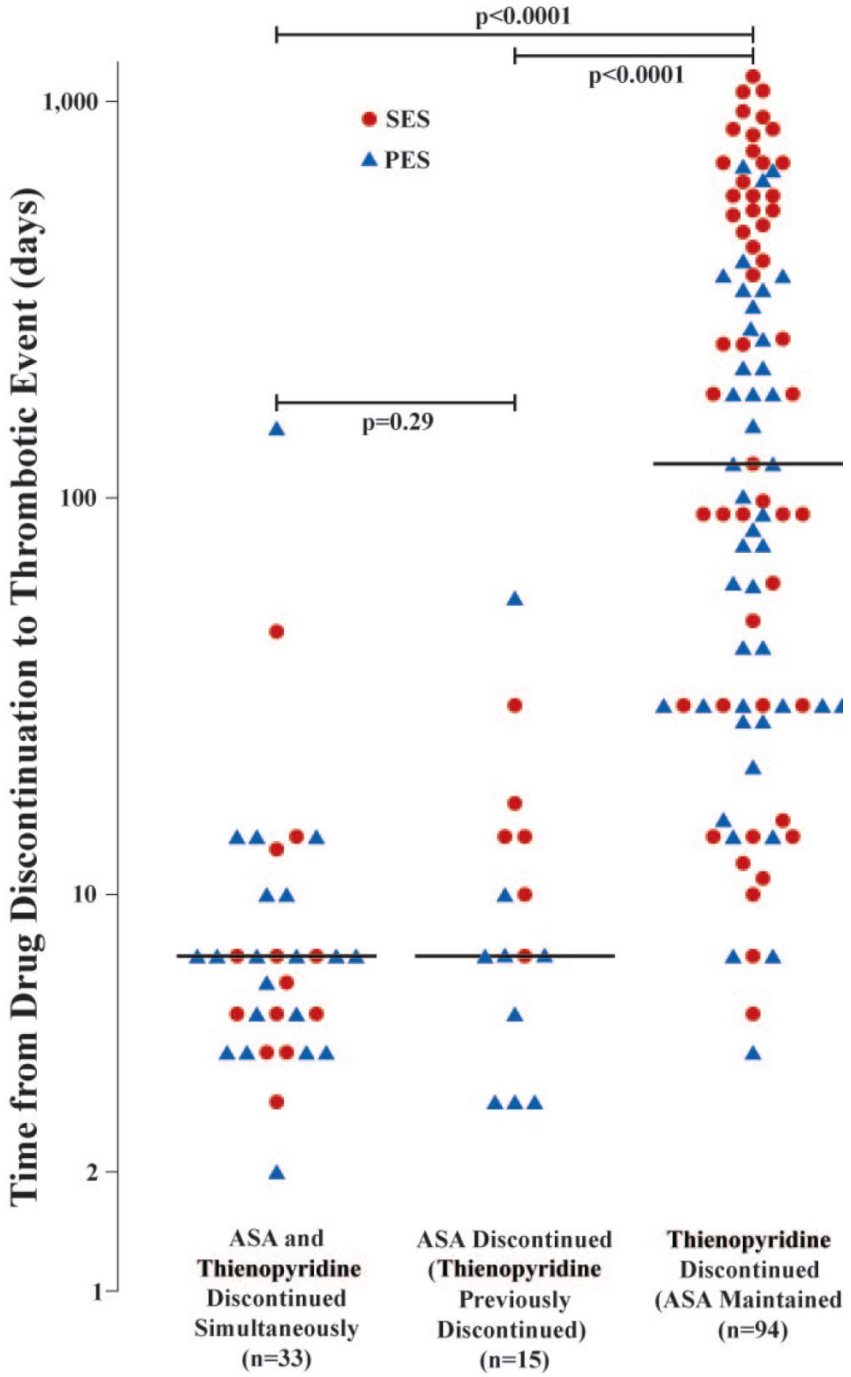




Discontinuation of Antiplatelet Therapy and Risk of Stent Thrombosis With DES

Eisenberg et al. *Circulation* 2009

161 cases of late/very late stent thrombosis



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

: Park SJ et al. NEJM 2010

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

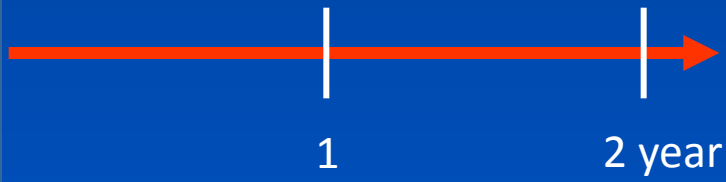
N=2,701

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

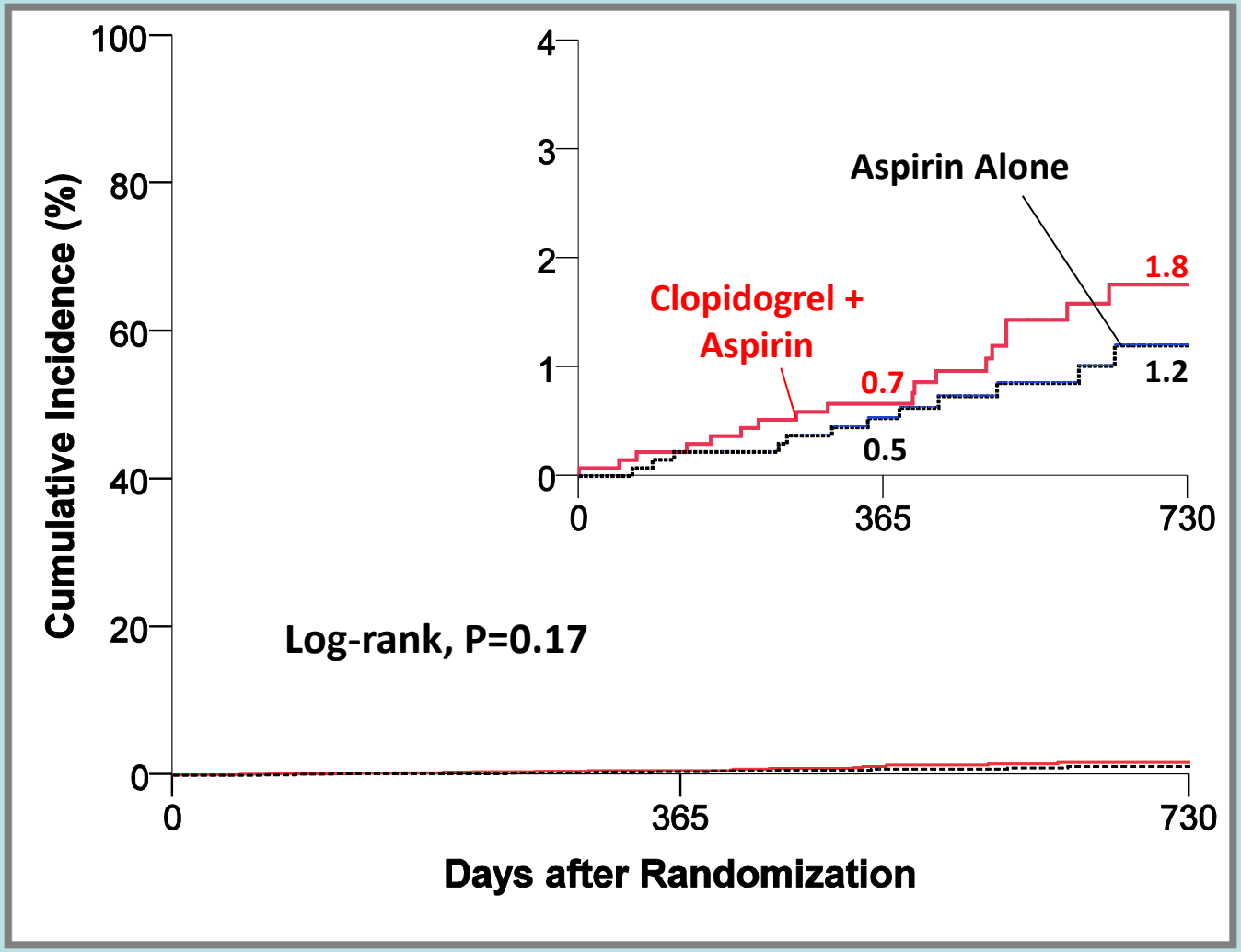
N=1,344
Aspirin Alone



From July 2007 through September 2008

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

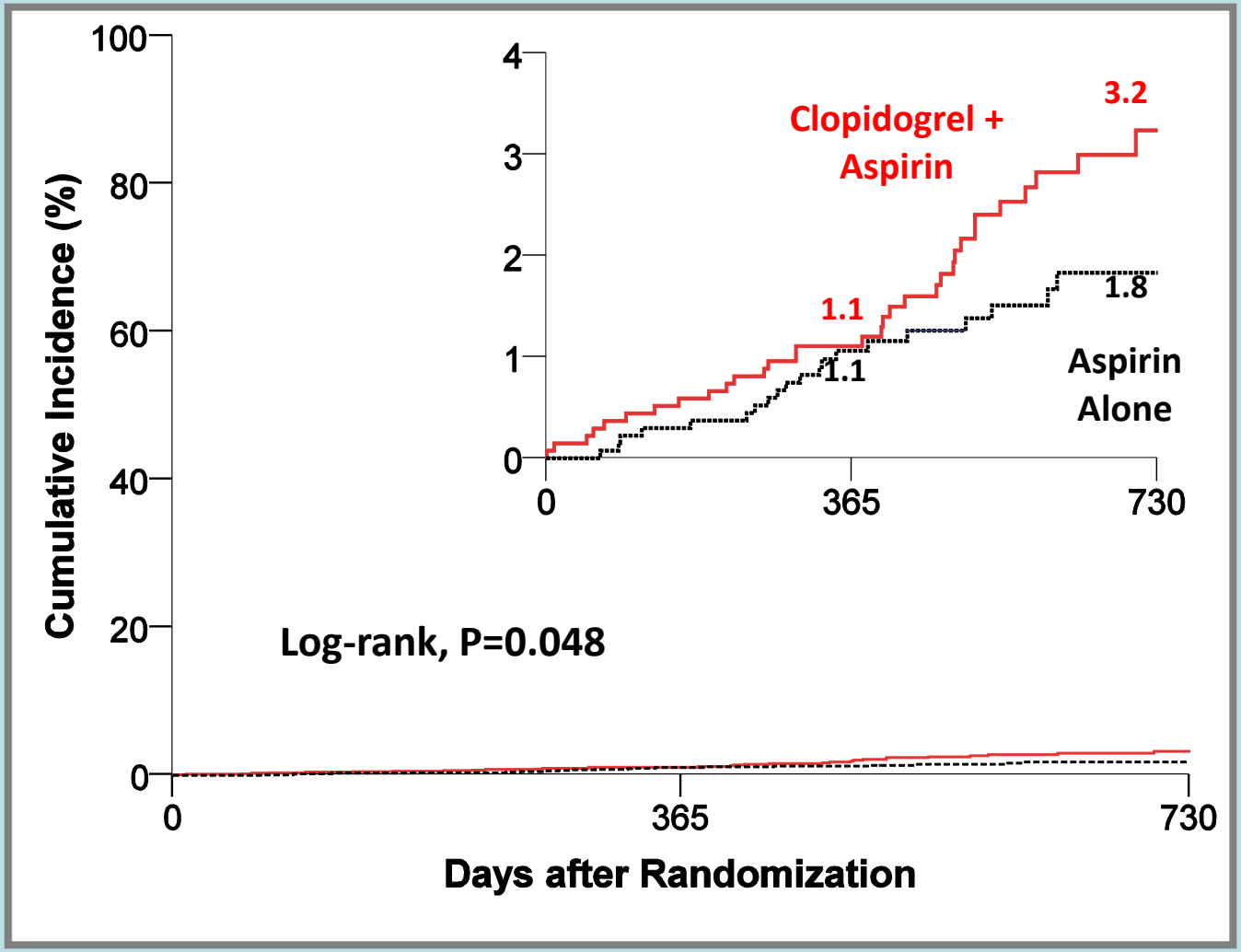
Primary End Point:
Cardiac Death or Myocardial Infarction



No. at Risk

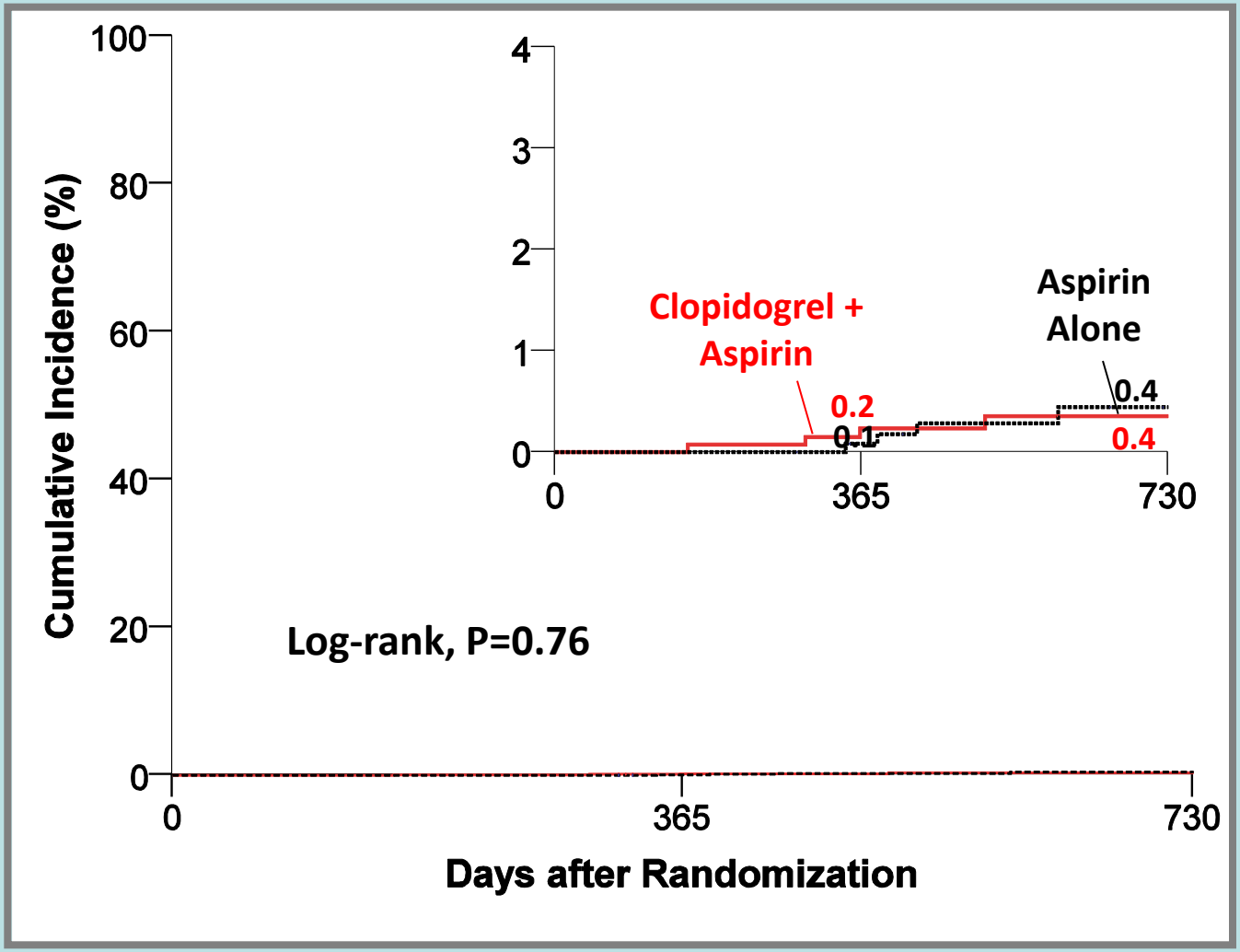
Continuation group	1357	1122	299
Discontinuation group	1344	1100	301

Death, Myocardial Infarction, or Stroke



No. at Risk			
Continuation group	1357	1119	295
Discontinuation group	1344	1097	300

Definite Stent Thrombosis



No. at Risk			
Continuation group	1357	1124	301
Discontinuation group	1344	1102	303

Limitations of REAL- & ZEST-LATE

1. Interim analysis of two ongoing, underpowered studies.
2. Observed primary outcome event rate is less than 25% of that anticipated
3. Higher thrombotic event rate in aspirin+clopidogrel group: not supported by any previous data and not scientifically feasible
4. Many received cilostazol during the year prior to enrollment.
5. Major statistical assumption: 50% RRR in the DAT group : too generous of an assumption, no prior studies have shown 50% RRR with DAT
6. Very short term follow up

Peter B. Berger. NEJM 2010

Antonio Colombo, Sanjay Kaul, theheart.org

Issues To Be Covered

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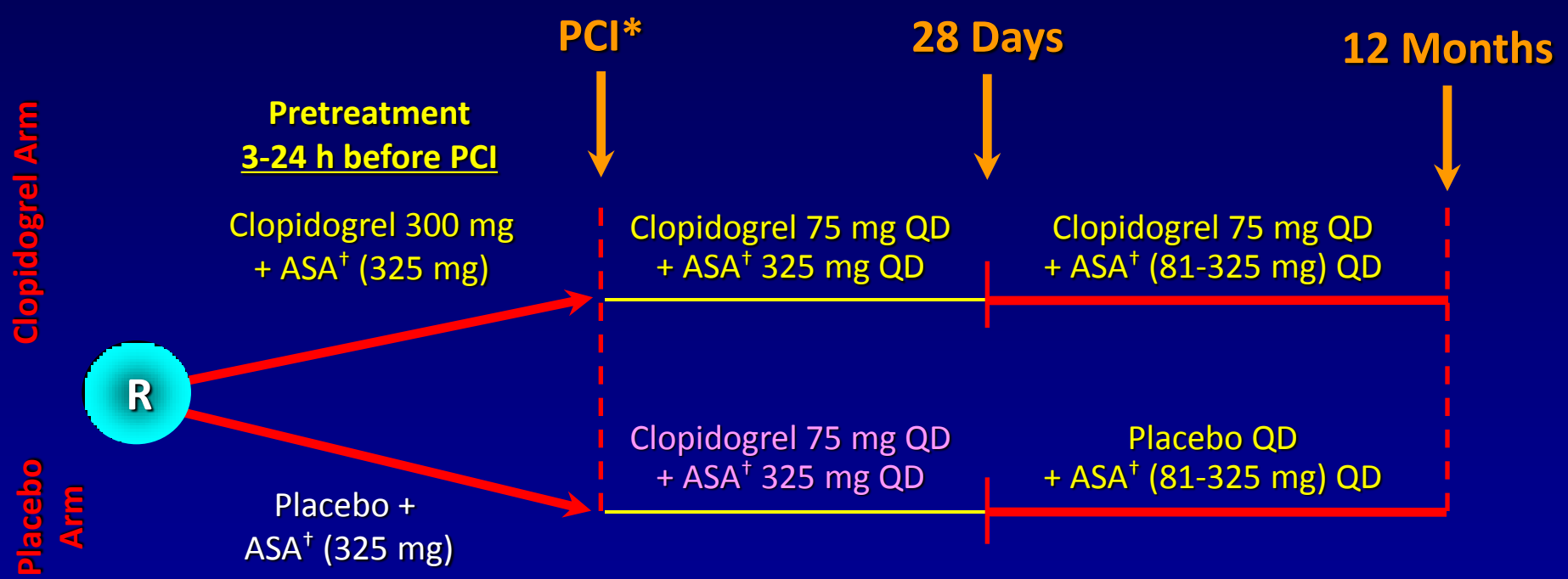
Old Historical Data

1. **L**ong-term DAT appears to reduce adverse events in ACS pts:
   - managed medically (CURE)
   - after balloon angioplasty (PCI-CURE)
   - after BMS (CREDO, RACS, PCI-CURE)
2. **L**ong-term DAT appears to reduce adverse events in post-PCI patients (BMS era)
   - CREDO
3. **L**ong-term DAT appears to reduce adverse events in selected group of stable patients receiving medical therapy
   - CHARISMA vs. 'CAPRIE like' CHARISMA

CREDO: Study Design

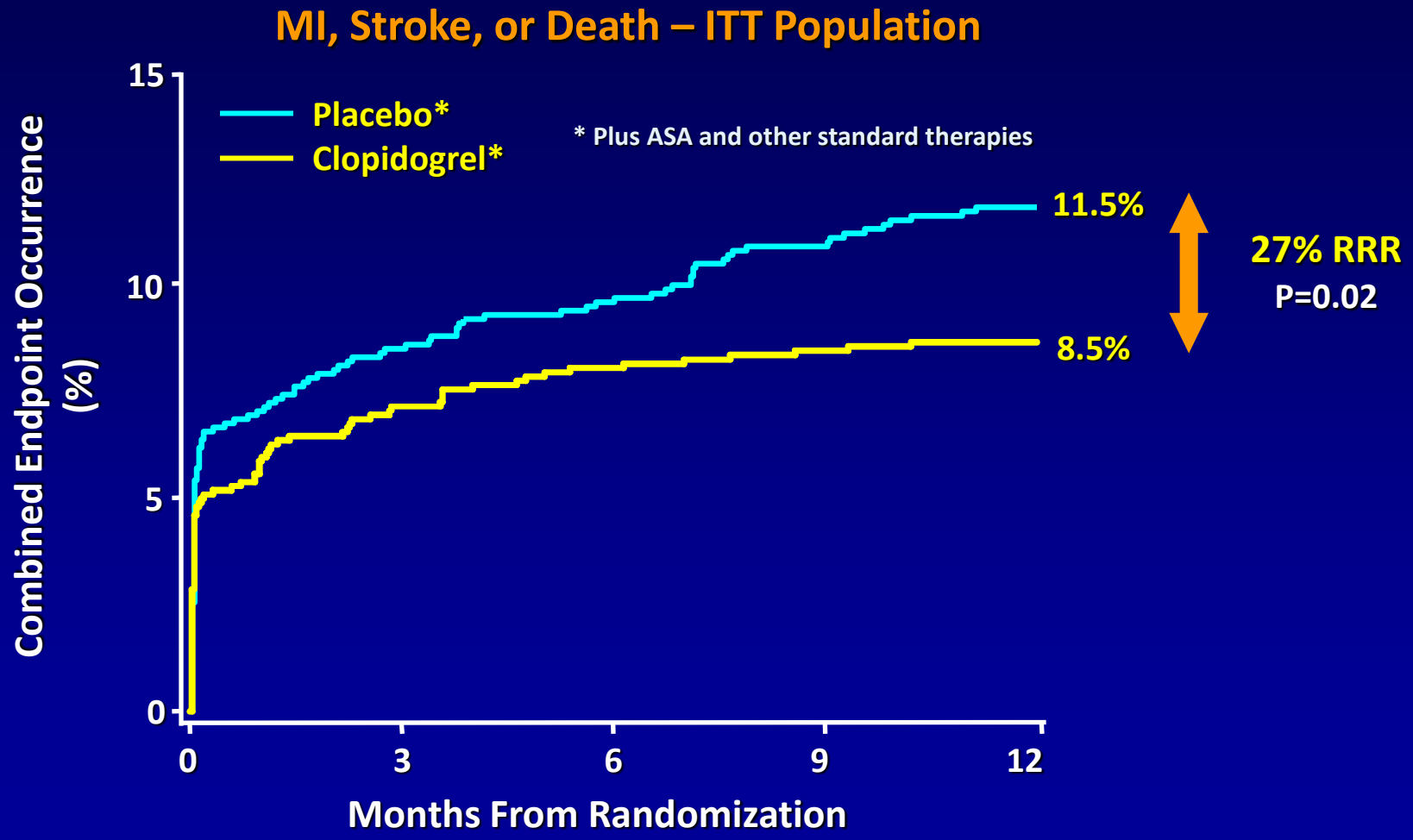


† Plus other standard therapies

* Both groups received clopidogrel 75 mg + ASA 325 mg at time of procedure

Steinhubl S, Berger P, Tift Mann III J et al. *JAMA*. 2002;Vol 288,No 19:2411-2420.

CREDO:
Long-Term Benefits of Clopidogrel in PCI Patients

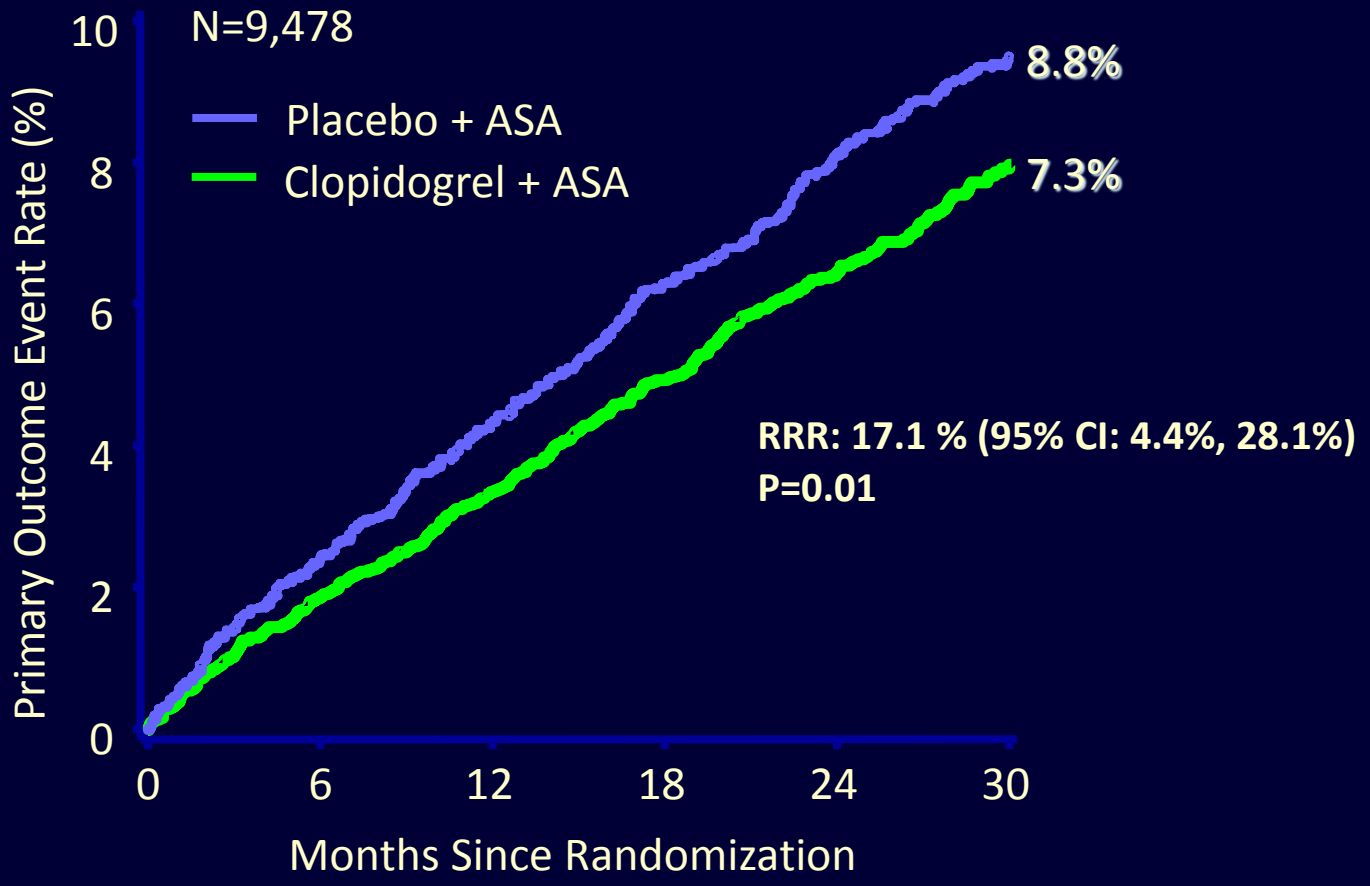


Steinhubl S, Berger P, Tift Mann III J et al. *JAMA*. 2002;Vol 288,No 19:2411-2420.

‘CAPRIE like’ CHARISMA

in Patients With Previous MI, IS, or PAD*

Primary Endpoint (MI/Stroke/CV Death)



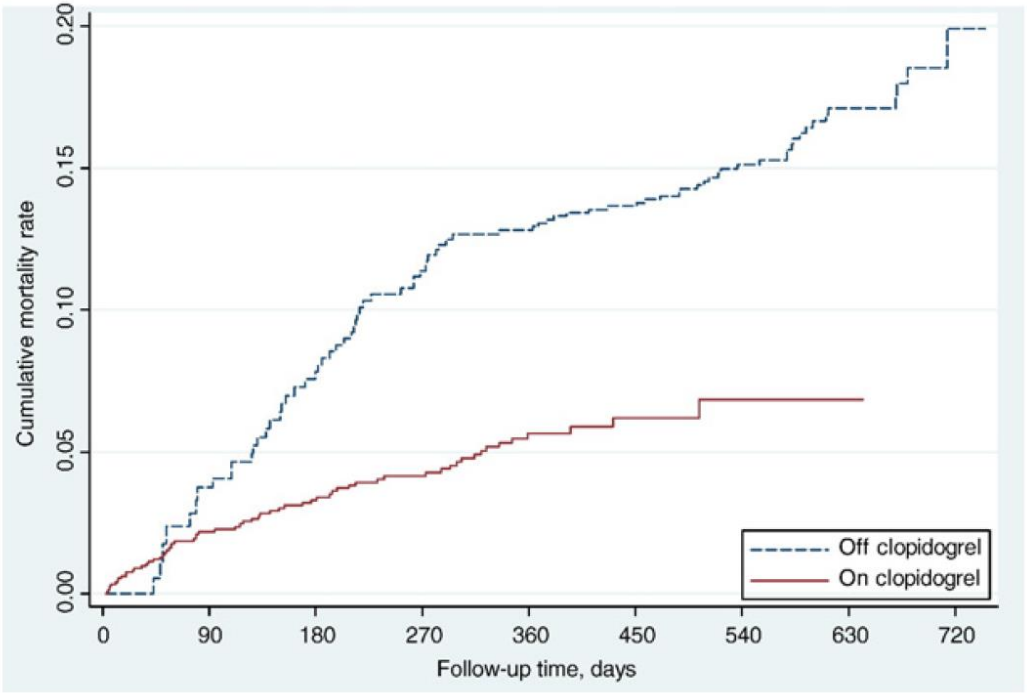
* Post hoc analysis.

Bhatt DL, Flather MD, Hacke W, et al. J Am Coll Cardiol. 2007;49:1982-1988.

Clopidogrel and long-term outcomes after stent implantation for acute coronary syndrome

1/3 with DES

P. Michael Ho, MD, PhD, FACC,[a,b] Stephan D. Fihn, MD, MPH,[c,d,e] Li Wang, MS,[c,d] Chris L. Bryson, MD, MS,[d,e] Elliott Lowy, PhD,[c,d,e] Charles Maynard, PhD,[c,d,e] David J. Magid, MD, MPH,[b,f] Eric D. Peterson, MD, MPH, FACC,[g] Robert L. Jesse, MD, PhD, FACC,[h] and John S. Rumsfeld, MD, PhD, FACC[a,b] *Denver and Aurora, CO; Seattle, WA; Durham, NC; and Richmond, VA*



Cumulative all-cause mortality between patients continuing and discontinuing clopidogrel

Among patients who were event free at 6 months, similar trend as main results

Main results:

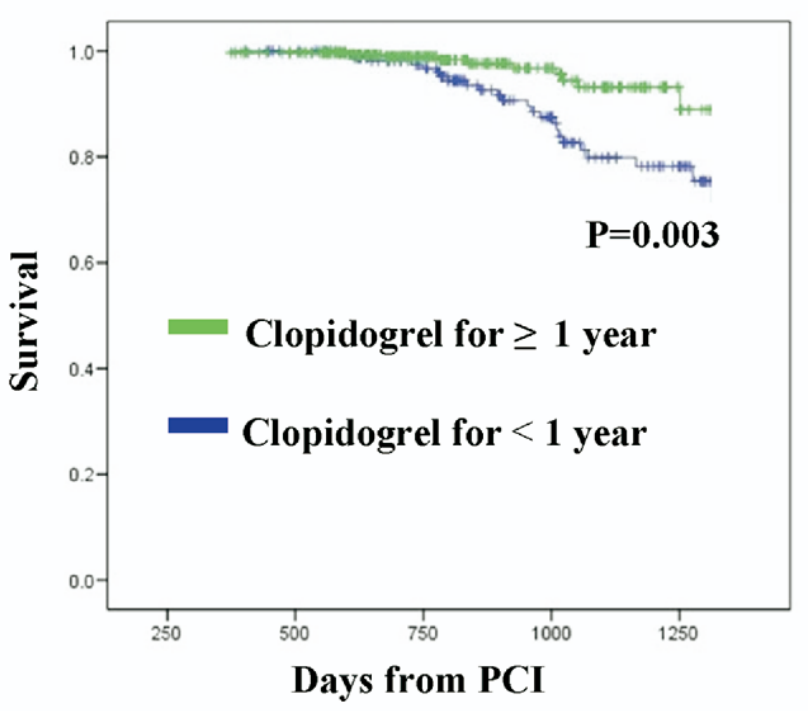
All cause mortality HR 2.40, 95% CI 1.61-3.58.

[Consistent among patients receiving BMS (HR 2.65, 95% CI 1.59-4.42) or DES (HR 2.00, 95% CI 1.06-3.75).]

Ho PM et al. AHJ 2007

Comparison of the Impact of Short (<1 Year) and Long-Term (≥1 Year) Clopidogrel Use Following Percutaneous Coronary Intervention on Mortality

Subhash Banerjee, MD[a,b,*], Cyril Varghese, MS[a], Jepsin Samuel, MD[a], Rick A. Weideman, PharmD[a], Bertis B. Little, PhD[a], Kevin C. Kelly, PharmD[a], Sunil V. Rao, MD[c,d], Robert F. Reilly, MD[a,b], and Emmanouil S. Brilakis, MD, PhD[a,b]

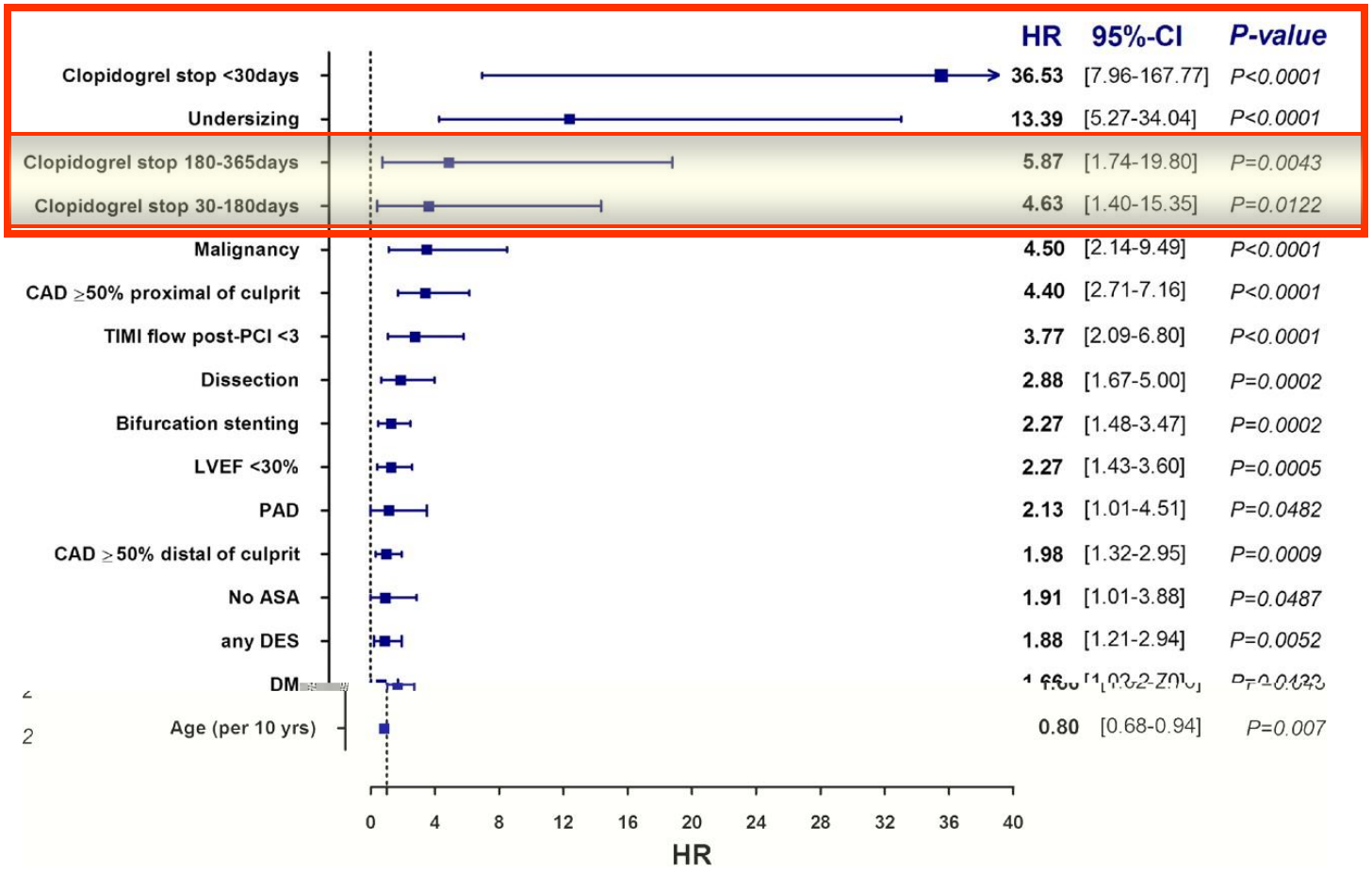


In conclusion, the use of clopidogrel for >1 year after PCI was associated with lower mortality.

Banerjee S, Brilakis ES et al. AJC 2008

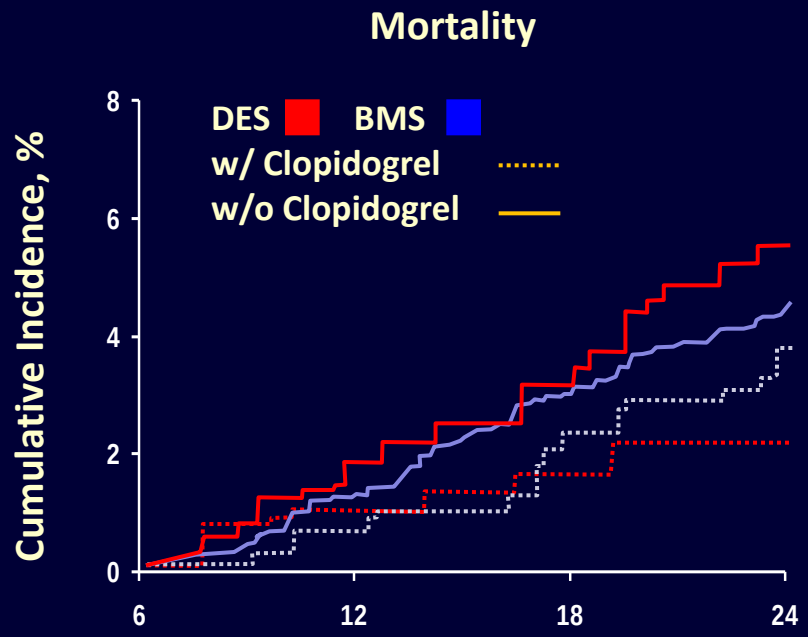
Dutch Stent Thrombosis Registry

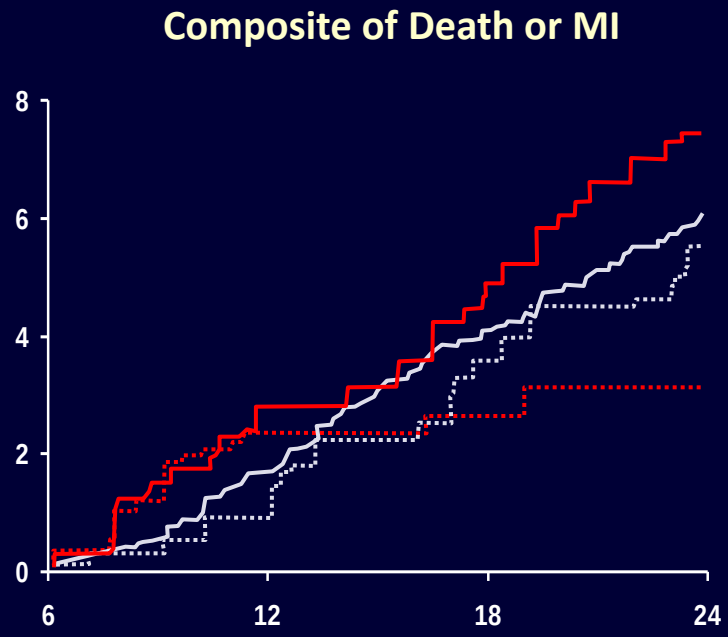
Independent Risk Factors for ST, N=21,009



van Werkum, J. W. et al. J Am Coll Cardiol 2009;53:1399-1409

Adjusted Cumulative Mortality and MI Rates Using the 6-Month Landmark Analysis



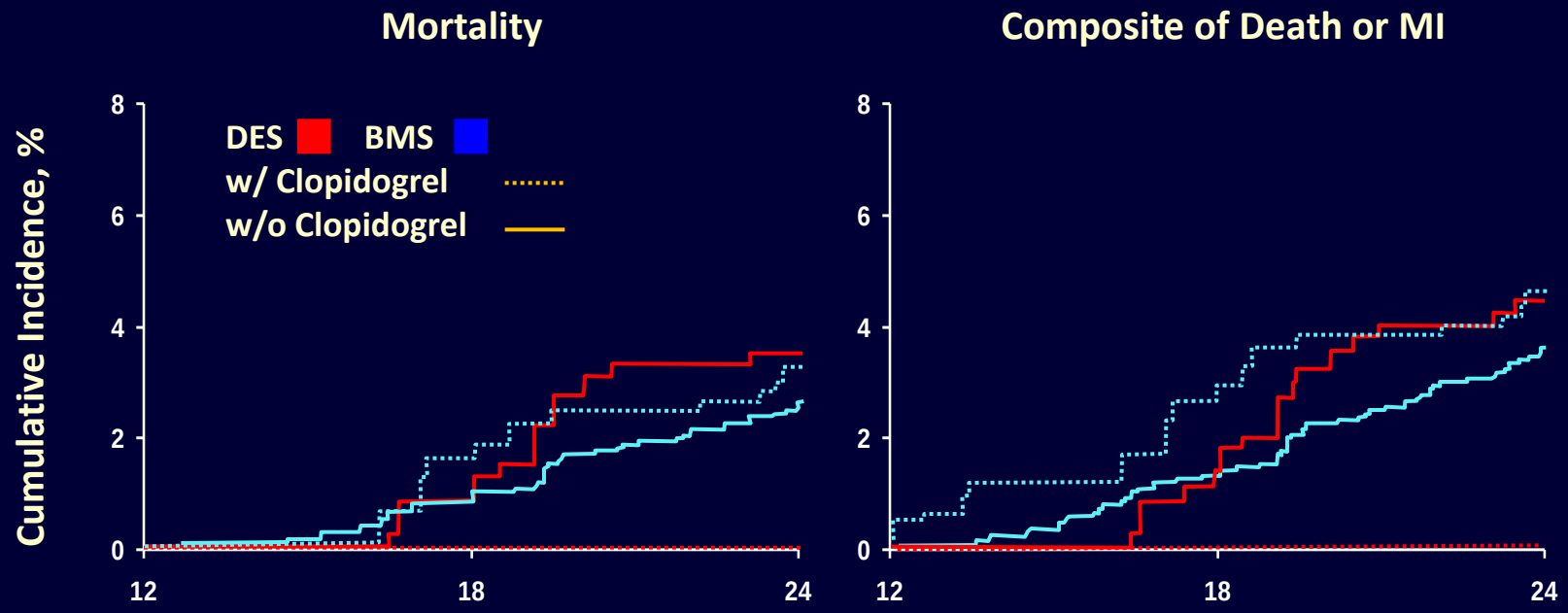


No. at Risk								
DES								
w/ Clopidogrel	637	618	303	290	637	613	300	287
w/o Clopidogrel	579	532	267	245	579	526	262	238
BMS								
w/ Clopidogrel	417	413	397	387	417	412	394	382
w/o Clopidogrel	1976	1948	1896	1852	1976	1941	1879	1825

Duke Registry Eisenstein EL, et al. *JAMA*. 2007;10;297(2):159-168.

Adjusted Cumulative Mortality and MI Rates

Using the 12-Month Landmark Analysis



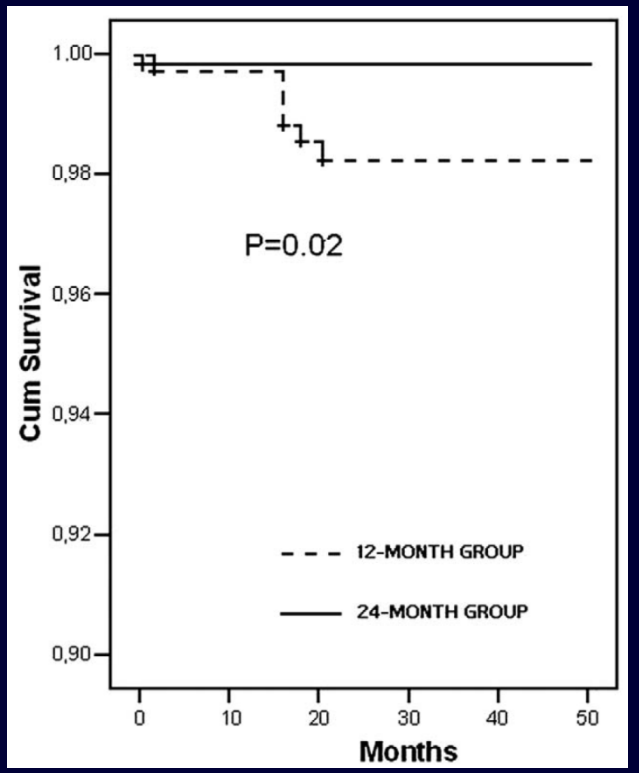
No. at Risk						
DES						
w/ Clopidogrel	252	237	230	252	237	230
w/o Clopidogrel	276	258	244	276	256	240
BMS						
w/ Clopidogrel	346	339	331	346	336	327
w/o Clopidogrel	1644	1627	1596	1644	1621	1582

Duke Registry . Eisenstein EL, et al. *JAMA*. 2007;10;297(2):159-168.

TYCOON Registry

Clinical outcome up to 4 yrs post-PCI

Variable	DES	
	12 mos (n = 173)	24 mos (n = 274)
Clinical events		
Cardiac death	4 (2%)	5 (2%)
Target lesion revascularization	6 (3%)	8 (3%)
Target vessel revascularization	10 (6%)	10 (4%)
Myocardial infarction	3 (2%)	1 (0.4%)
Stent thrombosis		
Acute thrombosis	0	0
Subacute thrombosis (1–30 d)	1 (0.6%)	1 (0.4%)
Late thrombosis (1–12 mos)	0%	0
Very late thrombosis (>12 mos)	4 (2%)	0
All thromboses	5 (3%)	1 (0.4%)



Tanzilli G. et al. AJC 2009

Duration of DAT

Longer or shorter than 1 Yr for EVERYBODY??

→Not reasonable !!!

A Customized approach

would be more reasonable.

Then, which patients need extended duration of DAT?

10 centers in Korea

Successful DES implantation

May 2003 ~ May 2007

⇩

Cases: 123 ST Pts

(124 ST cases, 128 ST lesions)

definite, possible and probable ST

in Korea Stent Thrombosis registry (KoST)

⇳

Controls: 2,192 control pts without ST for at least 6mo

in SNUH DES registry

Park KW, Kim HS et al. Circulation J 2011

Seoul National University Hospital Cardiovascular Center

Frequency of DES Stent Thrombosis

(From the KoST registry)

Entire treated patients: 14150 pts

ST incidence 0.87% (123/14150)

SES (Cypher™)

0.77%

69 patients developed ST

8933 pts received SES

PES (TAXUS™)

1.04%

54 patients developed ST

5217 pts received PES

Park KW, Kim HS et al. Circulation J 2011

Independent Predictors of ST

	Hazard ratio (95% confidence interval)	p value
Both early and delayed ST		
AMI	3.91(2.66-5.74)	<0.001
Low EF	3.51(2.01-6.13)	<0.001
Stent diameter (per 1mm decrease)	2.71(1.45-5.05)	0.002
DES ISR	4.75(2.32-9.75)	<0.001
Only Early ST		
Bifurcation stenting	2.39 (1.27-4.52)	0.007
Only Delayed ST (Late + VL)		
Younger Age (per decade decrease)	1.8 (1.5-2.1)	<0.001
Hypertension / Anti-HT Med	0.50 (0.27-0.92)	0.025
Renal insufficiency	2.16(1.05-6.31)	0.031
LAD PCI	2.47(1.36-4.51)	0.003

Park KW, Kim HS et al. Circulation J 2011

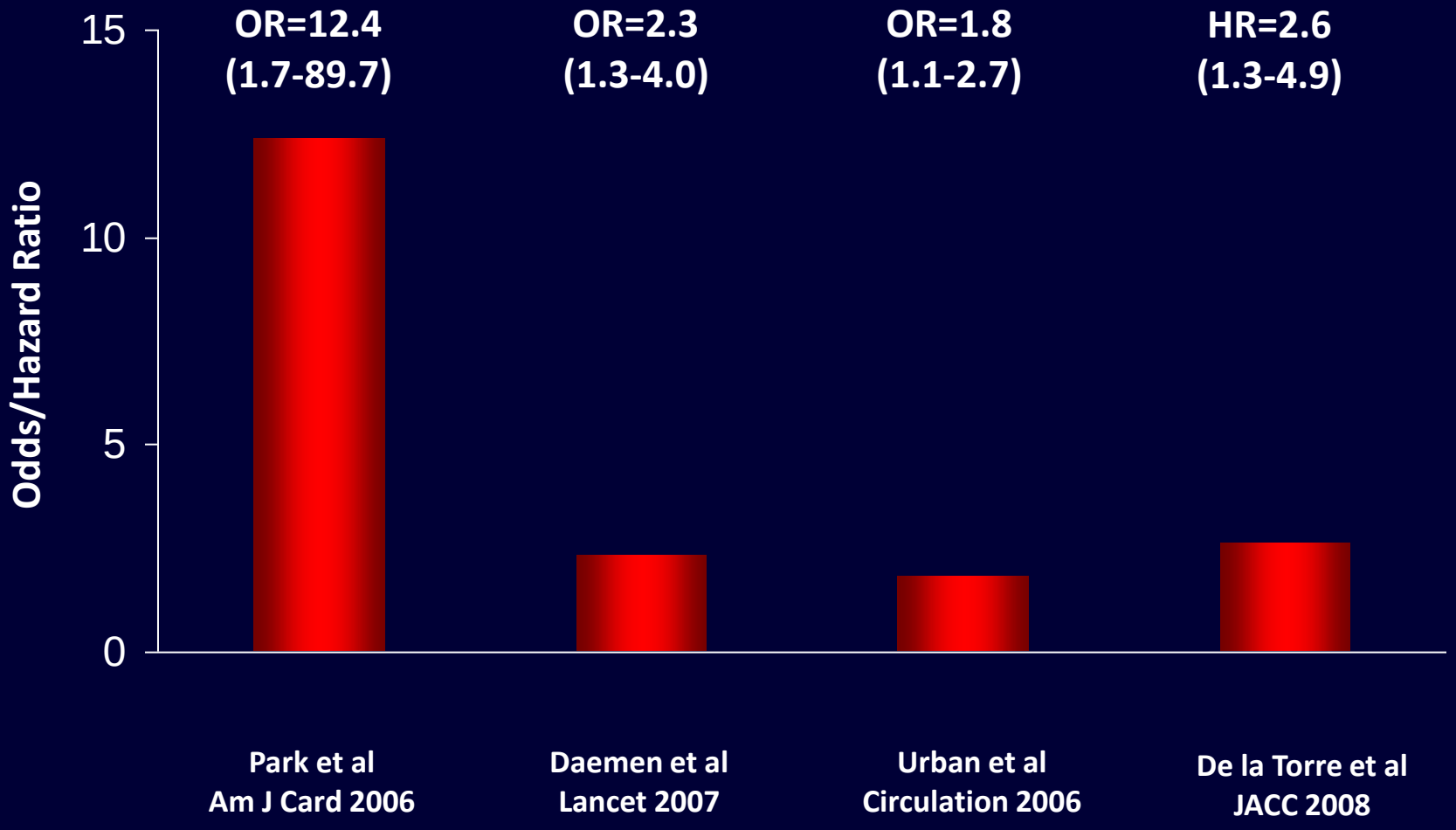
Message from the KoST registry

Attention to the overlapped risk factors

- Young AMI Patient with CHF and
- Insufficient Dilatation of
- Small-sized DES in
- Bifurcation Lesion for
- DES ISR lesion

Very High Risk for ST

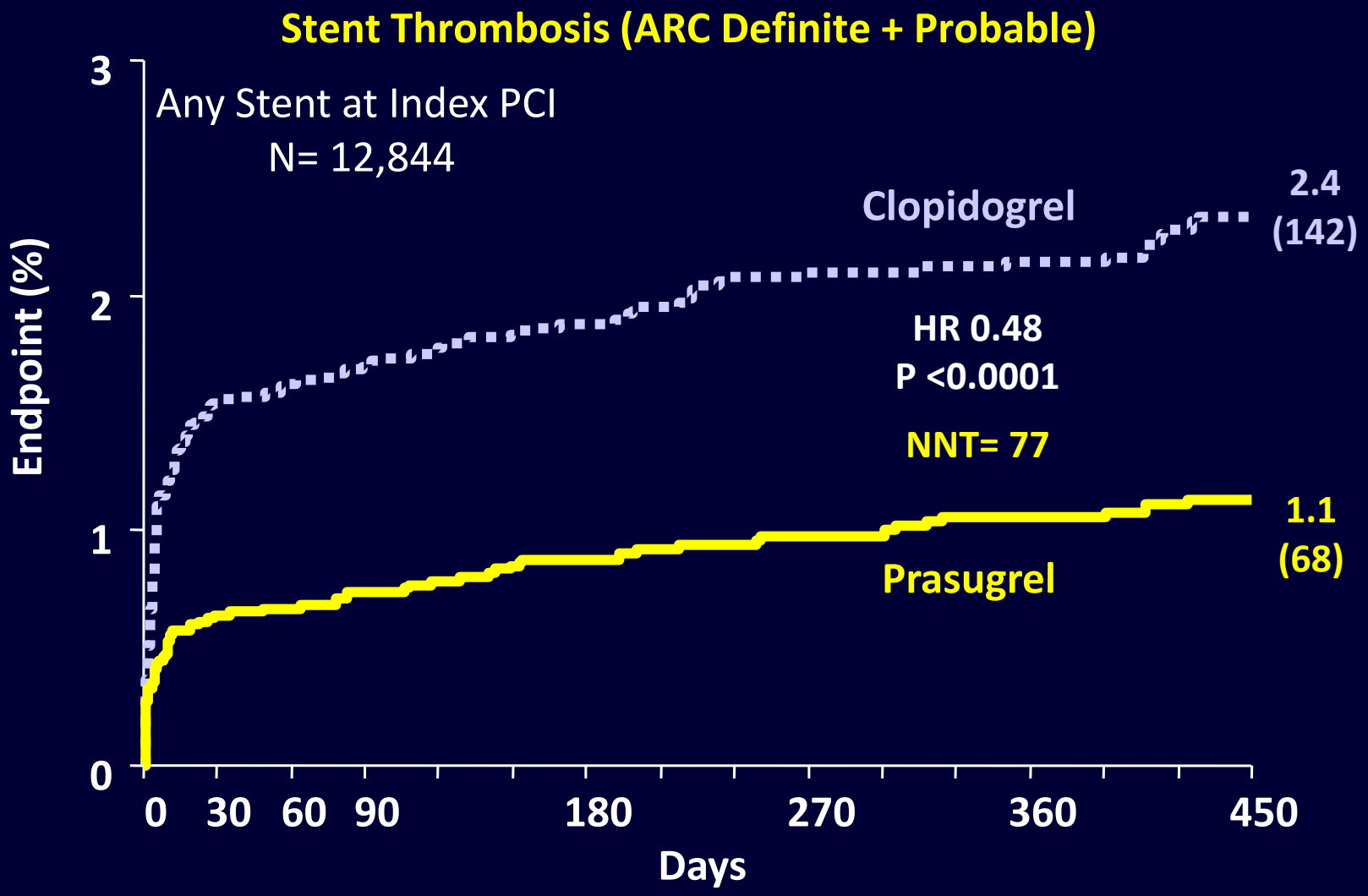
ACS as Predictor of Stent Thrombosis



ACS Patients: Triton TIMI 38

– Prasugrel vs. Clopidogrel

Wiviott SD et al. *N Engl J Med* 2007;357:2001-15

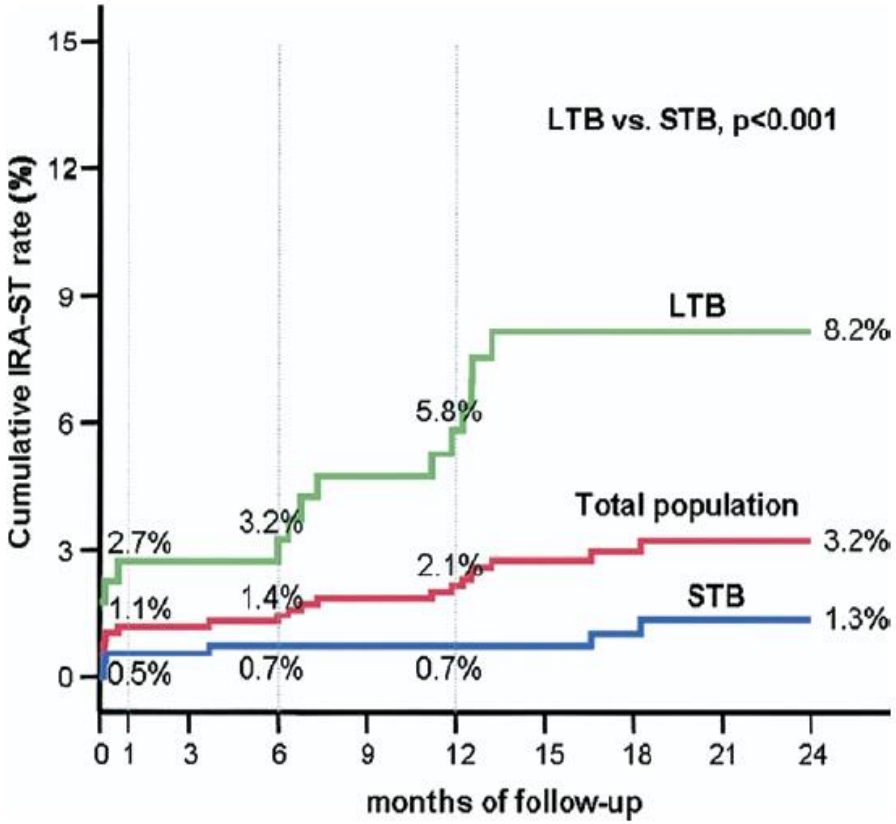


Impact of Thrombus Burden on Risk of Stent Thrombosis With DES in Patients With STEMI

Sianos G et al. *J Am Coll Cardiol* 2007;50:573-83

Independent Predictors of ST

Variable	*Hazard Ratio*	*95% CI*
Age	0.6	0.4-0.8
Index ST	6.2	2.1-18.9
Bifurcation	4.1	1.6-10.0
Thrombectomy	0.1	0.01-0.8
Large thrombus	8.7	3.4-22.5



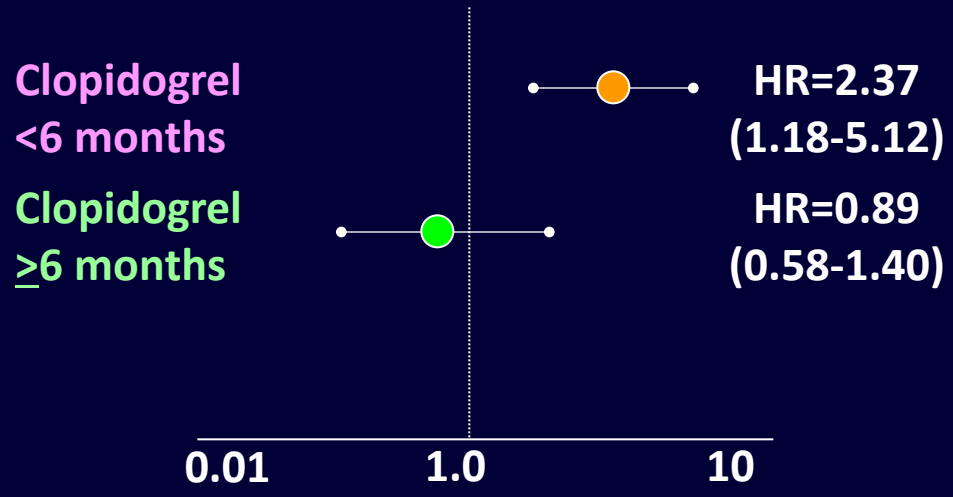
Overall Mortality in Diabetic Patients

Meta-Analysis of 3,853 Diabetic Patients

Stettler C et al. *Brit Med J 2008*

Impact of Dual Antiplatelet Therapy Duration

SES vs. BMS



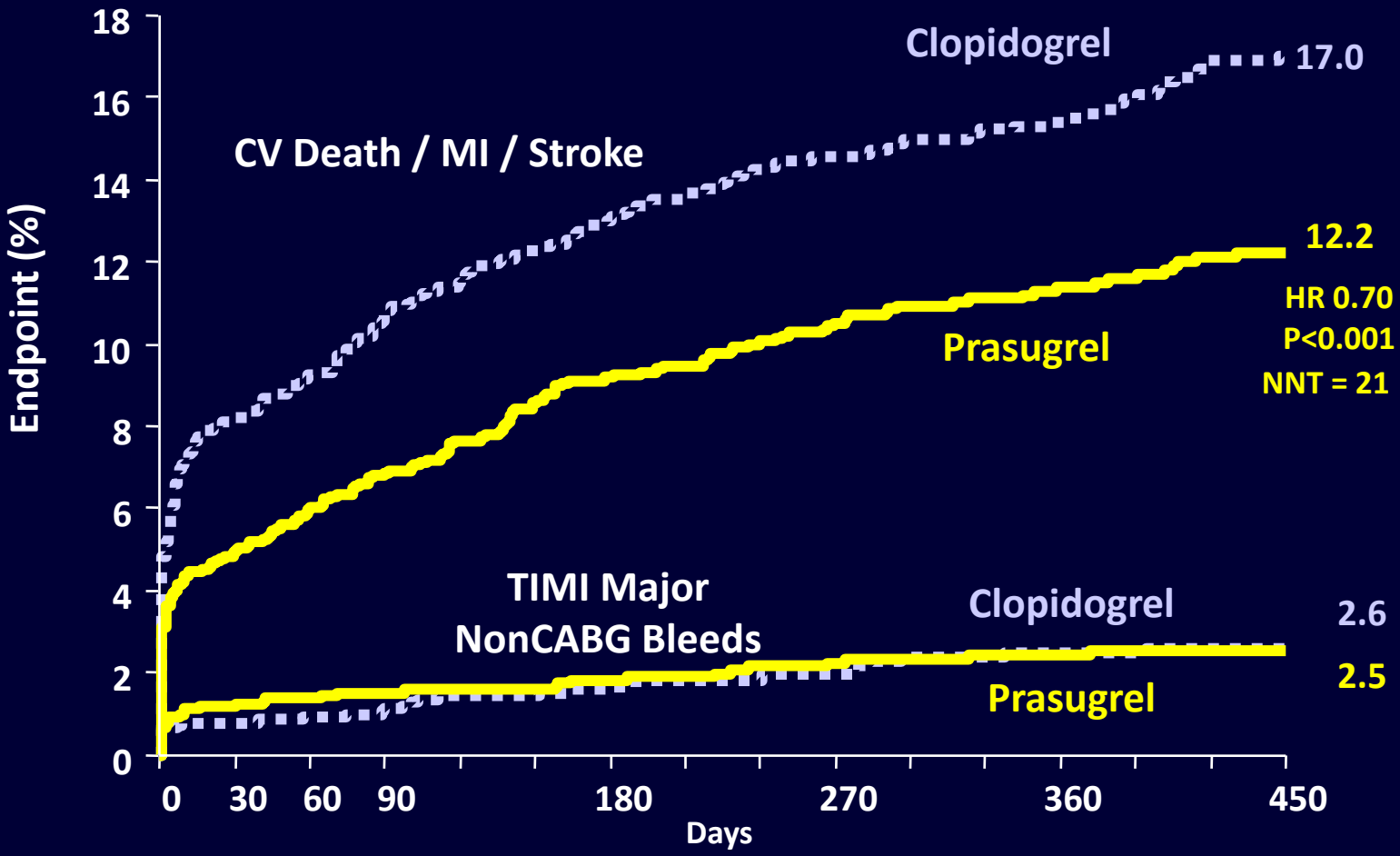
P value for interaction = 0.02

Diabetic Patients: Triton TIMI 38

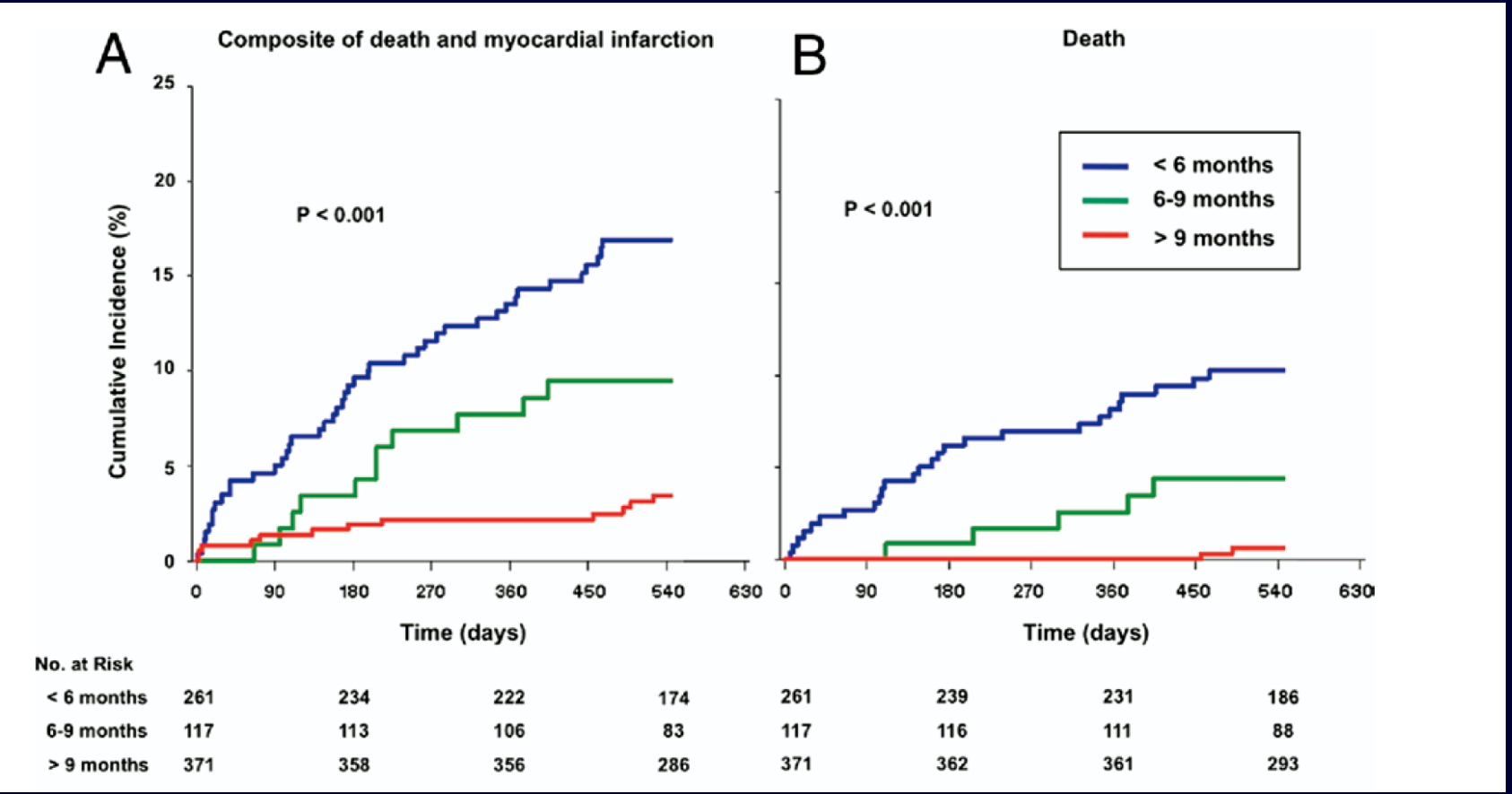
– Prasugrel vs. Clopidogrel

Wiviott SD et al. *N Engl J Med* 2007;357:2001-15

Diabetic Subgroup (N=3,146)



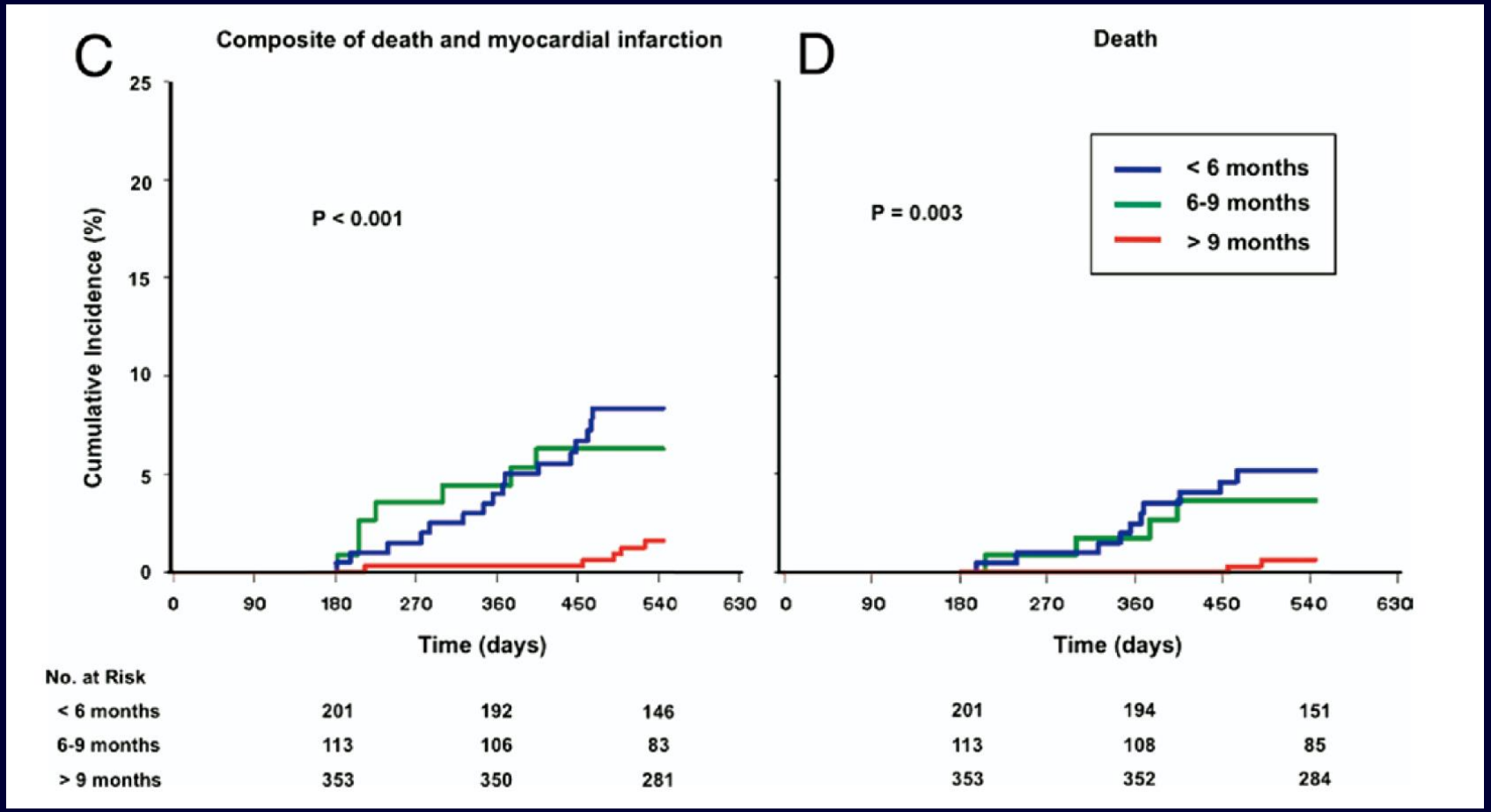
Long-term outcomes by clopidogrel duration : DM patients



All Patient Analysis

Brar et al. J Am Coll Cardiol 2008; 51:2220-7

Long-term outcomes by clopidogrel duration : DM patients -6-mo Landmark Analysis



6-mo Landmark Analysis

Brar et al. J Am Coll Cardiol 2008; 51:2220-7

Issues To Be Covered

1. Prolonged use of DAPT

    a. Data that don't support prolonged DAPT

    b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?

SNUH Meta-analysis

- Study level meta-analysis
- Clinical studies comparing EES vs. SES
- Regardless of study design ; RCT, cohort study
- Search ; Pubmed, Cochrane central register of Controlled Trials, Clinicaltrials.org and internet-based sources (http://www.theheart.org, http://www.tctmd.com)
- Keywords ; everolimus + sirolimus, Xience/Promus + Cypher

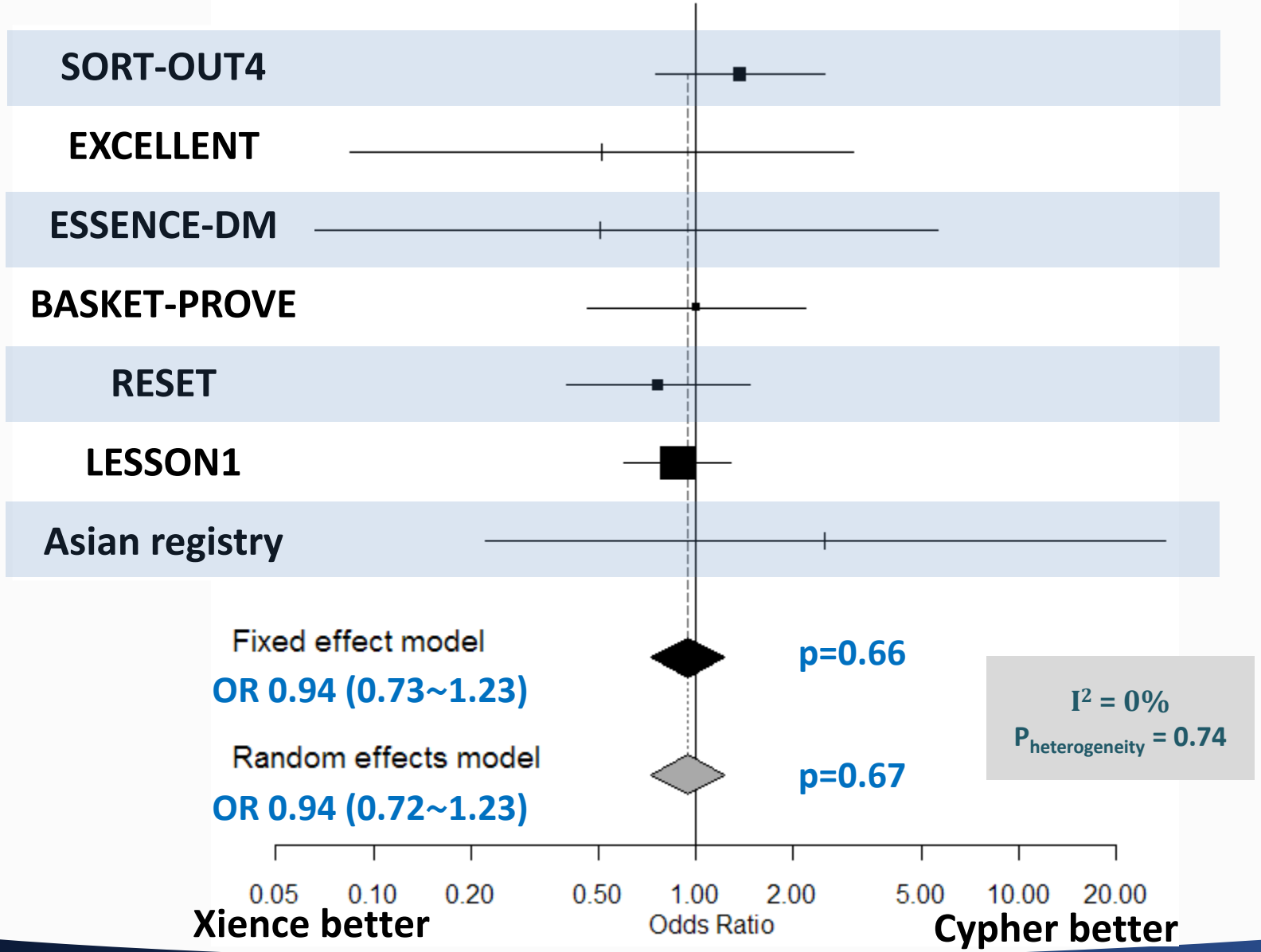
Shin DH, Park KW, Kim HS et al. unpublished data

XienceV vs Cypher

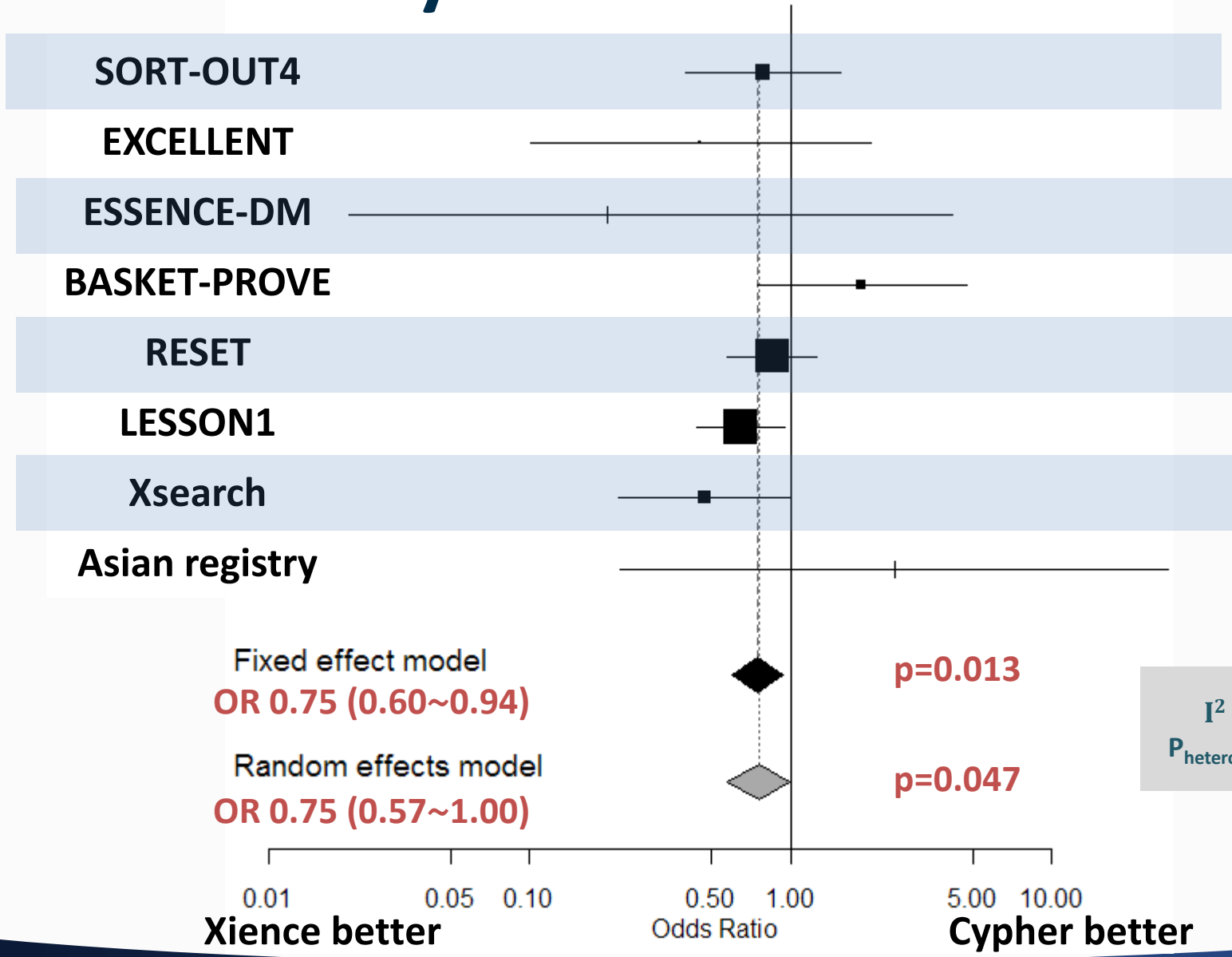
Release	Study	Design
TCT 2010	SORT-OUT4	RCT
	EXCELLENT-RCT	
	ISAR-TEST4	
	ESSENCE-DM	
AHA 2010	BASKET-PROVE	
ESC 2011	RESET	
ESC 2010	LESSON1	Cohort (historical control)
AHA 2008 / JACC 2009	Xsearch	
TCT 2009	Asian registry	

Meta-analysis of 6 RCTs and 3 registries comparing EES vs SES From SNUH

Cardiac death



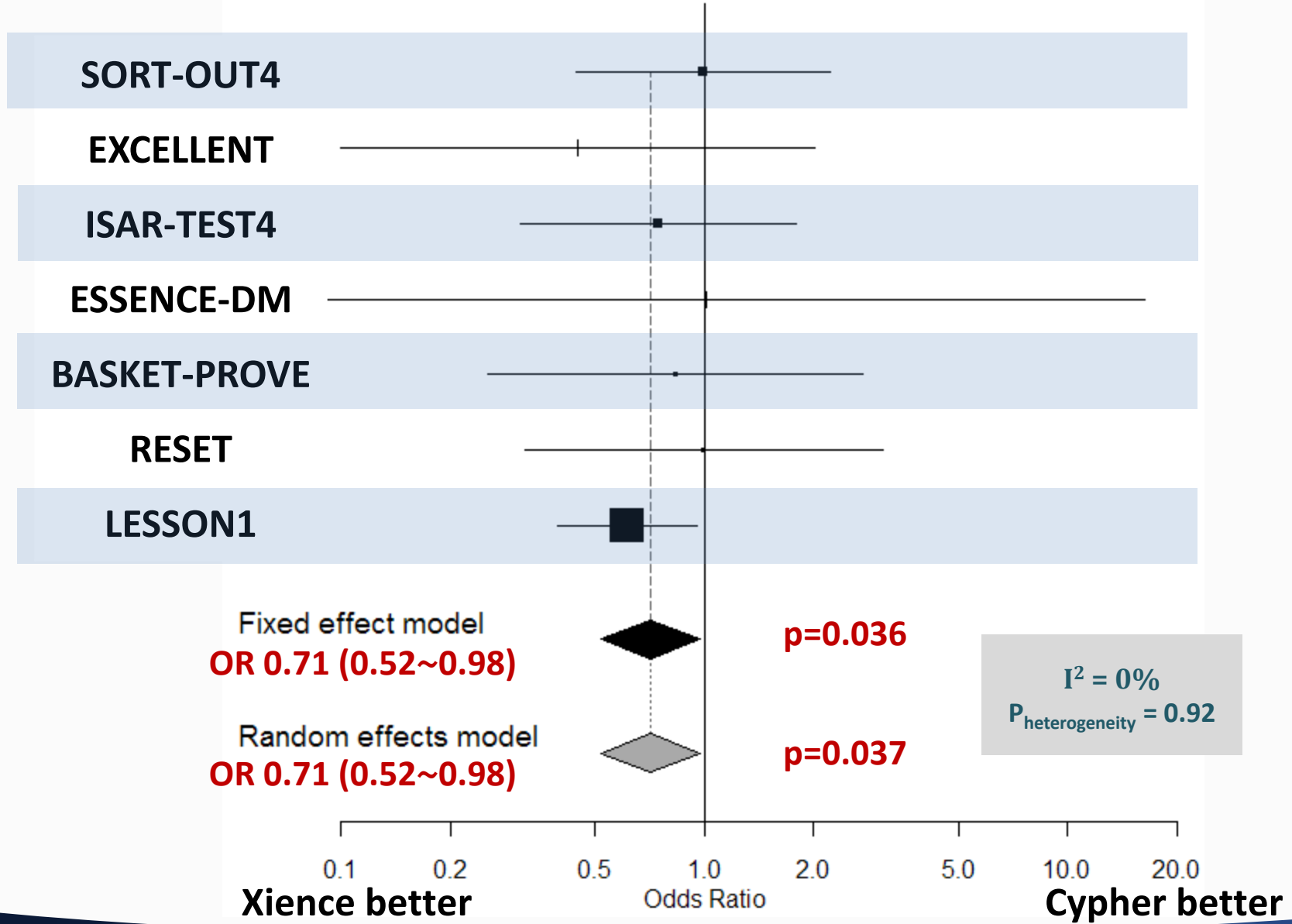
Myocardial infarction



$I^2 = 16.2\%$

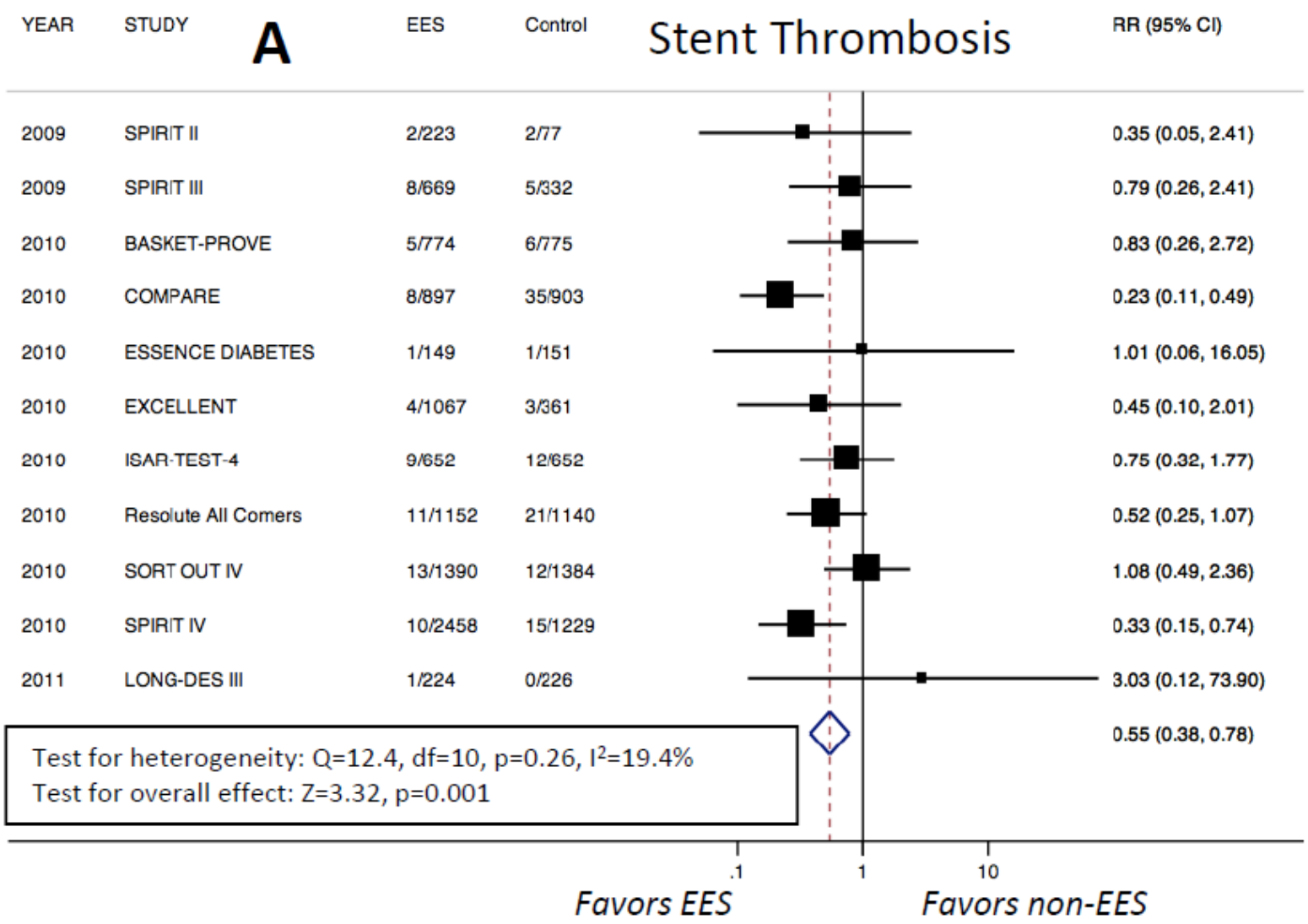
$P_{heterogeneity} = 0.30$

Stent thrombosis



EES vs. 1st gen DES: ST

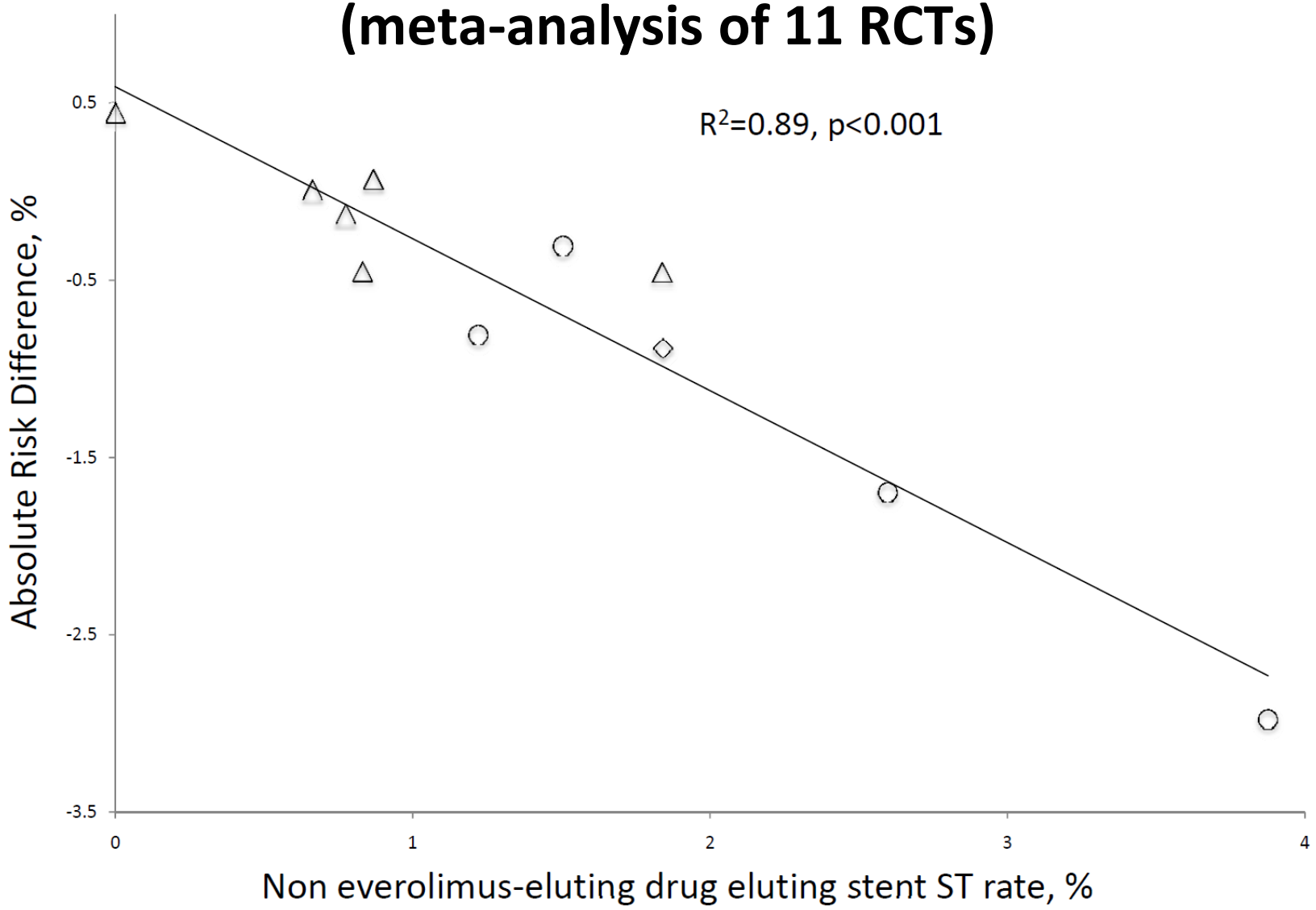
(meta-analysis of 11 RCTs: 45% RR reduction)



Baber U, Kim HS, Dangas G et al. JACC 2011 in press

Risk reduction in ST

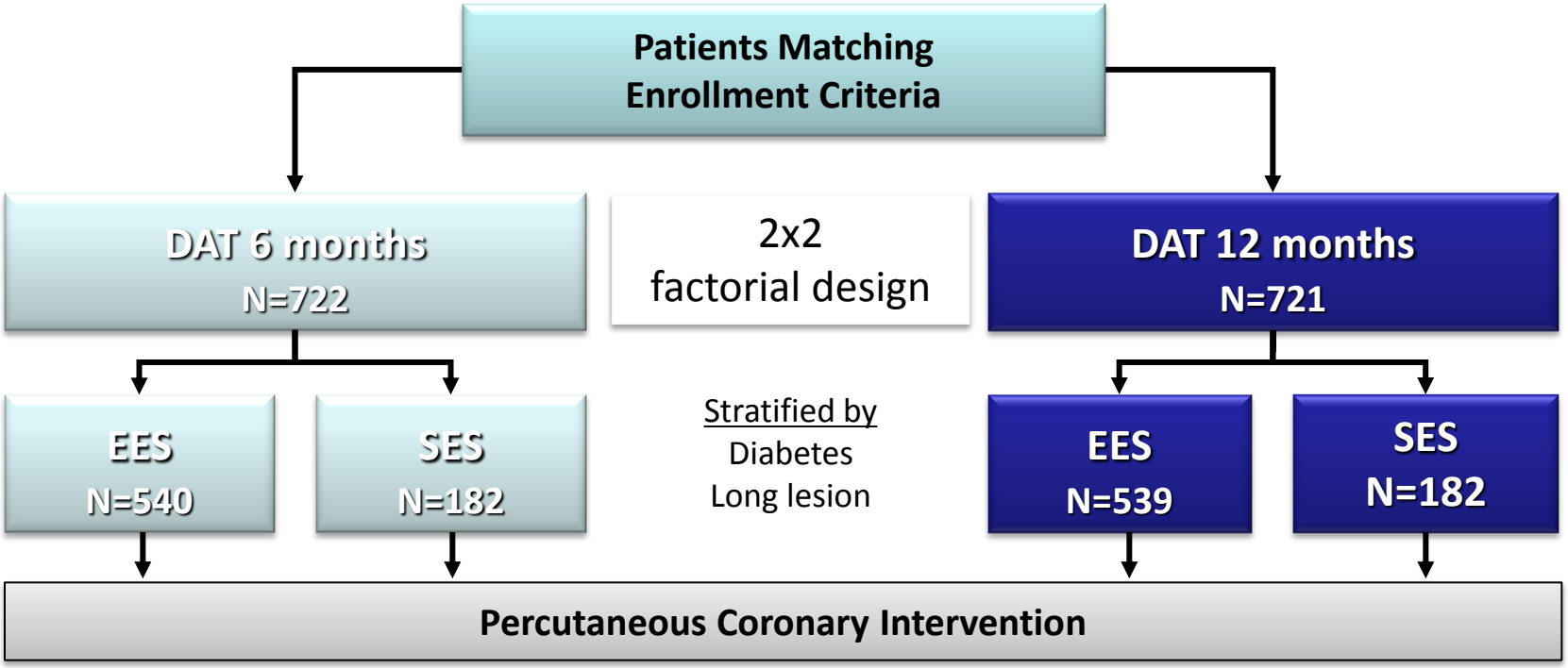
(meta-analysis of 11 RCTs)

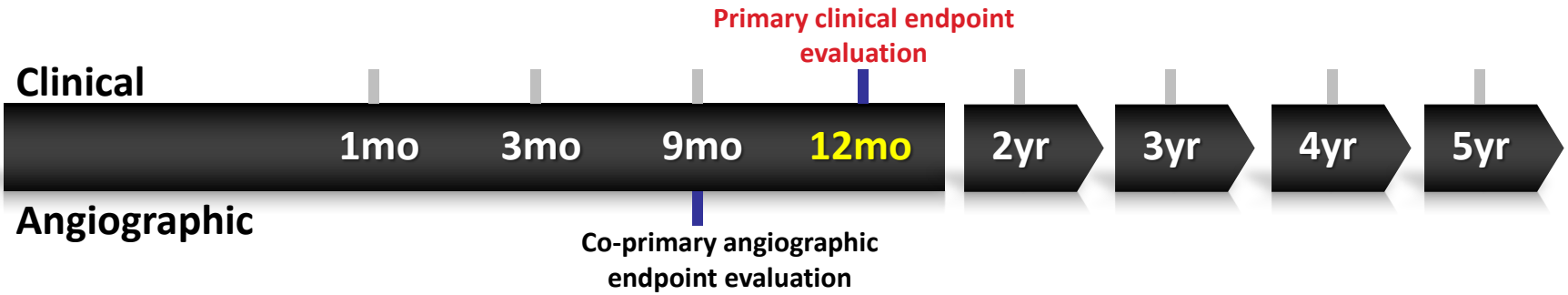


Baber U, Kim HS, Dangas G et al. JACC 2011

EXCELLENT Trial Design

Investigator-initiated, multi-center, open label, prospective randomized trial

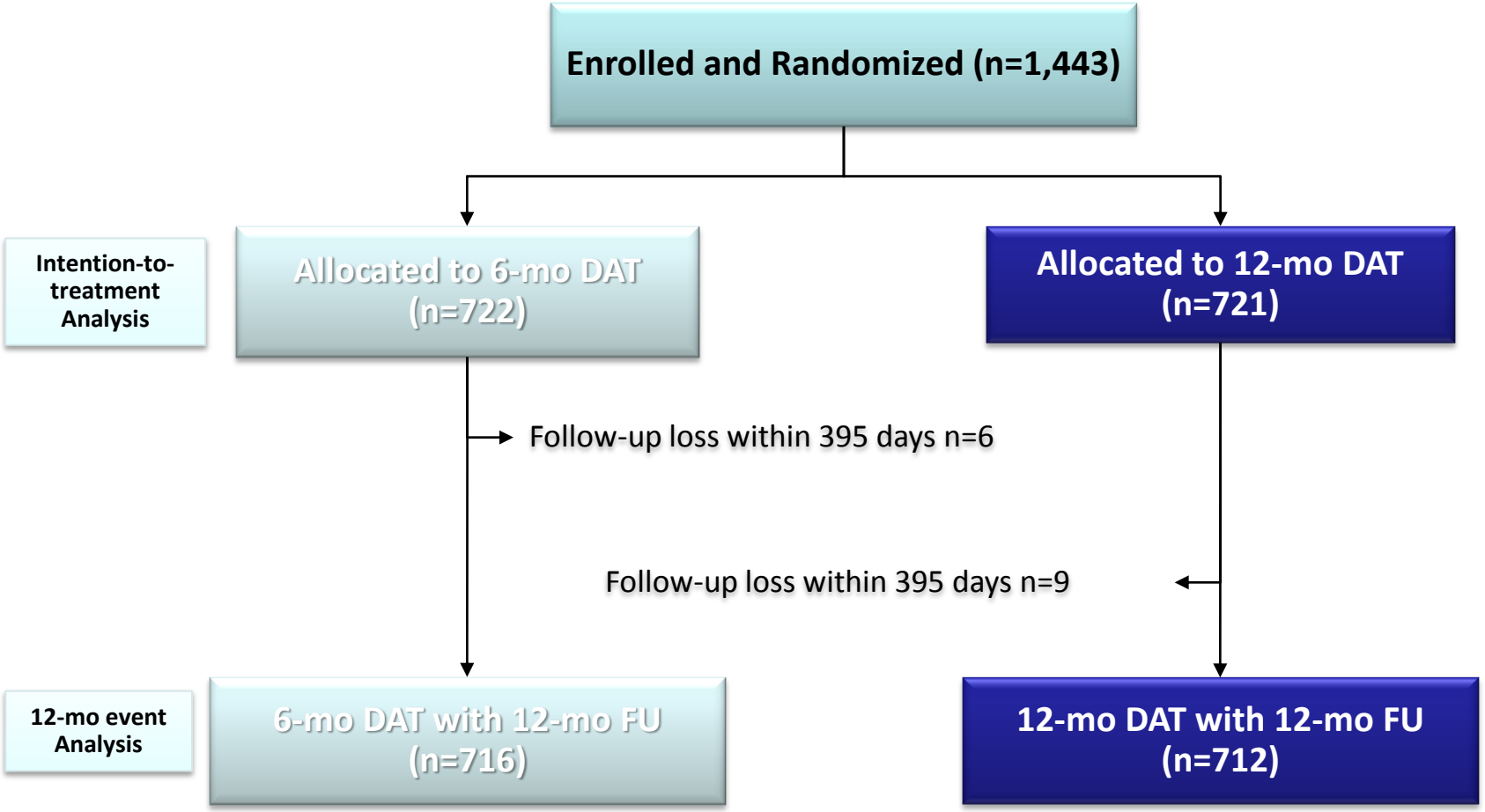




Park KW, Kim HS et al. Am Heart J 2009
Park KW, Kim HS et al. J Am Coll Cardiol 2011
Gwon HC, Park KW, Kim HS et al. ACC 2011, LBCT

www.clinicaltrials.gov (NCT00698607)

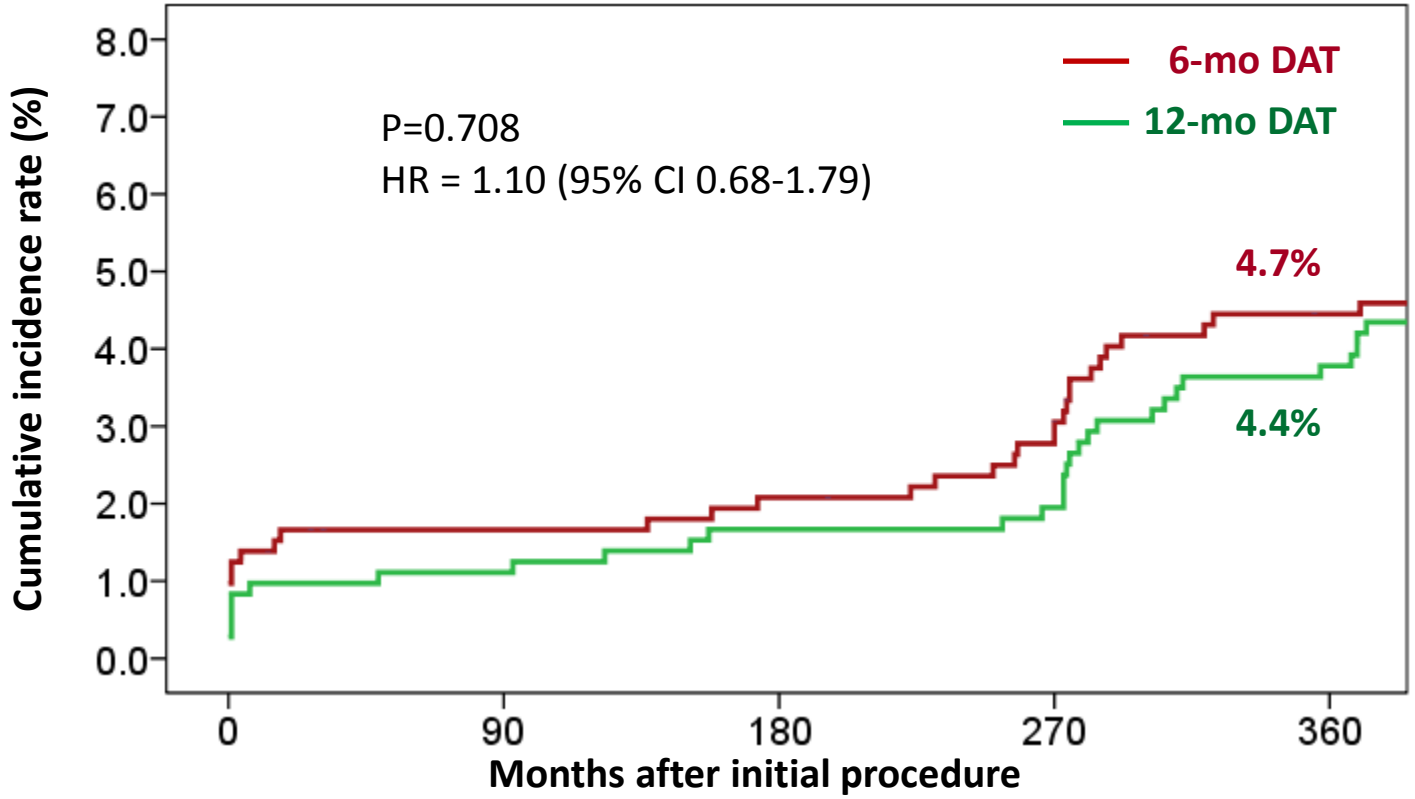
Study Flow



One-year clinical follow-up rate 99.0%

1° Endpoint

Target Vessel Failure

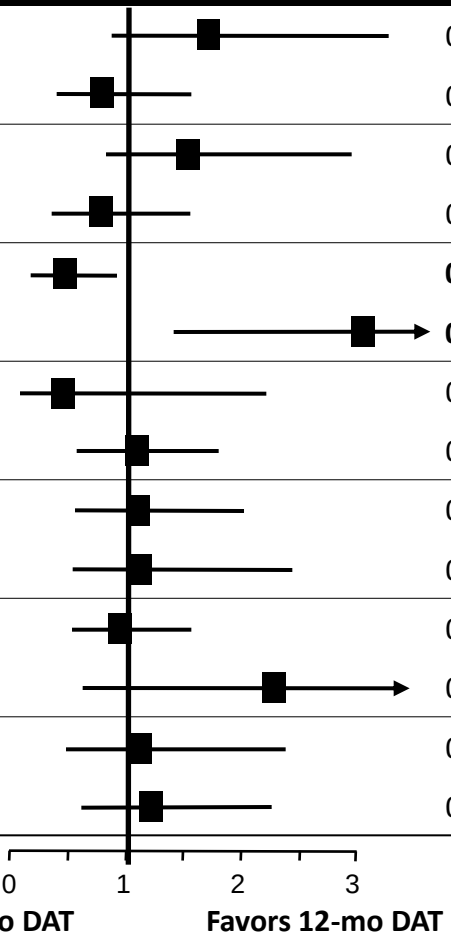


Patient Number at Risk					
6-month	722	707	704	698	682
12-month	721	710	703	698	682

Gwon HC, Park KW, Kim HS et al. ACC 2011 LBCT

Subgroup Analysis for TVF

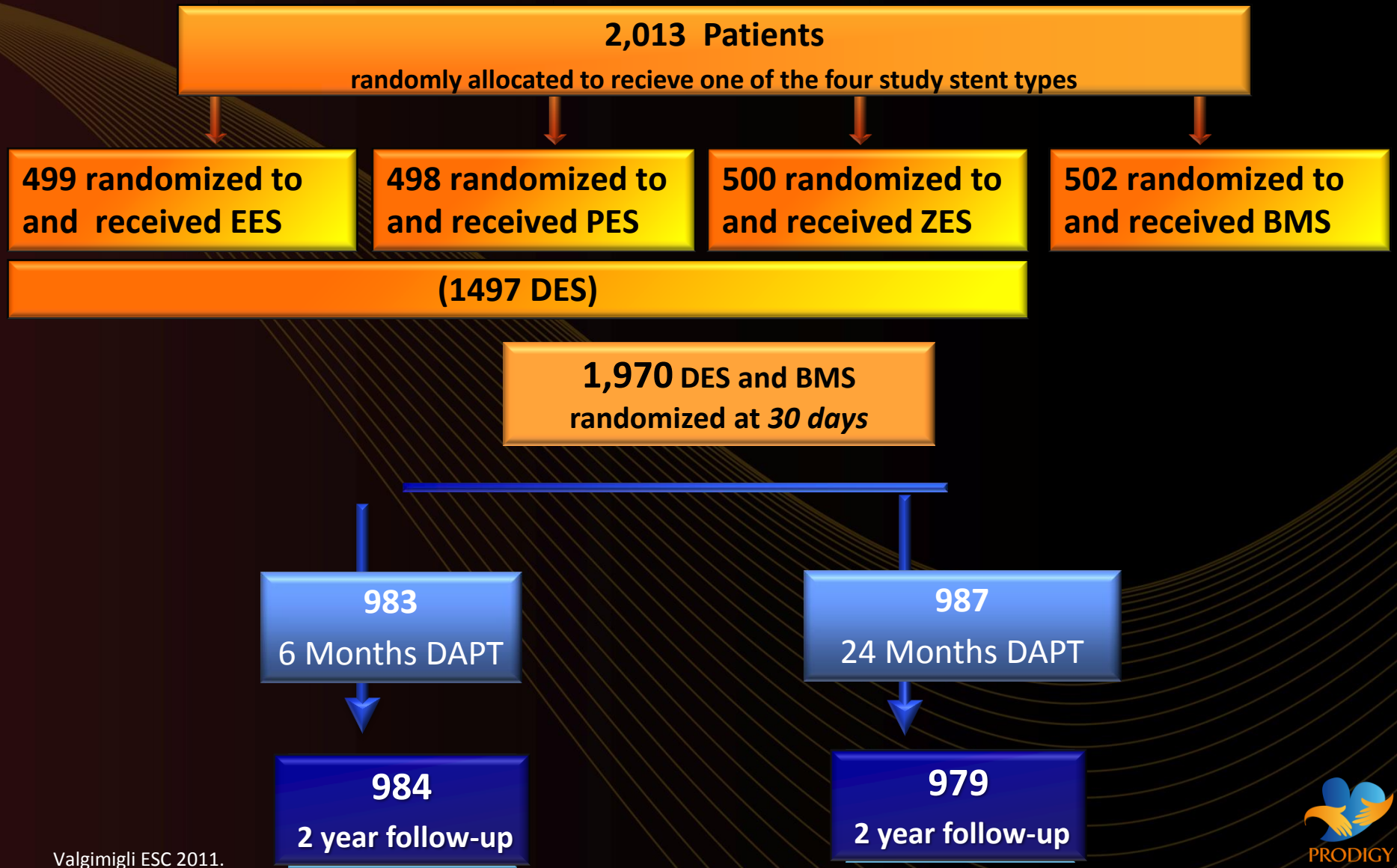
		N	6-mo DAT	12-mo DAT	X^2 p-value	Cox HR	Cox p-value	P for interaction
Age	< 65	761	19 (5.0%)	12 (3.2%)	0.202		0.202	0.155
	≥ 65	667	15 (4.5%)	19 (5.7%)	0.465		0.473	
ACS*	No	694	21 (6.9%)	14 (4.1%)	0.252		0.243	0.186
	Yes	734	13 (3.6%)	17 (4.6%)	0.474		0.471	
Diabetes	No	884	10 (2.2%)	23 (5.3%)	0.018		**0.022**	**<0.001**
	Yes	544	24 (8.8%)	8 (2.9%)	0.003		**0.005**	
LVEF	< 50%	123	3 (3.0%)	4 (7.1%)	0.286		0.290	0.287
	≥ 50%	1086	26 (4.8%)	25 (4.6%)	0.833		0.808	
Bifurcation	No	959	23 (4.7%)	20 (4.3%)	0.769		0.757	0.998
	Yes	469	11 (4.9%)	11 (4.5%)	0.830		0.830	
Stent	EES	1067	25 (4.7%)	27 (5.1%)	0.739		0.764	0.168
	SES	361	9 (5.0%)	4 (2.2%)	0.149		0.168	
Multi-stent	No	854	14 (3.2%)	12 (2.9%)	0.819		0.816	0.871
	Yes	563	20 (7.5%)	19 (6.4%)	0.601		0.585	



**ACS = unstable angina, NSTEMI, or STEMI*

PRODIGY

6 vs 24m DAPT after DES or BMS



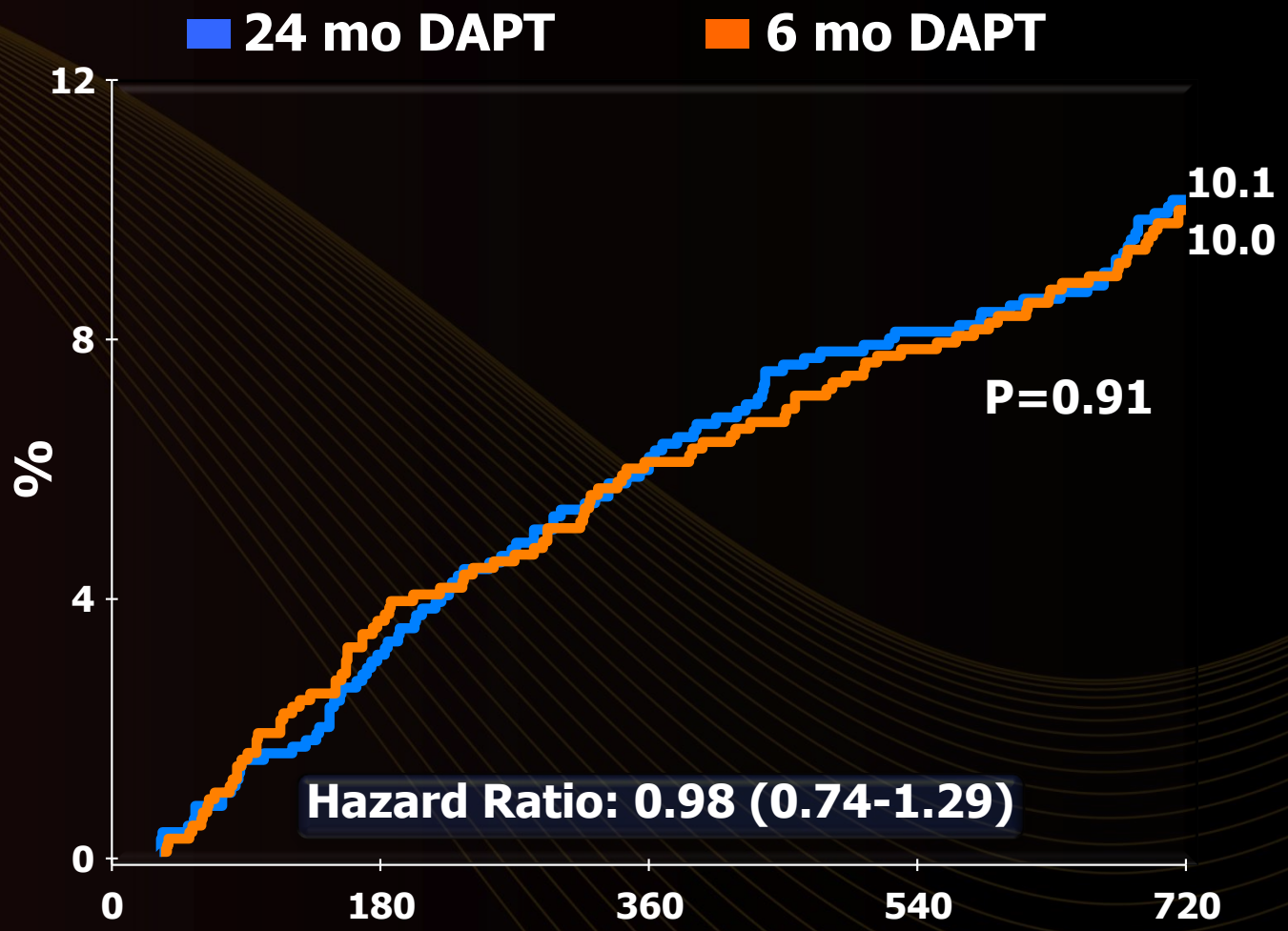
Valgimigli ESC 2011.

PRODIGY

Primary Endpoint

Overall Death, MI or CVA

CEC adjudicated

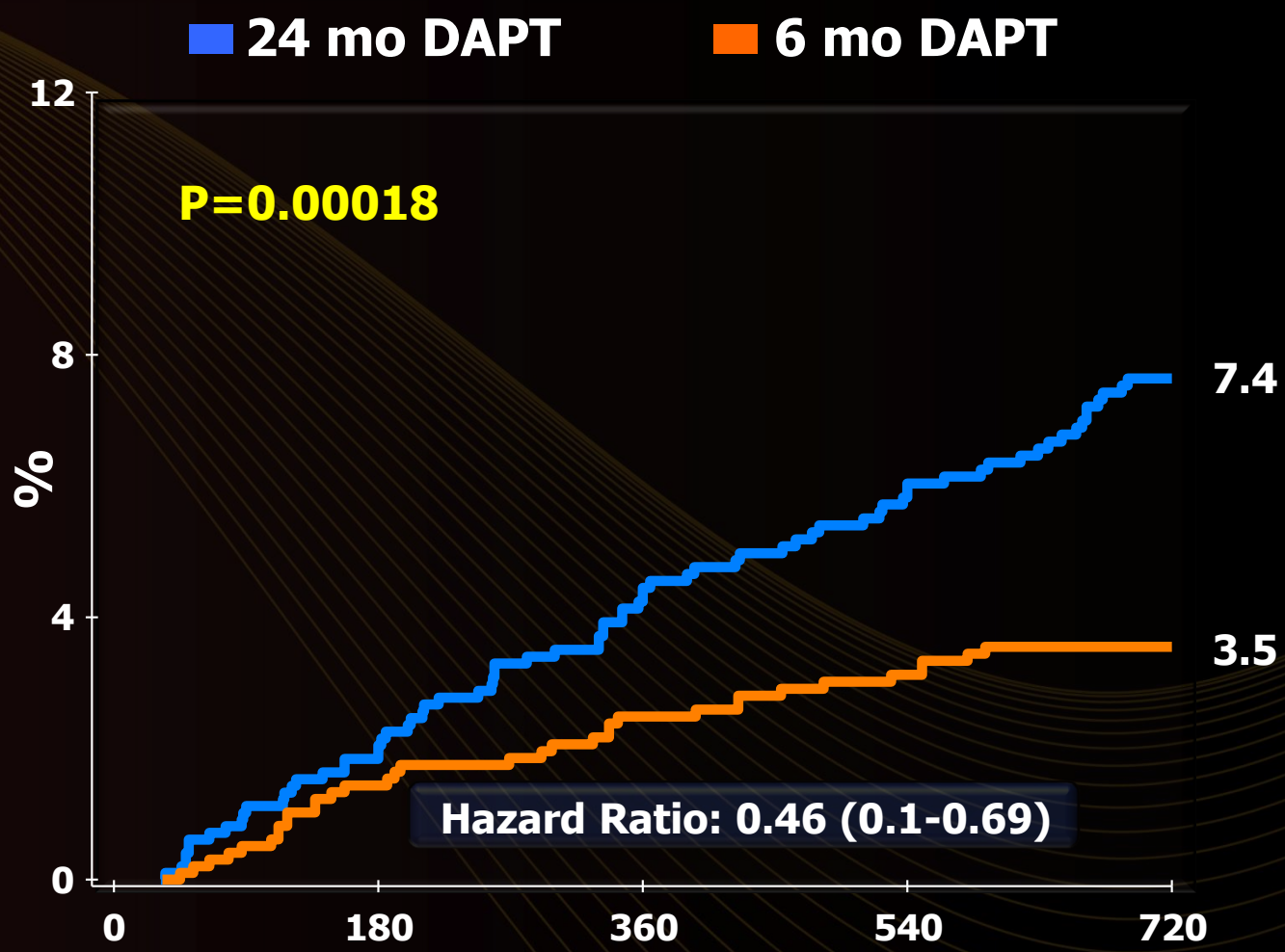


No. at Risk				
24-Month Clopidogrel	987	925	884	
6-Month Clopidogrel	983	919		881

PRODIGY

Type II, III or V BARC bleeding

CEC adjudicated



No. at Risk

24-Month Clopidogrel	987	925	884	
6-Month Clopidogrel	983	919	881	

PRODIGY

Let's Summarize up to now

1. All studies are underpowered.
2. All studies are confounded and biased and have statistical limitations
3. Only one RCT data

   : interim data analysis from a unplanned pooled analysis of two unfinished studies.

→ <u>inconclusive & causing confusion!!</u>

Issues To Be Covered

1. Prolonged use of DAPT

    a. Data that don't support prolonged DAPT

    b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?

Randomized Antiplatelet Rx Duration Trials

	Inclusion Group, N	DAPT Duration	DES Type	1º Endpoint	2º Endpoint
REAL+ZEST LATE	2701 12-month event free	~12 vs 24	All DES	2-year cardiac death/MI	Presented ACC 2010
EXCELLENT	1443 Non-STEMI	6 vs 12	SES or EES	1-year cardiac death/MI/TVR	Death/MI/CVA/ bleeding — Presented ACC 2011
PRODIGY	1357 12-month event free	6 vs 24	DES and BMS	2-year death/MI	Presented ESC 2011
ITALIC	3200	6 vs 12	EES	1-year death/M revasc/stroke	Enrolling
ISAR-SAFE	6000 6-month event free	6 vs 12	All DES	Death/MI/stroke/ TIMI major bleed a 15 months	Individual endpoints — Enrolling
OPTIMIZE	3120 non-STEMI	3 vs 12	ZES	1-year death/MI/ stroke/bleed	Enrolling
DAPT	20,645 12-month event free	12 vs 30	1.DES 2.BMS	1. Death/MI/stroke at 33 months 2. Def/prob ST at 33 months	Enrollment Complete

PES = paclitaxel-eluting stent
ZES = zotarolimus-eluting stent
SES = siroliumus-eluting stent
EES = everolimus-eluting stent

Optimal Duration of Clopidogrel Therapy

ISAR-SAFE

A double-blind, placebo-controlled RCT

6000

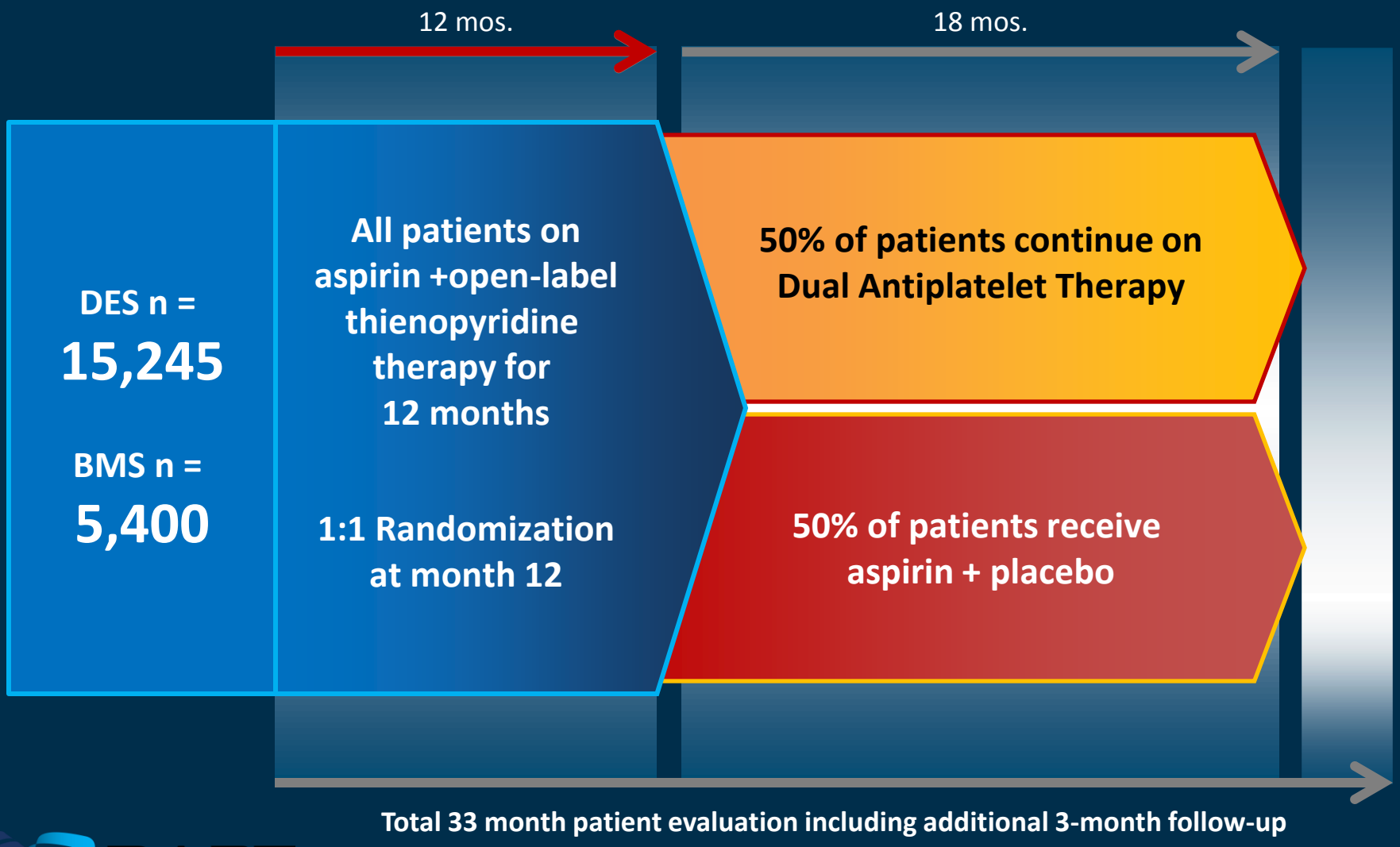
DES Patients

6-month therapy | **12-month therapy**

<u>Primary end point at 15 months</u>

A composite of death, MI, stent thrombosis, stroke, major bleeding

Dual Antiplatelet Therapy (DAPT) Study



DAPT STUDY

Optimal duration of DAPT?

1. No study has adequately assessed prospectively whether long term DAPT would be clinically better than short term DAPT

2. Several on-going studies will try to address this issue.

3. Until we have more evidence, it is too premature to say that 1 year of DAPT is enough, or less or greater than 1yr is ok for all patients post-PCI.

4. A 'One size fits all' strategy does not seem wise. Customized approach would be ideal !

long-term DAPT: targeting high risk patient with previous ST, AMI, poor LV fxn, small vessel stenting, DM, CRF, and Bifurcation multi-stenting

HOST-Duration: Trial Design

Prospective, open label, randomized multi-center trial

8500 Non-AMI Patients Receiving Single Type of 2nd generation DES

100 centers from Korea, China, Japan

6mo DAPT
N=4250

Randomization
1:1

12mo DAPT
N=4250

Percutaneous Coronary Intervention

Primary Endpoint
Net clinical outcome

Clinical

1mo | 6mo | 12mo | 15mo | 2yr | 3yr

Composite of
Any death, MI, Def/Prob ST,
stroke, PLATO major bleeding
From 6mo-15monthts

Conclusions and Take Home Message

1. The optimal duration of DAPT may vary from patient to patient. The 'One size fits all' approach may not be appropriate.

2. The body of evidence is adding up suggesting that 2nd gen DES may be safer than 1st gen DES.
   → May need a dedicated trial to test a shorter duration of DAPT in pts receiving 2nd gen DES

Thank you for your attention!!