Optimal Duration and Dose of Antiplatelet Therapy after PCI

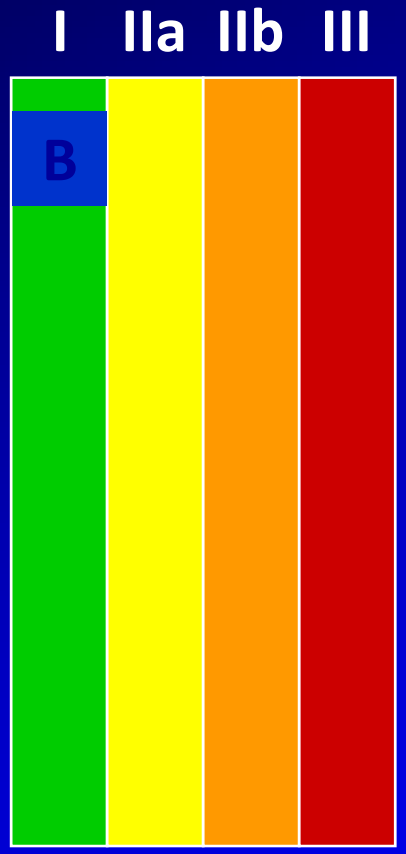
Donghoon Choi, MD, PhD
Severance Cardiovascular Center
Yonsei University College of Medicine

Optimal Duration of Antiplatelet Therapy after PCI

ACC/AHA/SCAI 2007 Focused Update for PCI

Oral Antiplatelet Adjunctive Therapies

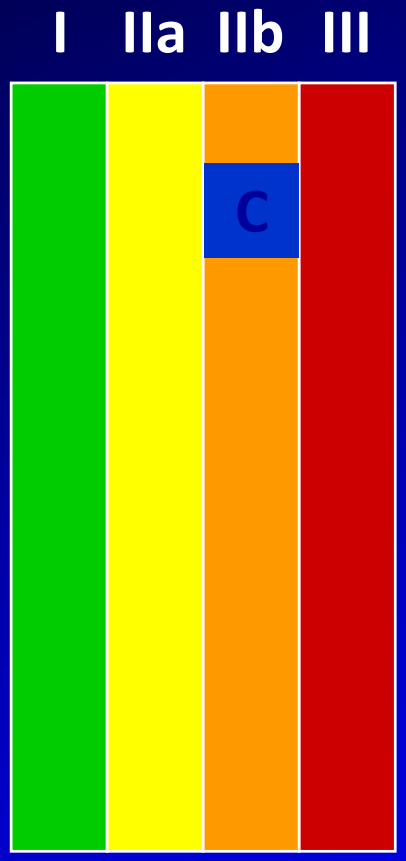
(Modified from 2005 PCI Guideline Recommendation)



- For all post-PCI stented patients receiving a DES, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding.
- For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).

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)

Contents

1. Clinical Data of long term use in dual anti-platelet therapy
   - Controversial
   - Supporting
2. Answers from on-going trials for long term use?

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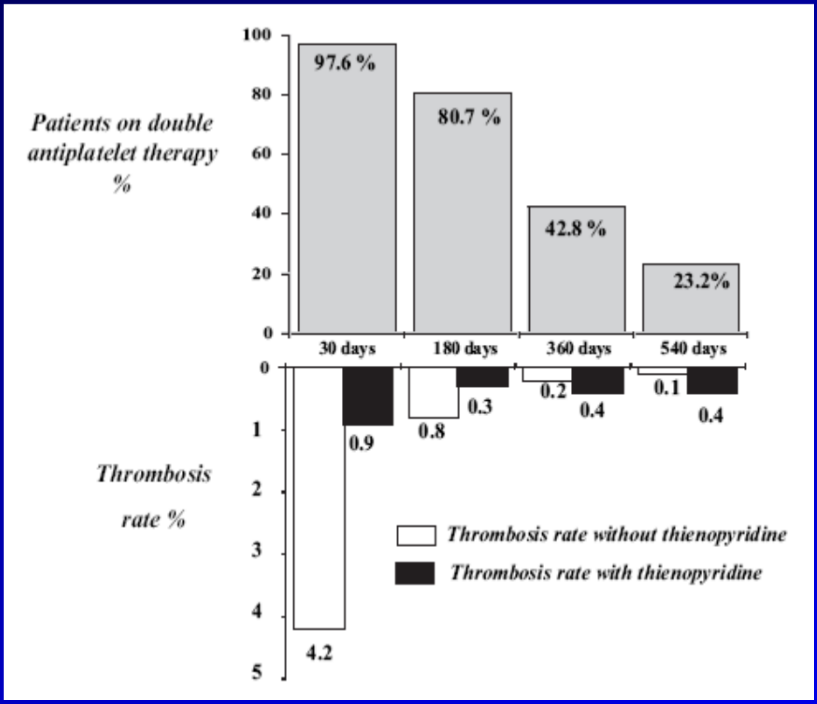
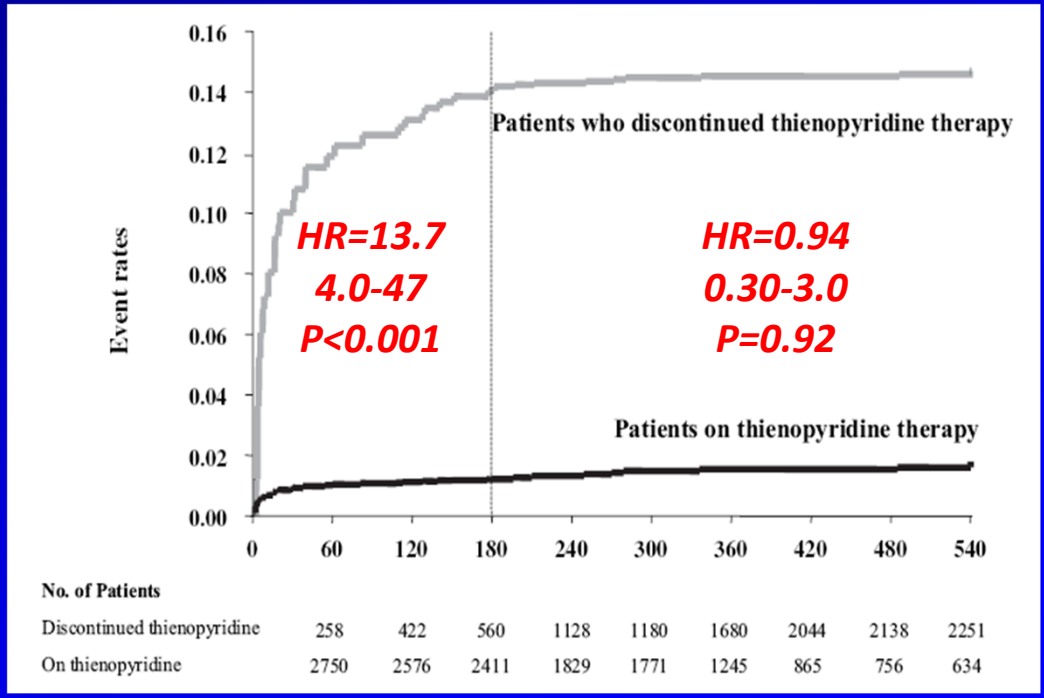
Discontinuation of Thienopyridine and Risk of Stent Thrombosis: Milan-Siegburg Cohort Study

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

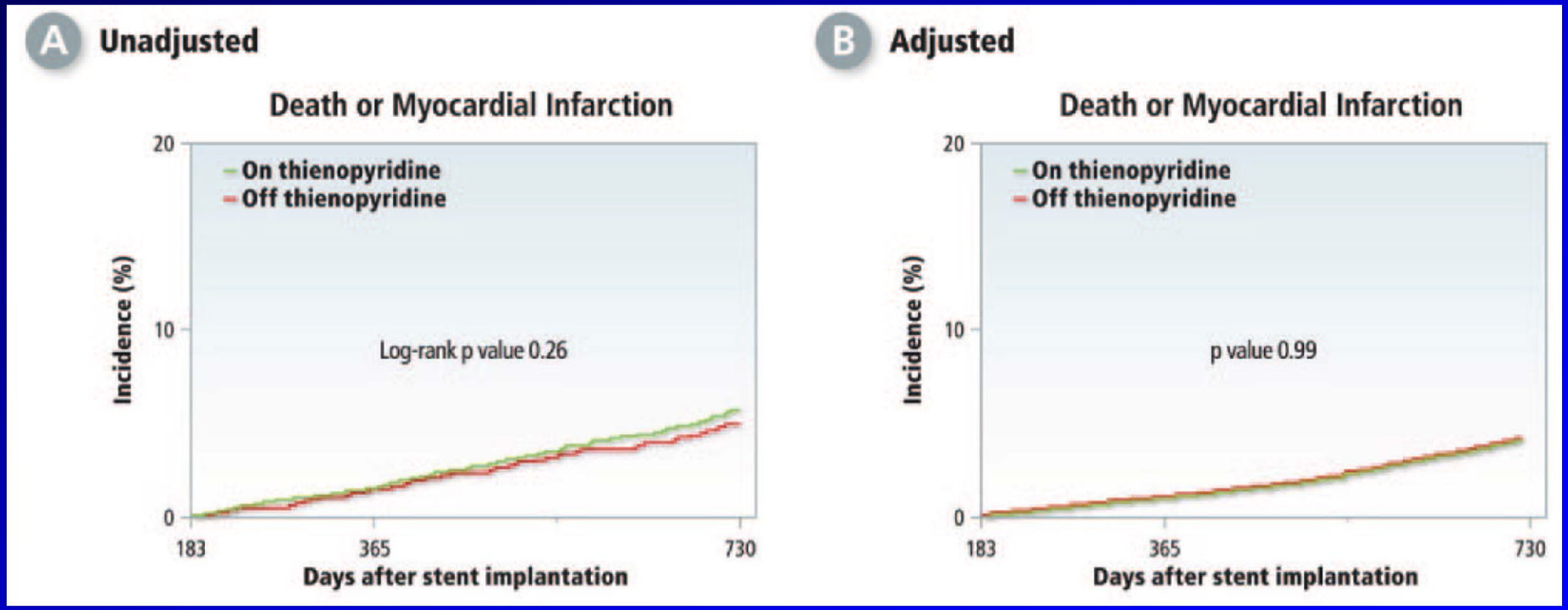




Airoldi F et al. *Circulation* 2007;116:745-54

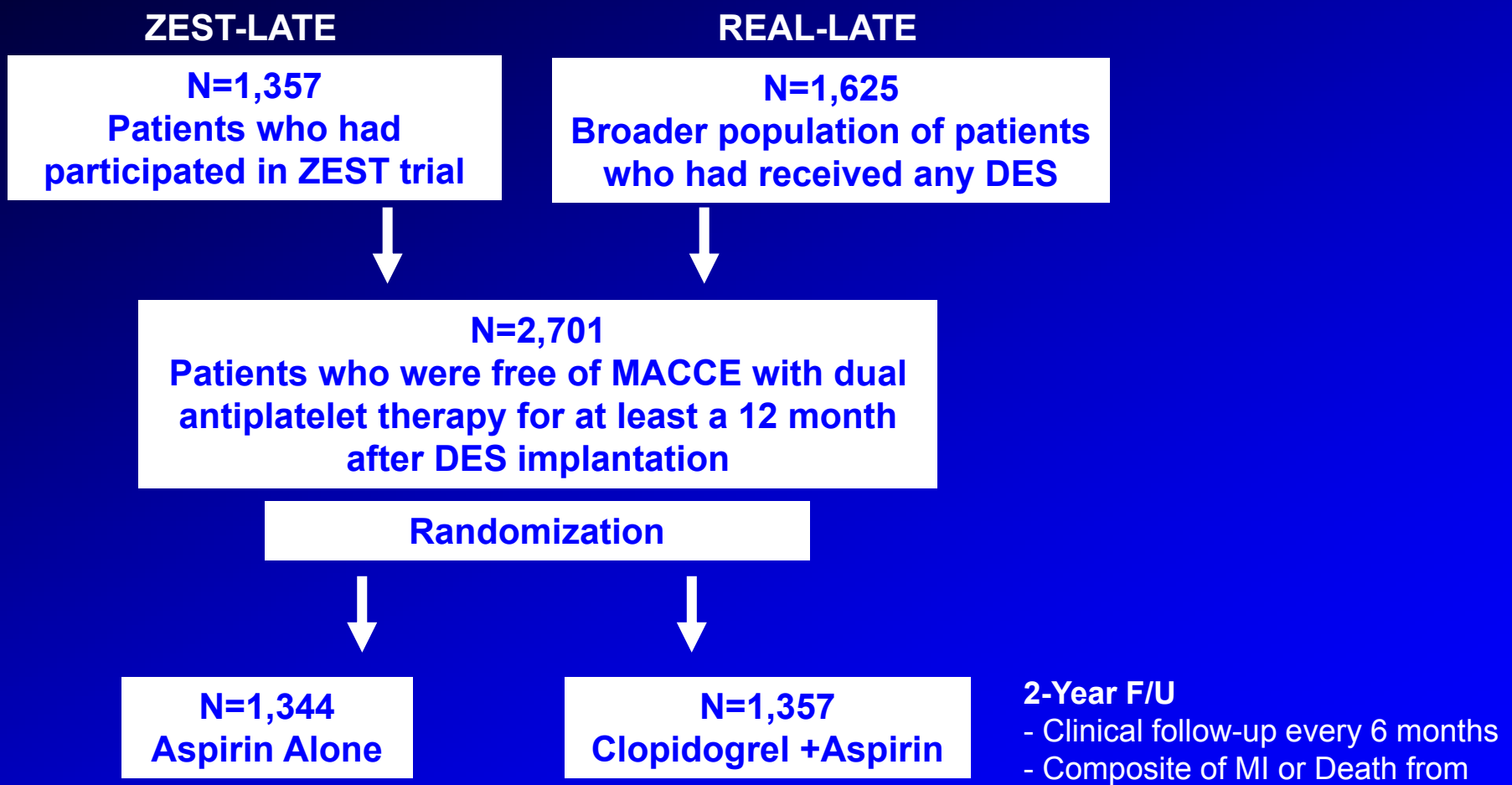
Discontinuation of Thienopyridine and Risk of Stent Thrombosis With Sirolimus-Eluting Stents

Landmark Analysis on Thienopyridine Use Beyond 6 Months



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

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

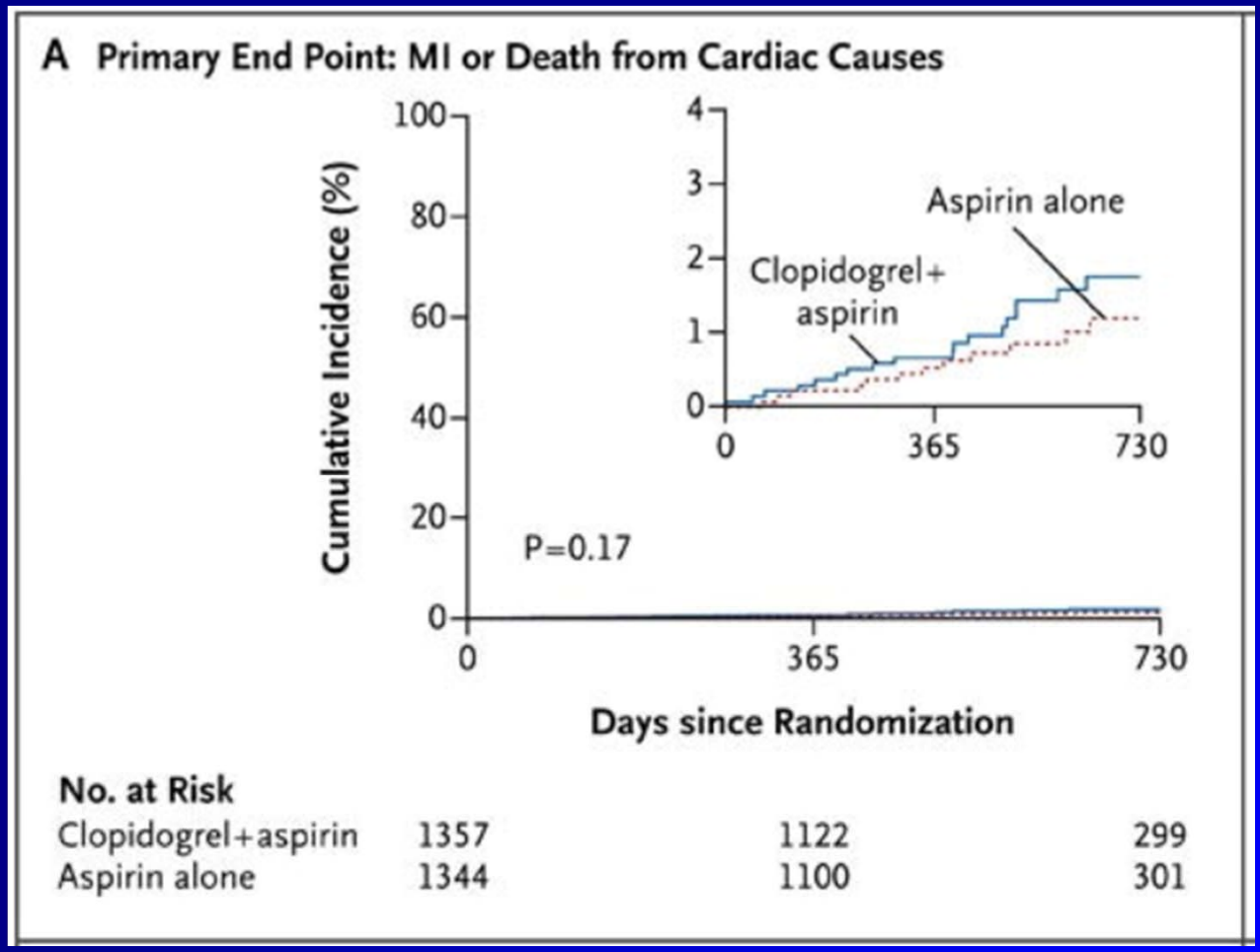


2-Year F/U
- Clinical follow-up every 6 months
- Composite of MI or Death from cardiac causes

From July 2007 through September 2008

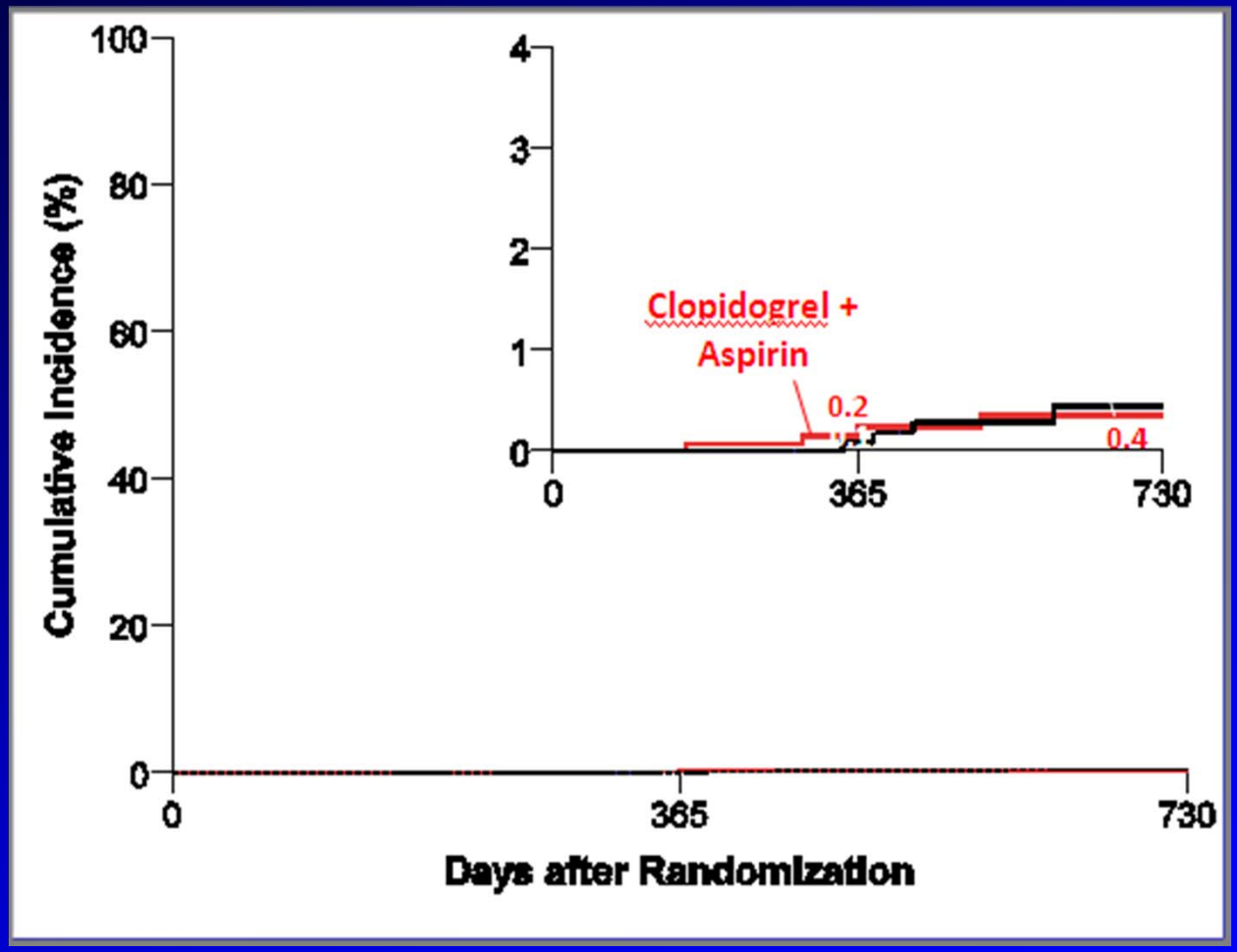
Park SJ et al. *NEJM* 2010

Primary End Point: Cardiac Death or Myocardial Infarction



Park SJ et al. *NEJM* 2010

Definite Stent Thrombosis



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

Park SJ et al. *NEJM* 2010

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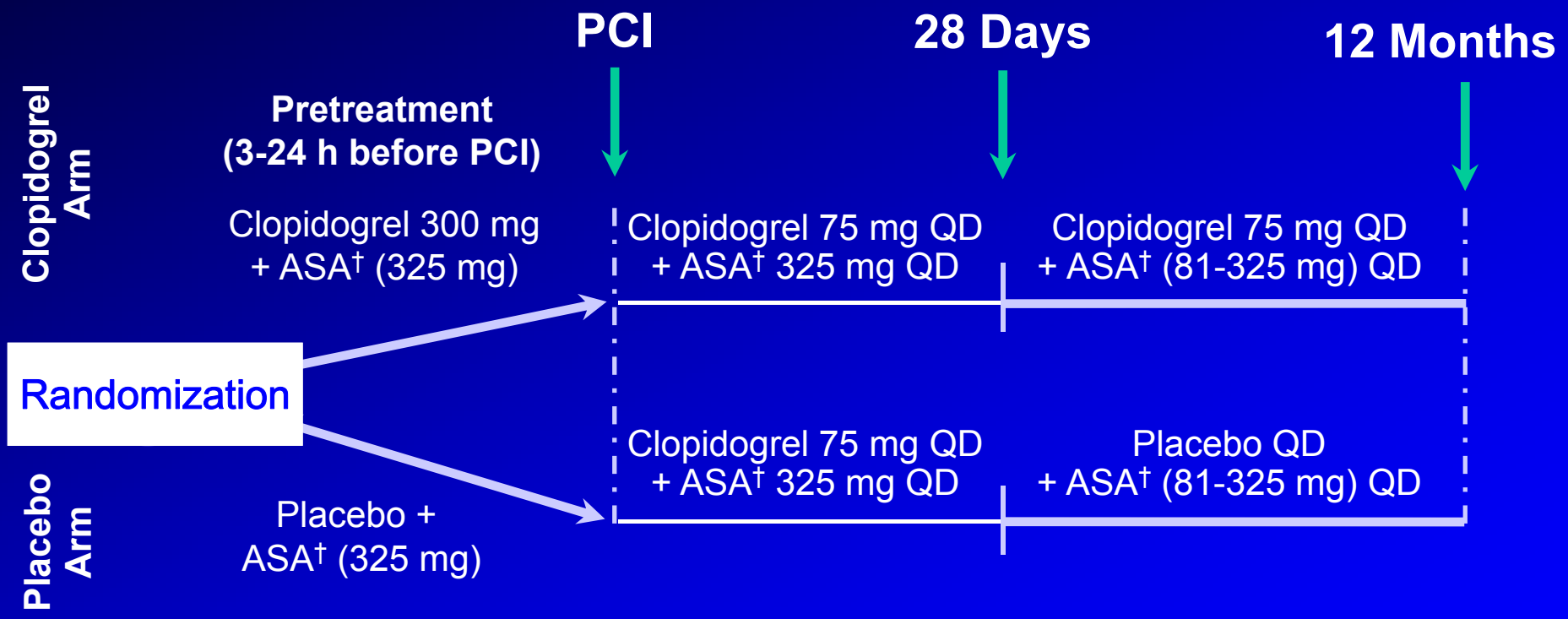
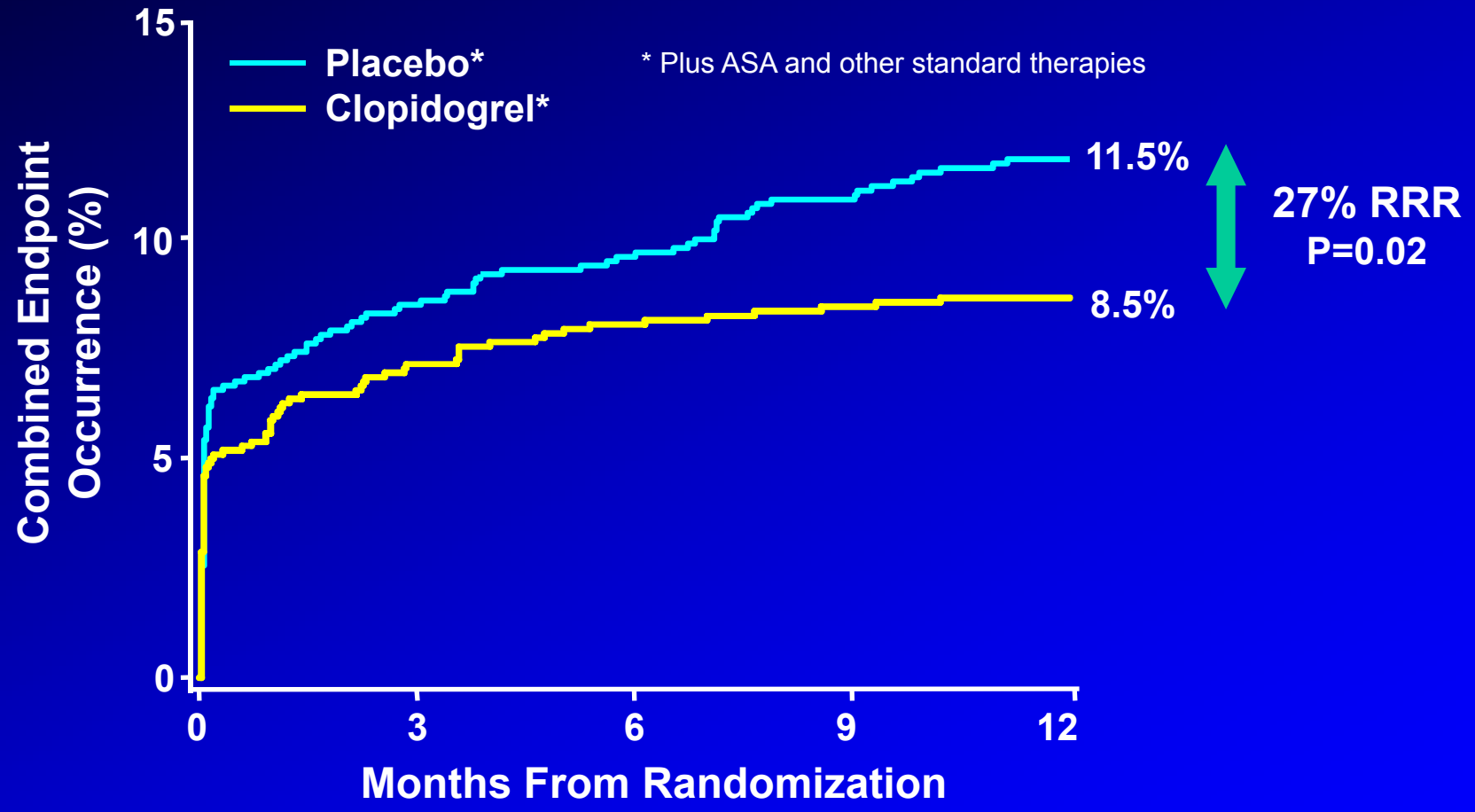
CREDO: Study Design



† Plus other standard therapies

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



MI, Stroke, or Death – ITT Population

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

CREDO: Overall Safety of DAT at 1 Year

- Major bleeding at 1 year (p=0.07)
  - 8.8% clopidogrel
  - 6.7% placebo
- Minor bleedings rates were comparable (p=0.84)
  - 5.3 % clopidogrel
  - 5.6 % placebo
- No fatal bleeds or intracranial hemorrhages

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

Benefits of Long-term DAT

1. ‘CAPRIE-like subgroup’ in CHARISMA

   DAT for 30 months is better than ASA monotherapy

2. Duke Registry

   DAT > 6 months or 12 months is better than DAT<6 months

3. Denver, Seattle, Durham, & Richmond Network Data

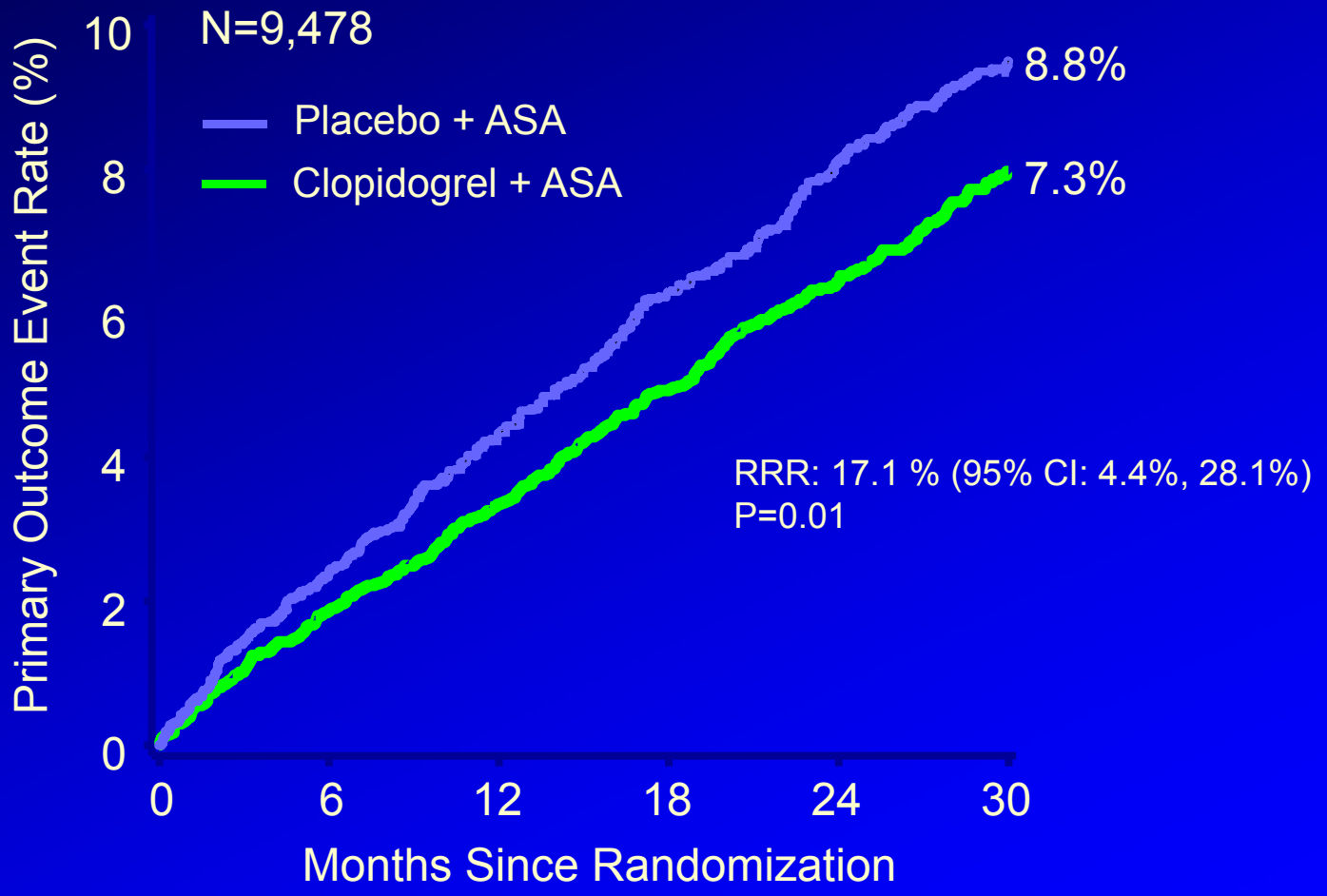
   DAT > 6 months is better than DAT <6 months

4. European data

   DAT> 1 year is better than DAT < 1 year

‘CAPRIE like’ CHARISMA in Patients With Previous MI, IS, or PAD (Post hoc analysis)

Primary Endpoint (MI/Stroke/CV Death)



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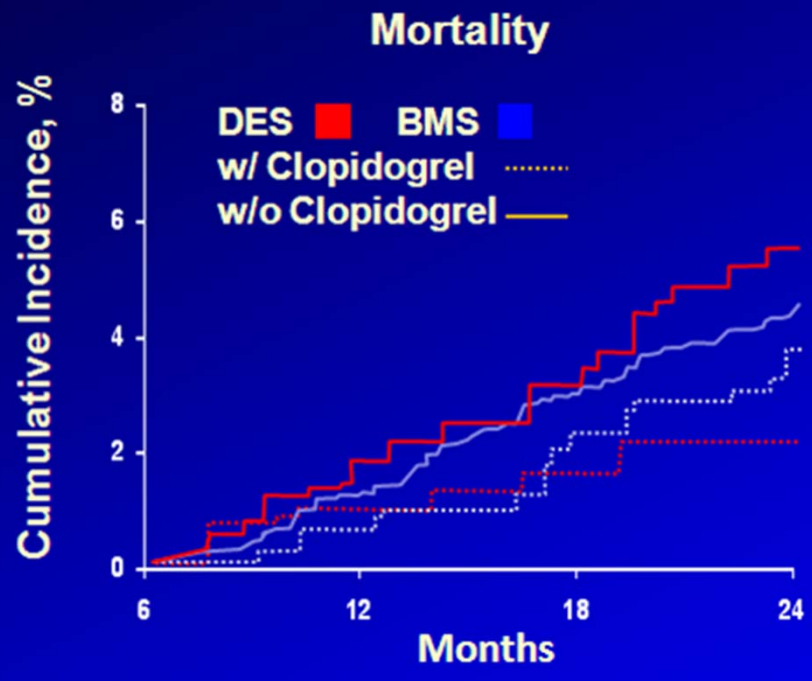
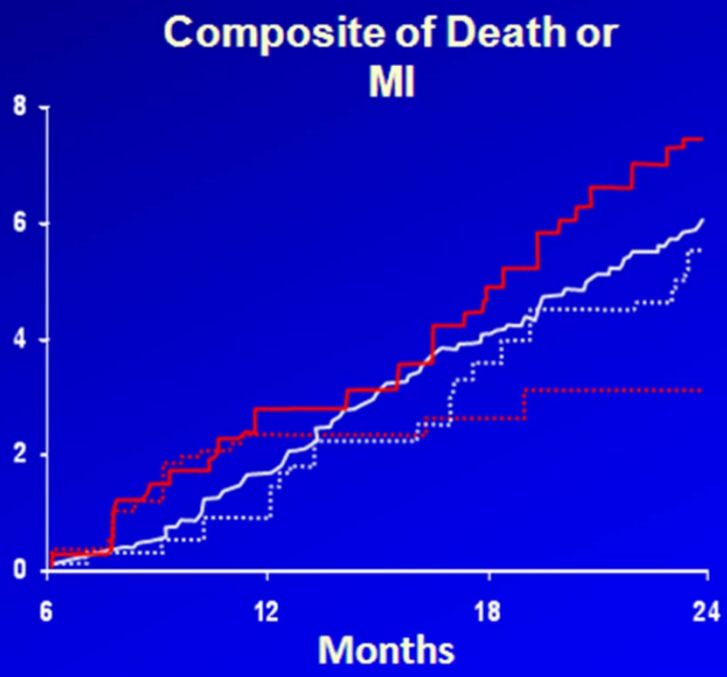
Bhatt DL, Flather MD, Hacke W, et al. J Am Coll Cardiol. 2007;49:1982-1988.

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

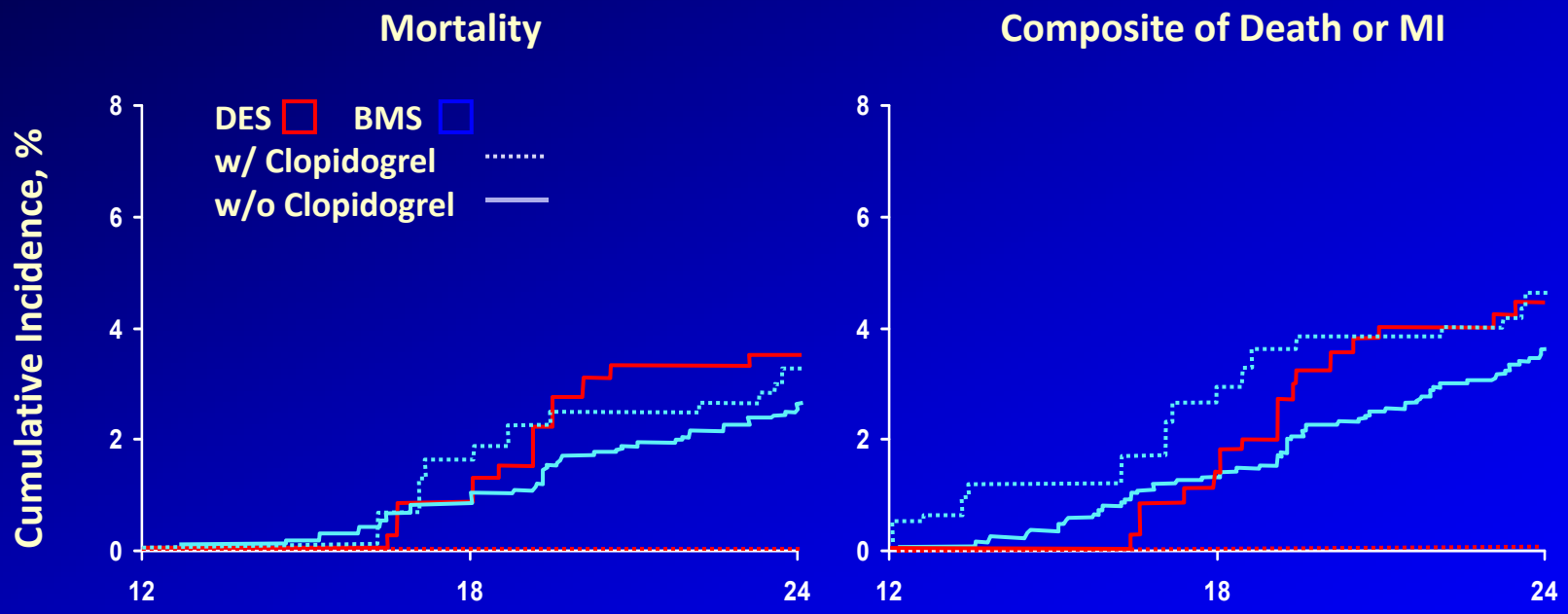




No. at Risk								
DES								
w/ Clopidogrel	637	618	303	290	637	613	300	287
w/o Clopidogrel	579	532	267	245	579	526	262	238
BMS								
w/ Clopidogrel	417	413	397	387	417	412	394	382
w/o Clopidogrel	1976	1948	1896	1852	1976	1941	1879	1825

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

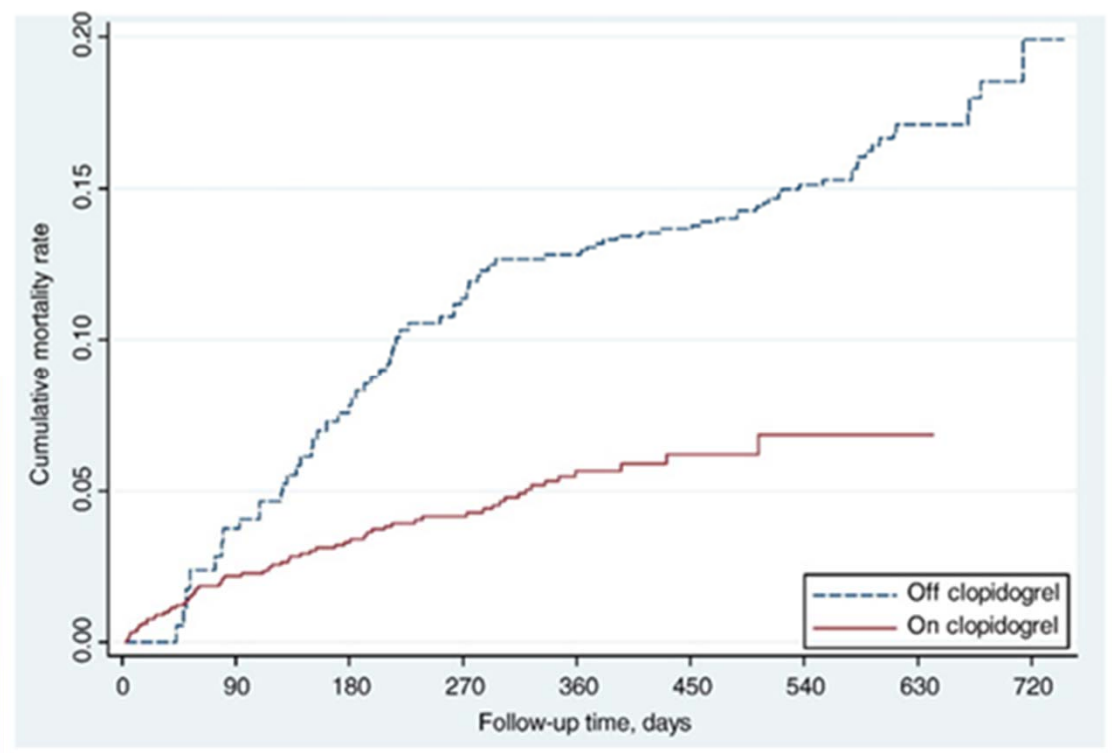
Adjusted Cumulative Mortality and MI Rates Using the 12-Month Landmark Analysis



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.

Clopidogrel and Long-Term Outcomes after Stent Implantation for Acute Coronary Syndrome

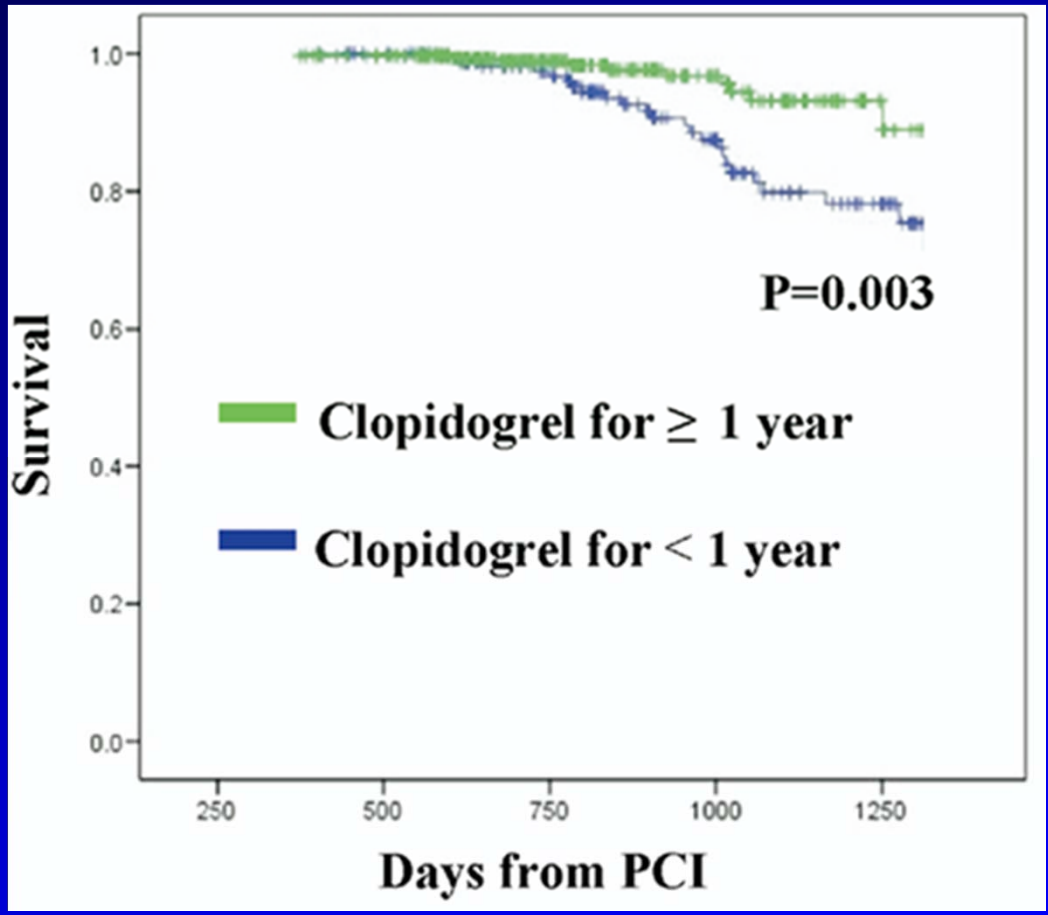


Cumulative all-cause mortality

between patients continuing and discontinuing clopidogrel

Ho PM et al. *AHJ* 2007

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



- The use of clopidogrel for ≥ 1 year after PCI was associated with lower Mortality.

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

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1. Clinical Data of long term use in dual anti-platelet therapy
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2. Answers from on-going trials for long term use?

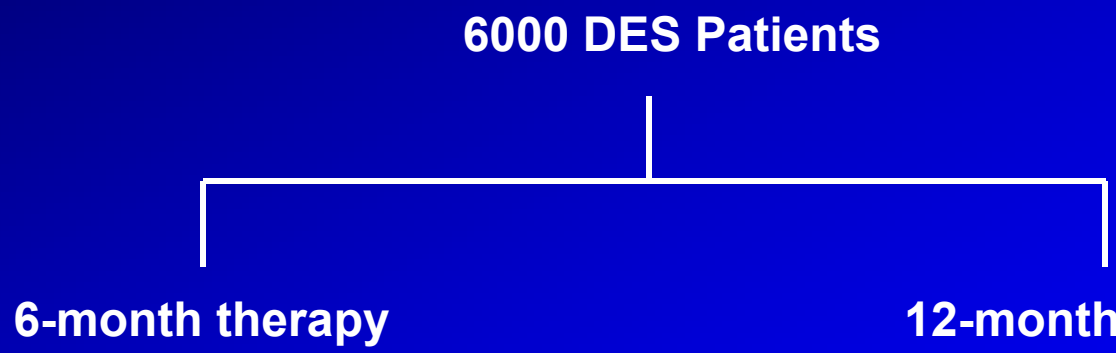
Answer of the optimal duration of DAT from on-going Trials

1. ISAR-SAFE (Germany)
2. OPTIMIZE (Brazil)
3. DAPT Trial (USA)

Optimal Duration of Clopidogrel Therapy

ISAR-SAFE

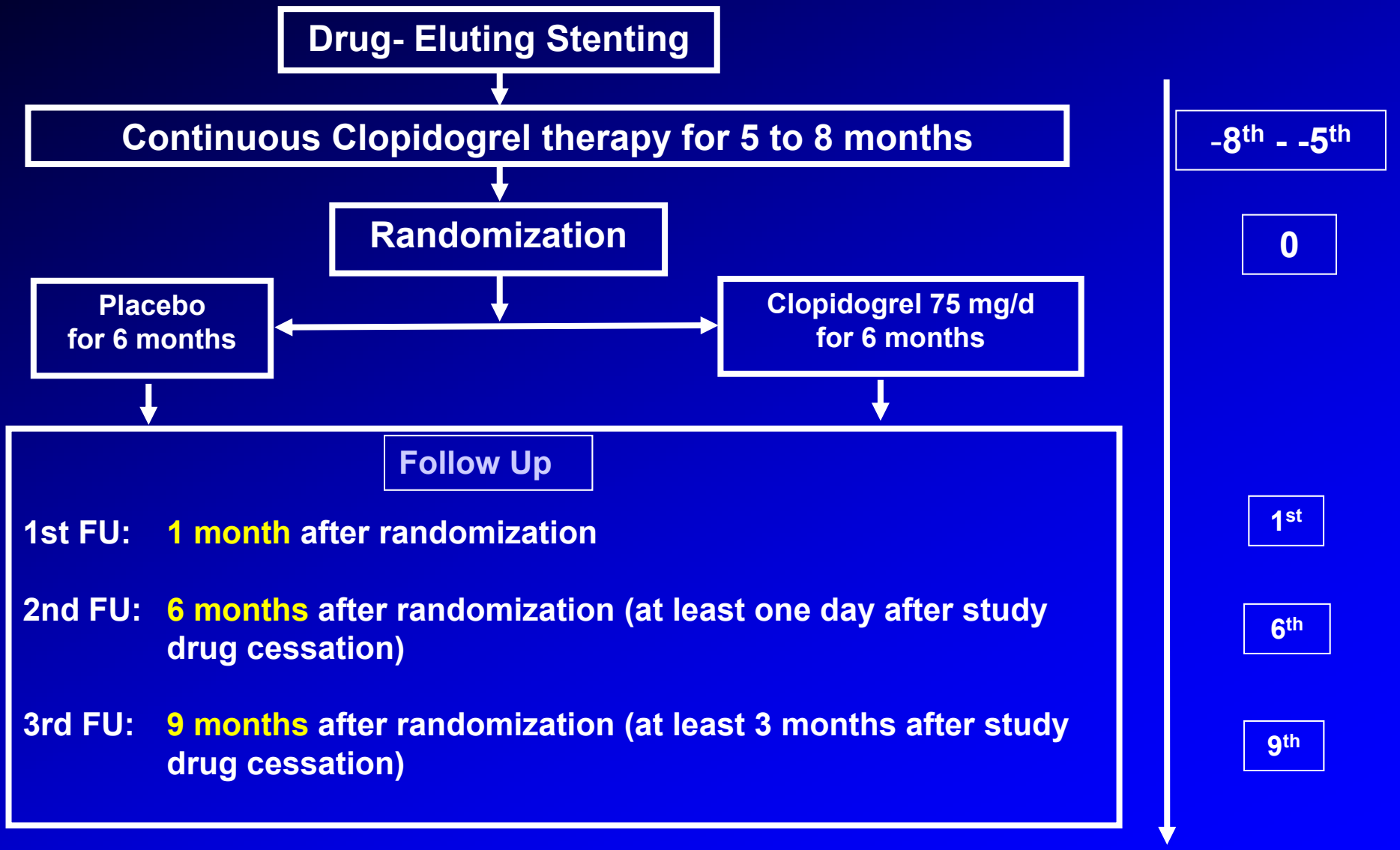
A double-blind, placebo-controlled RCT



<u>Primary end point at 15 months</u>
A composite of death, MI, stent thrombosis, stroke, major bleeding

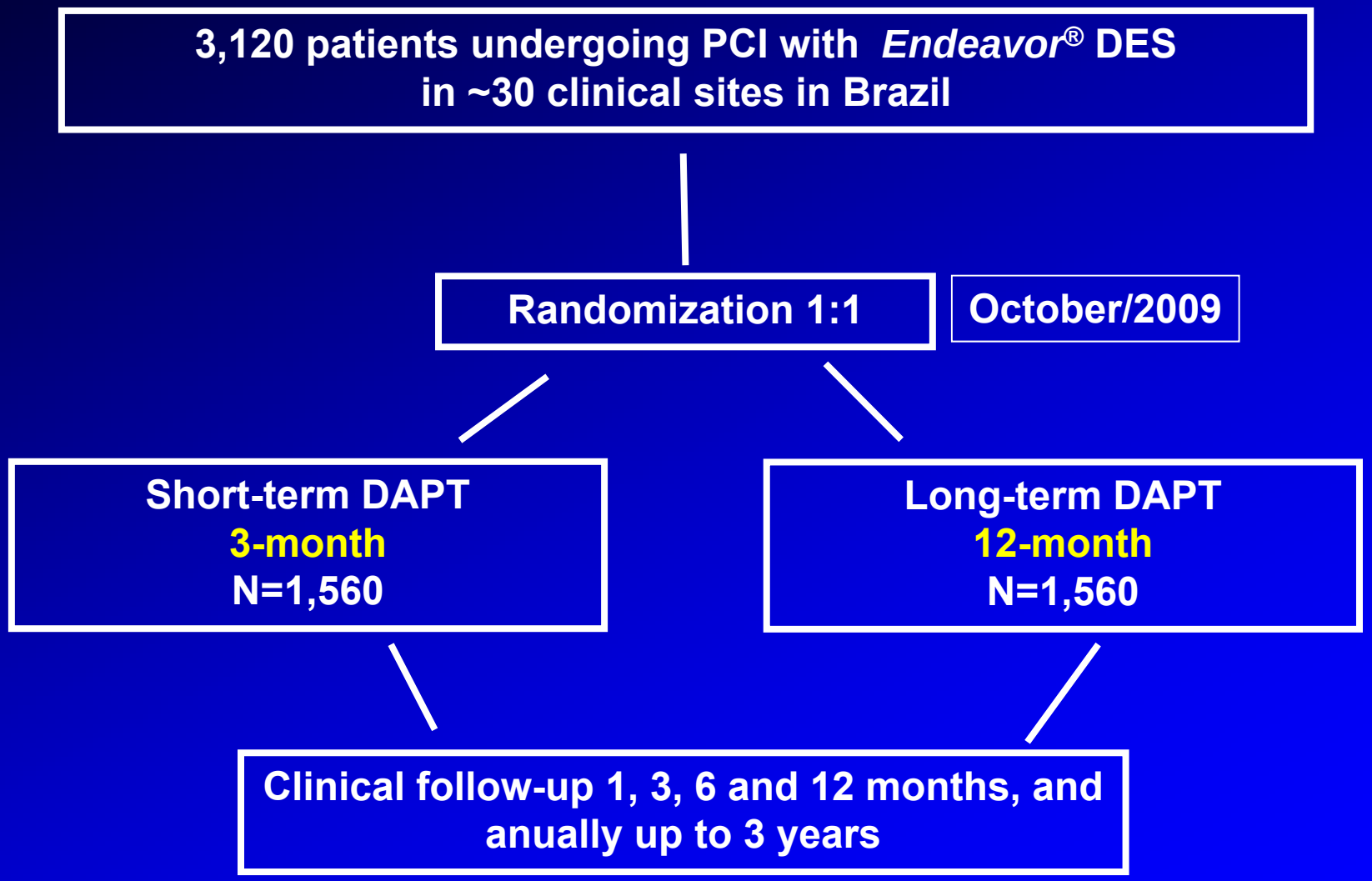
Byrne RA et al. *Am Heart J.* 2009 Apr;157(4):620-4.

ISAR-SAFE

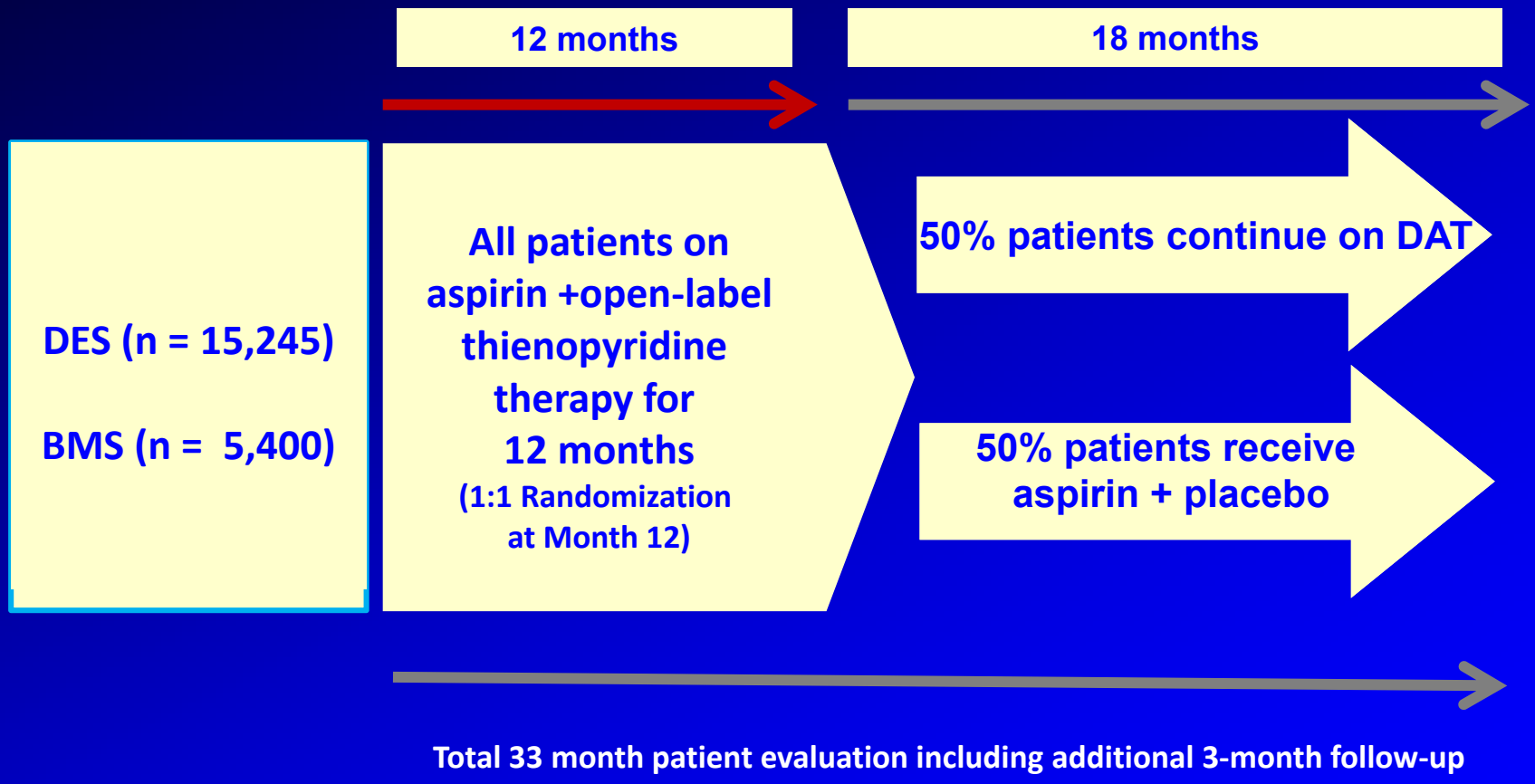


Byrne RA et al. *Am Heart J.* 2009 Apr;157(4):620-4.

OPTIMIZE Randomized Trial



Dual Antiplatelet Therapy (DAPT) Study



Optimal duration of DAT

1. Several on-going studies may give us the answers to questions that “long term DAT would be clinically better than short term DAT?”
2. It might be too early to say that 1 year of DAT is enough for all patients post-PCI till we have more evidence.
3. Patient-based approach would be ideal !

   “Long-term DAT would be reasonable for high risk patients with previous ST, AMI, DM, and Bifurcation multi-stenting.”

Optimal Dose of Antiplatelet Therapy after PCI

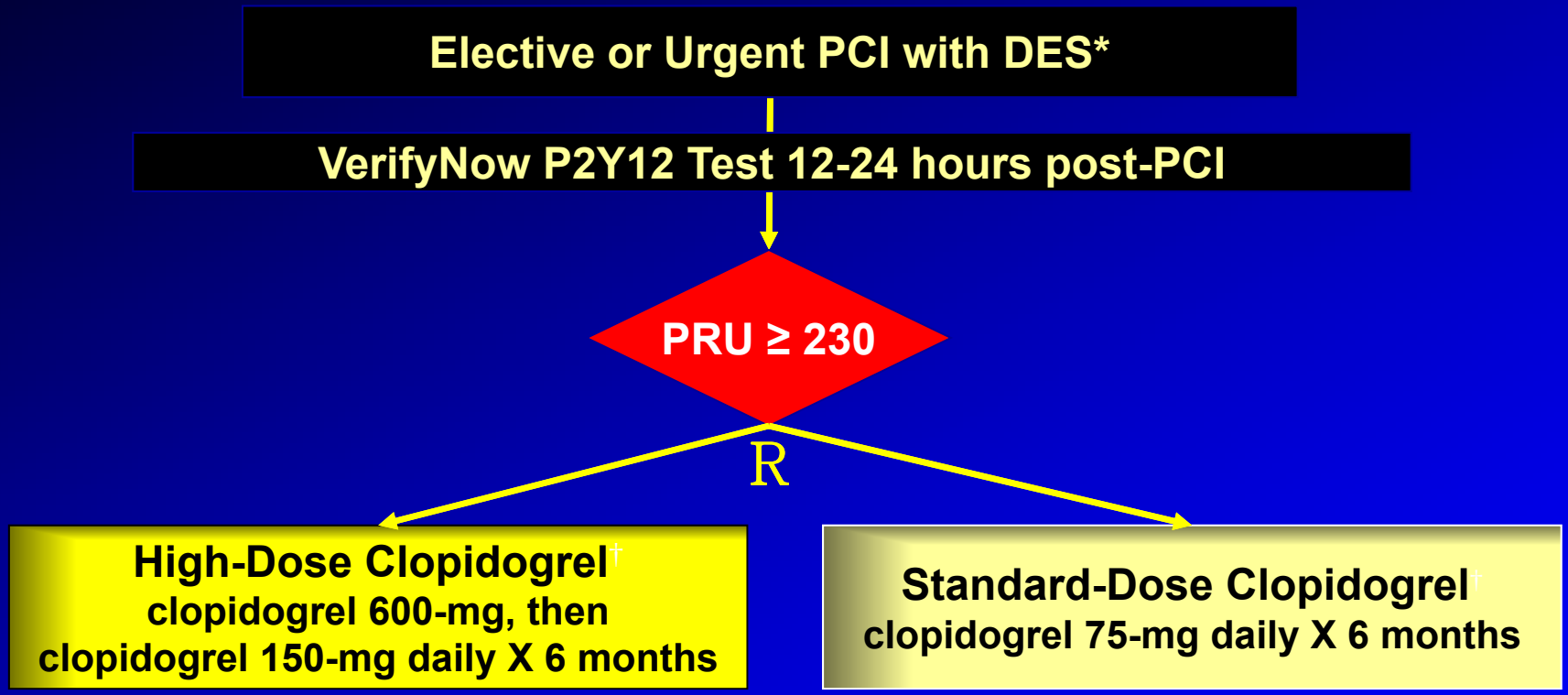
Primary Results of The Gauging Responsiveness with A VerifyNow Assay - Impact on Thrombosis And Safety Trial

GRAVITAS

AHA 2010

Matthew J. Price, MD
On behalf of the GRAVITAS Investigators

GRAVITAS Study Design

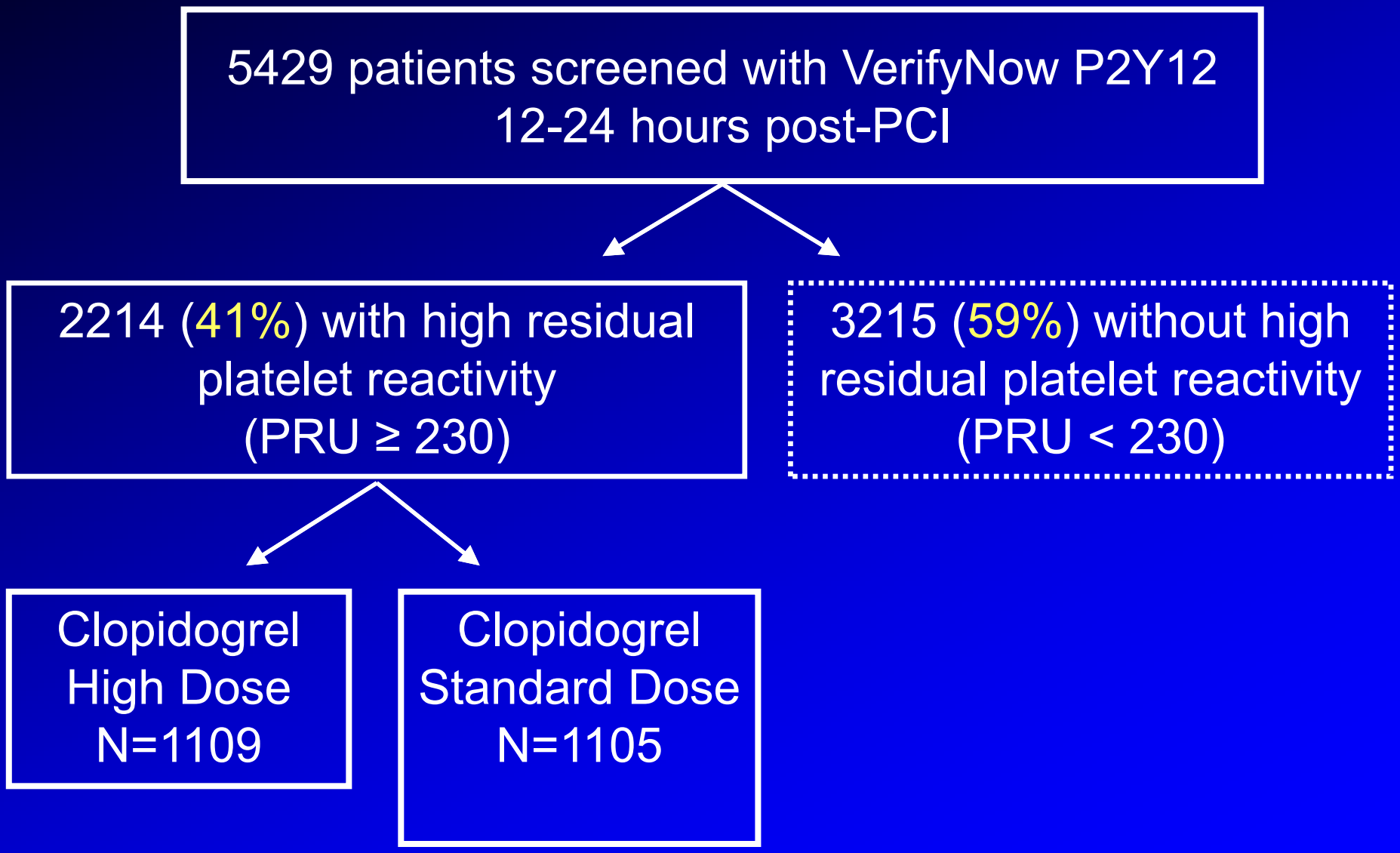


Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
Key Safety Endpoint: GUSTO Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

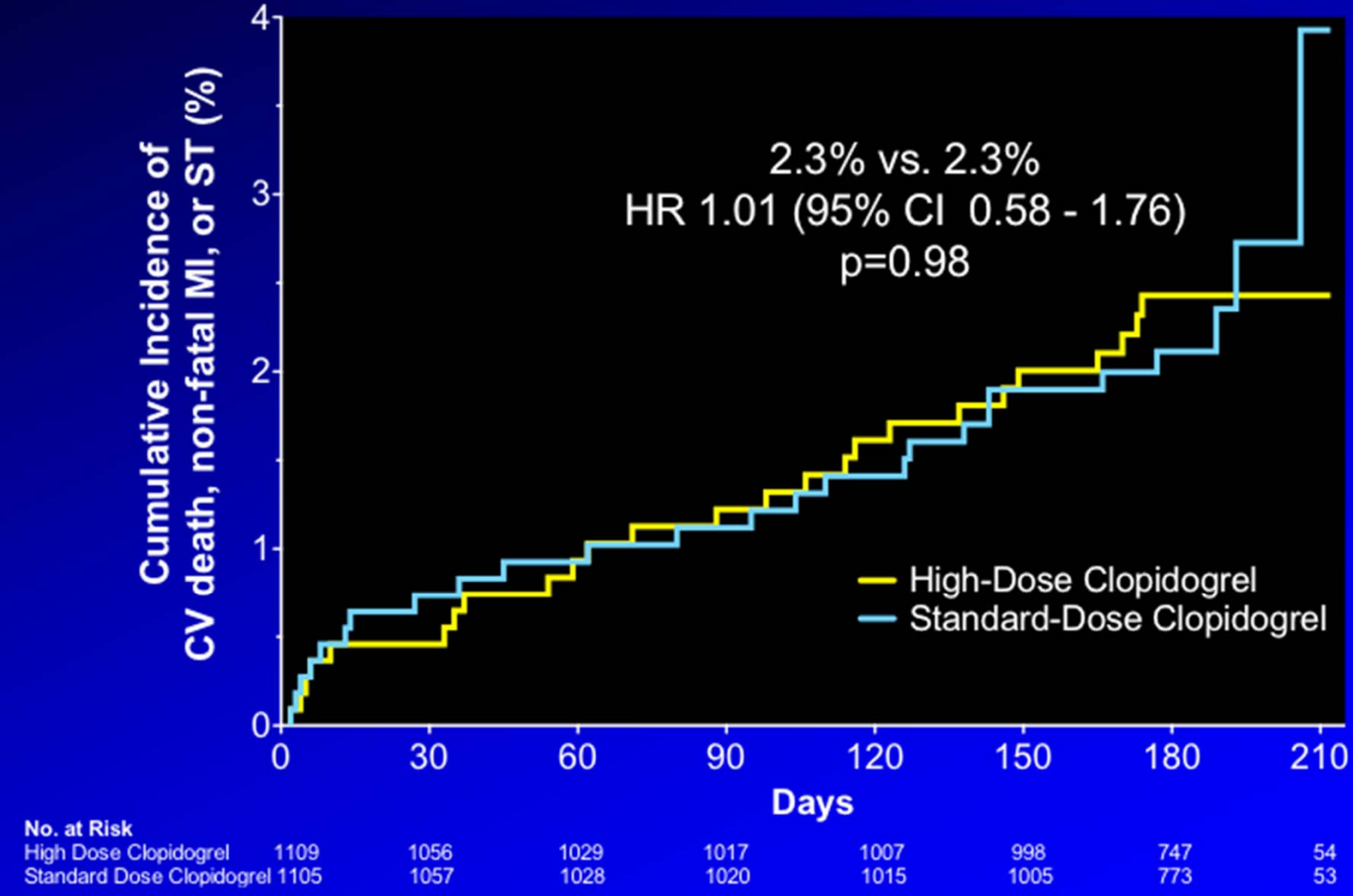
*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled All patients received aspirin (81-162mg daily)

GRAVITAS Patient Flow



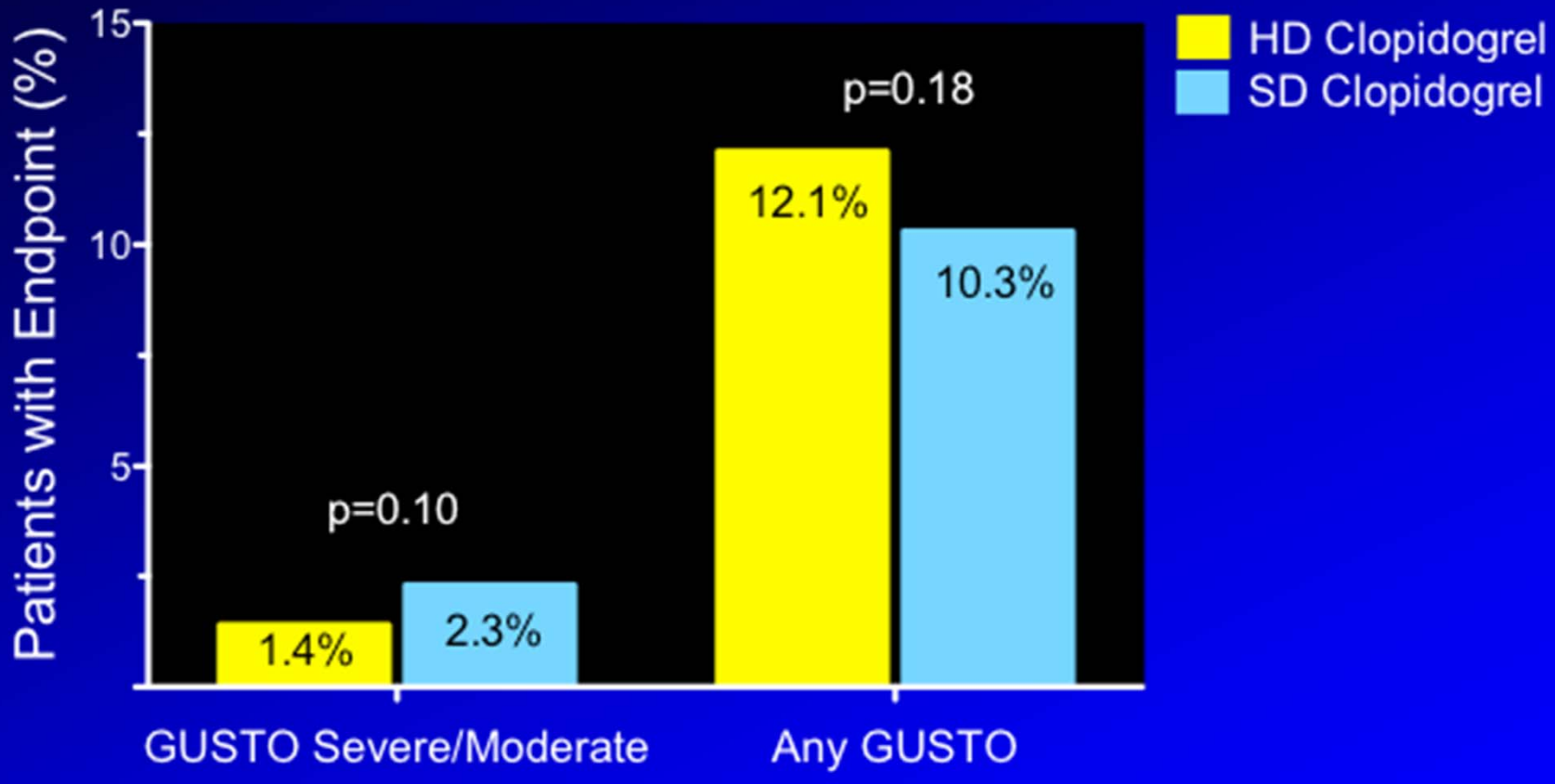
Primary Endpoint: CV Death, MI, Stent Thrombosis



No. at Risk								
High Dose Clopidogrel	1109	1056	1029	1017	1007	998	747	54
Standard Dose Clopidogrel	1105	1057	1028	1020	1015	1005	773	53

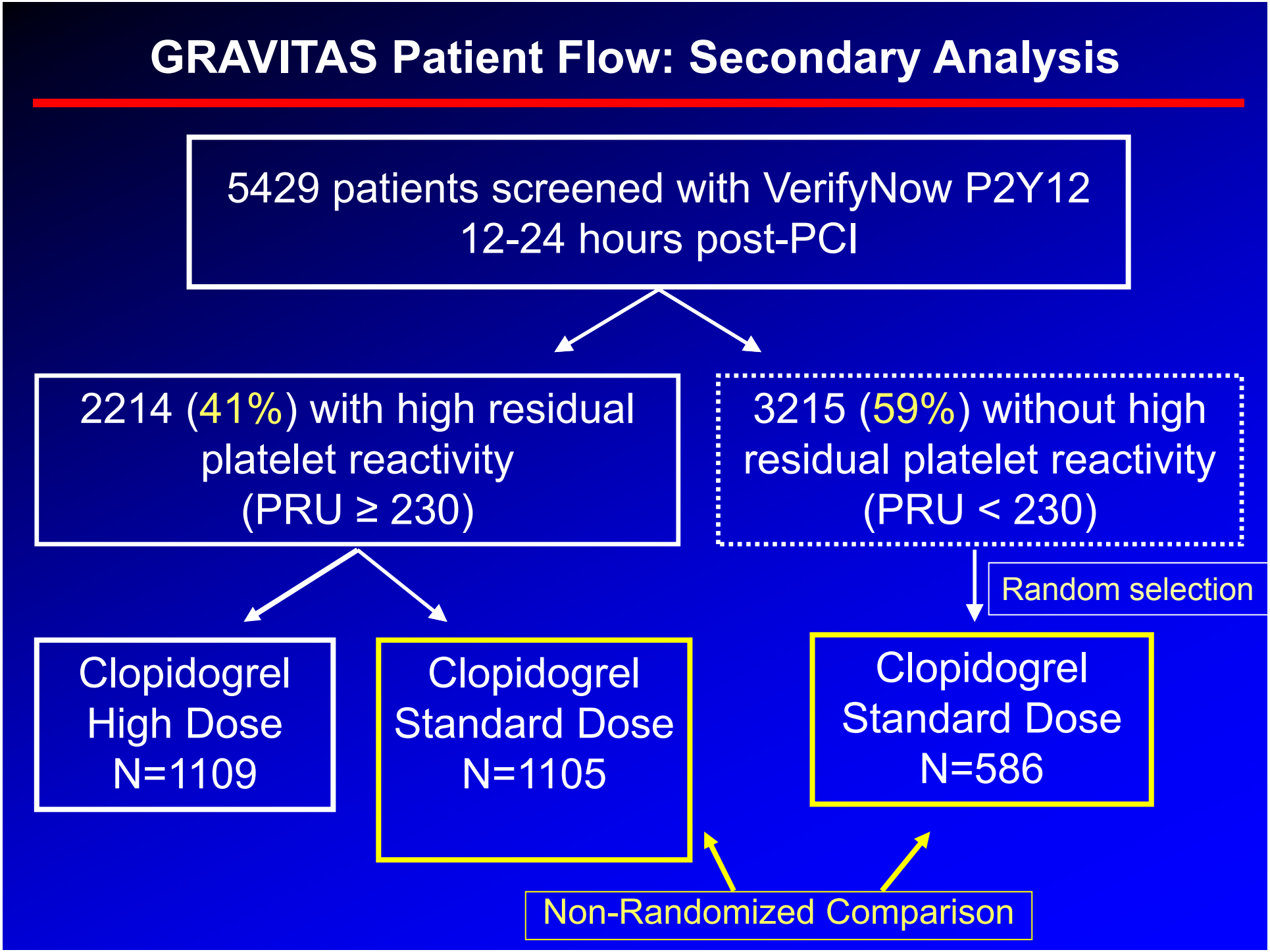
Observed event rates are listed; P value by log rank test.

Bleeding Events: Safety Population

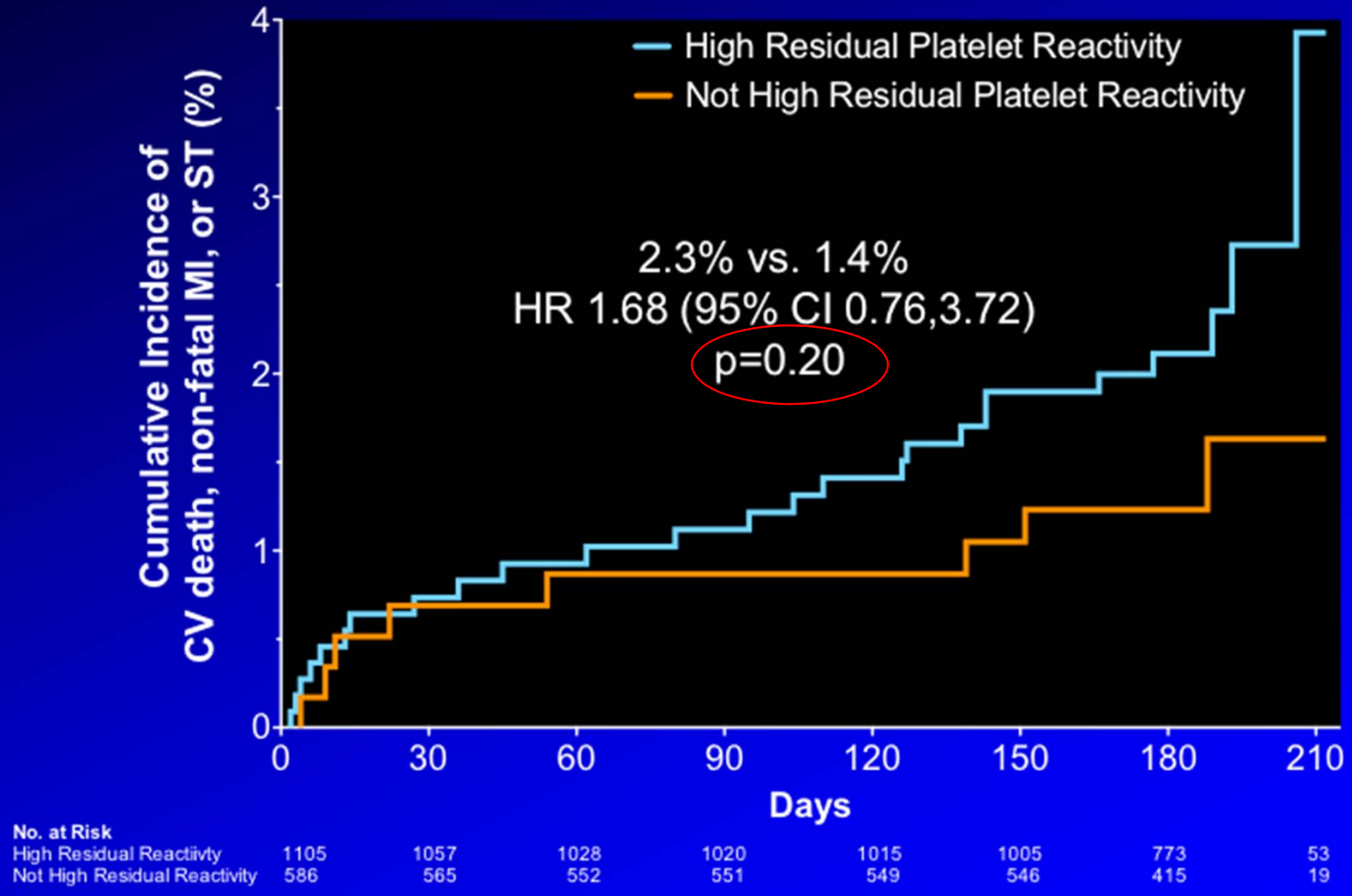


Severe or life-threatening: Fatal bleeding, intracranial hemorrhage, or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention
Moderate: Bleeding that leads to transfusion but does not meet criteria for severe bleeding

GRAVITAS Patient Flow: Secondary Analysis

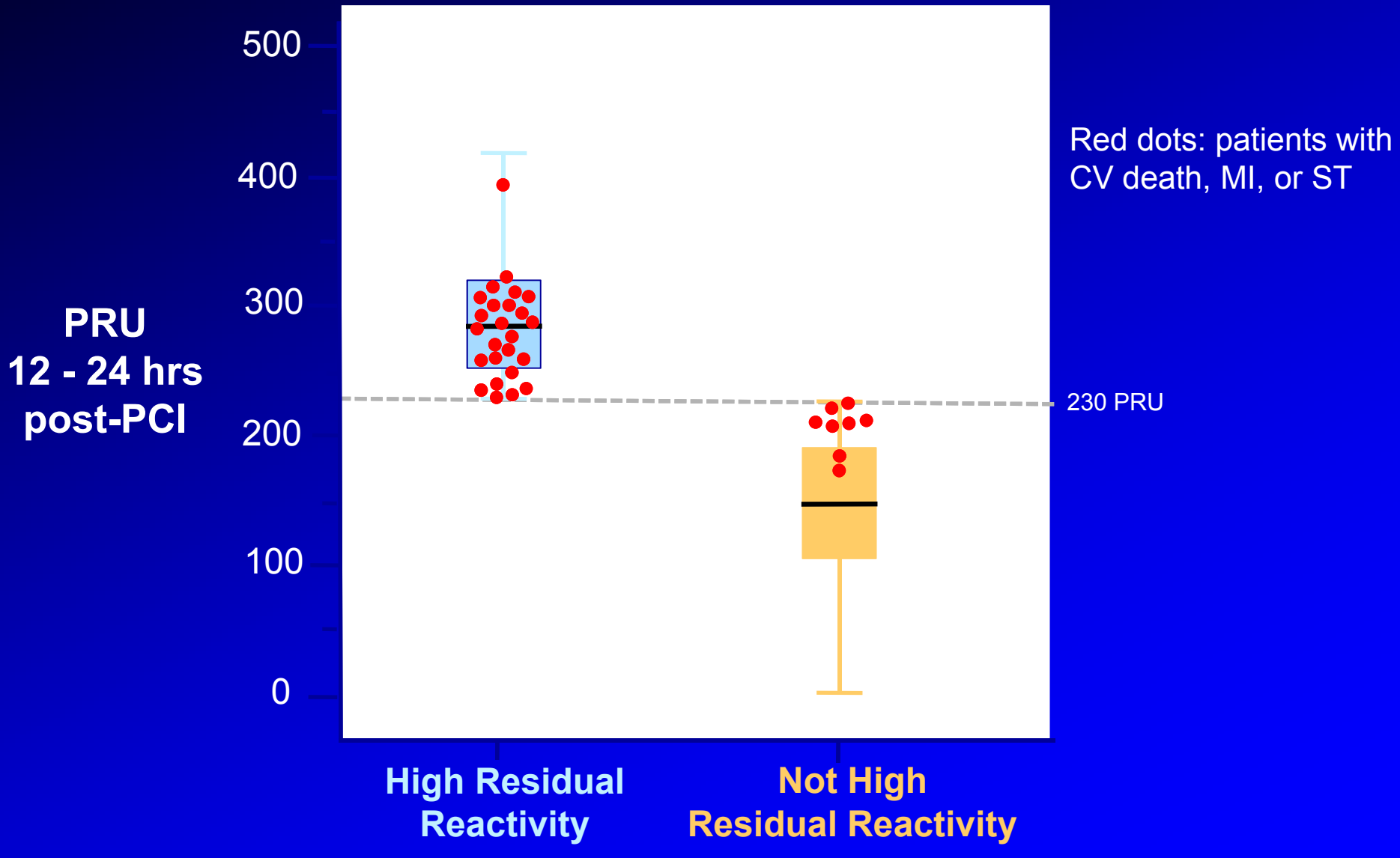


Secondary Comparison: High vs. Not High Reactivity Treated with Clopidogrel 75-mg daily



Observed event rates are listed. P value by log-rank test.

CV Events and Post-PCI PRU In Patients With High and Not High Reactivity Treated With Clopidogrel 75-mg Daily



ITT population

GRAVITAS: Summary

- In patients with high residual reactivity measured after PCI, 6-months of high-dose clopidogrel did not reduce the rate of cardiovascular death, non-fatal MI, or stent thrombosis and did not increase GUSTO severe or moderate bleeding.

- **GRAVITAS** does not support a treatment strategy of high-dose clopidogrel in patients with high residual reactivity identified by a single platelet function test after PCI.

CURRENT

OASIS-7

CURRENT OASIS 7: A 2X2 Factorial Randomized Trial of Optimal Clopidogrel and Aspirin Dosing in Patients with ACS Undergoing an Early Invasive Strategy with Intent For PCI

Shamir R. Mehta on behalf of the CURRENT Investigators

Disclosures: CURRENT OASIS 7 was funded by a grant from sanofi-aventis and Bristol Myers Squibb. All data were managed independently of the sponsor at the PHRI, McMaster University and the trial was overseen by an international steering committee of experts.

Study Design

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ Planned Early (<24 h) Invasive Management with **intended PCI**
- ✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 7d then 75 mg/d) **vs**

Standard dose (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)

Angio 24,769 (99%)

PCI 17,232 (70%)

No PCI 7,855 (30%)

No Sig. CAD 3,616

CABG 1,809

CAD 2,430

Compliance:

Clop in 1st 7d (median) 7d | **7 d** | **2 d** | **7d**

Efficacy Outcomes: CV Death, MI or stroke at day 30
Stent Thrombosis at day 30

Safety Outcomes: Bleeding (CURRENT defined Major/Severe and TIMI Major)

Key Subgroup: PCI v No PCI

Complete F/U 99.8%

ASA Dose Comparison

Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	**4.2**	**4.1**	**0.98**	**0.84-1.13**	**0.76**
No PCI (2N=7855)	**4.7**	**4.4**	**0.92**	**0.75-1.14**	**0.44**
Overall (2N=25,087)	**4.4**	**4.2**	**0.96**	**0.85-1.08**	**0.47**
Stent Thrombosis	**2.1**	**1.9**	**0.91**	**0.73-1.12**	**0.37**
TIMI Major Bleed	**1.03**	**0.97**	**0.94**	**0.73-1.21**	**0.71**
CURRENT Major Bleed	**2.3**	**2.3**	**0.99**	**0.84-1.17**	**0.90**
CURRENT Severe Bleed	**1.7**	**1.7**	**1.00**	**0.83-1.21**	**1.00**

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups

Clopidogrel Dose Comparison

2 Significant Interactions:

1. PCI v No PCI (P=0.016)
2. ASA dose (P=0.043)

Clopidogrel: Double vs Standard Dose Primary Outcome and Components

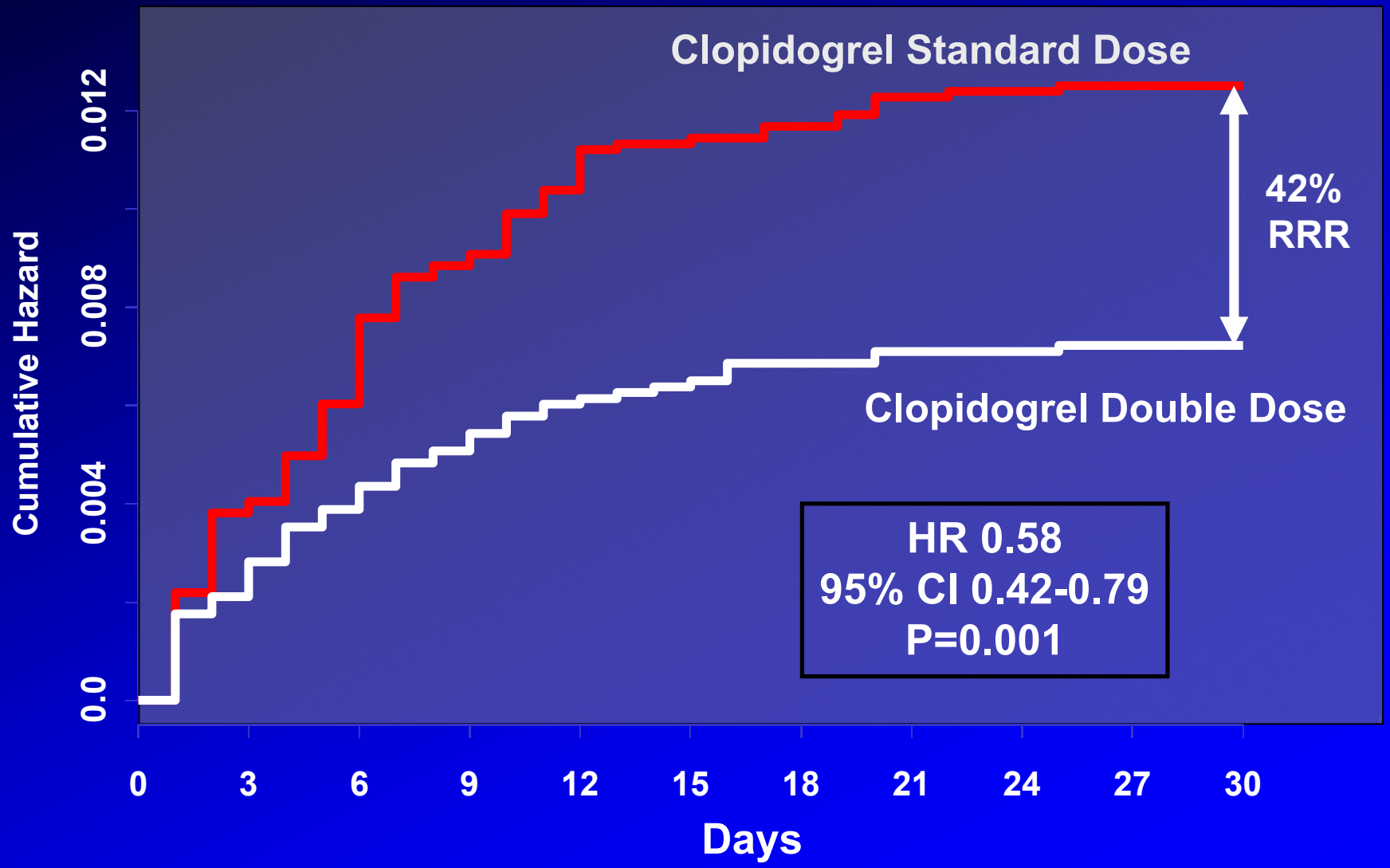
	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	**4.5**	**3.9**	**0.85**	**0.74-0.99**	**0.036**	**0.016**
No PCI (2N=7855)	**4.2**	**4.9**	**1.17**	**0.95-1.44**	**0.14**	
Overall (2N=25,087)	**4.4**	**4.2**	**0.95**	**0.84-1.07**	**0.370**	
MI						
PCI (2N=17,232)	**2.6**	**2.0**	**0.78**	**0.64-0.95**	**0.012**	**0.025**
No PCI (2N=7855)	**1.4**	**1.7**	**1.25**	**0.87-1.79**	**0.23**	
Overall (2N=25,087)	**2.2**	**1.9**	**0.86**	**0.73-1.03**	**0.097**	
CV Death						
PCI (2N=17,232)	**1.9**	**1.9**	**0.96**	**0.77-1.19**	**0.68**	**1.0**
No PCI (2N=7855)	**2.8**	**2.7**	**0.96**	**0.74-1.26**	**0.77**	
Overall (2N=25,087)	**2.2**	**2.1**	**0.96**	**0.81-1.14**	**0.628**	
Stroke						
PCI (2N=17,232)	**0.4**	**0.4**	**0.88**	**0.55-1.41**	**0.59**	**0.50**
No PCI (2N=7855)	**0.8**	**0.9**	**1.11**	**0.68-1.82**	**0.67**	
Overall (2N=25,087)	**0.5**	**0.5**	**0.99**	**0.70-1.39**	**0.950**	

Clopidogrel Double vs Standard Dose Bleeding Overall Population

	Clopidogrel				
	Standard N=12579	Double N=12508	Hazard Ratio	95% CI	P
TIMI Major[1]	**0.95**	**1.04**	**1.09**	**0.85-1.40**	**0.50**
CURRENT Major[2]	**2.0**	**2.5**	**1.25**	**1.05-1.47**	**0.01**
CURRENT Severe[3]	**1.5**	**1.9**	**1.23**	**1.02-1.49**	**0.03**
Fatal	**0.11**	**0.13**	**1.15**	**0.56-2.35**	**0.71**
ICH	**0.05**	**0.03**	**0.67**	**0.19-2.37**	**0.53**
RBC transfusion ≥ 2U	**1.76**	**2.21**	**1.26**	**1.06-1.51**	**0.01**
CABG-related Major	**0.9**	**1.0**	**1.10**	**0.85-1.42**	**0.48**

[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units

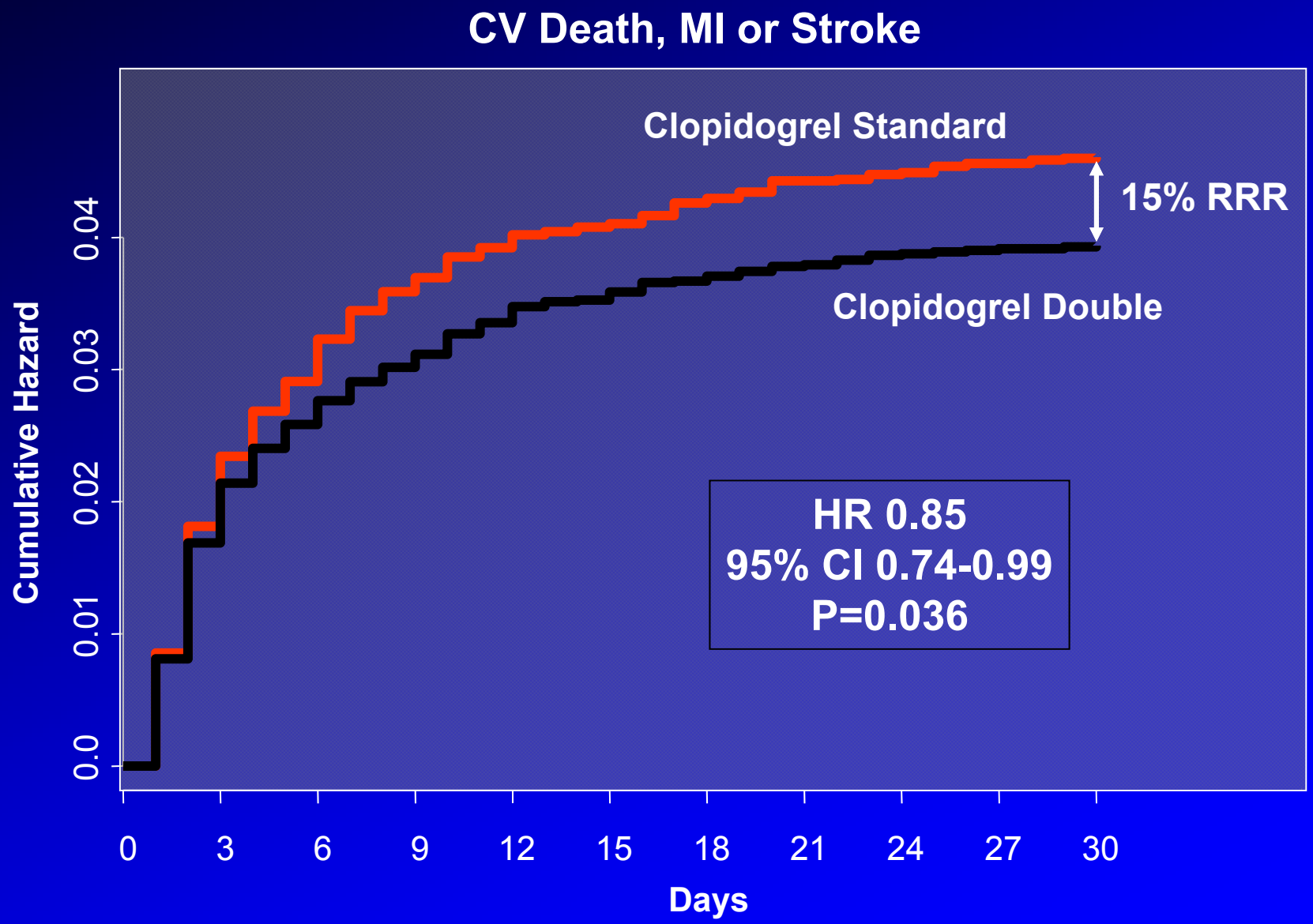
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)



Clopidogrel: Double vs Standard Dose Major Efficacy Outcomes in PCI Patients

Day 30	Clopidogrel				
	Standard N=8684 %	Double N=8548 %	Hazard Ratio	95% CI	P value
Stent Thrombosis	**2.3**	**1.6**	**0.71**	**0.57-0.89**	**0.002**
Definite	**1.2**	**0.7**	**0.58**	**0.42-0.79**	**0.001**
MI	**2.6**	**2.0**	**0.78**	**0.64-0.95**	**0.012**
MI or stent thrombosis	**3.7**	**3.0**	**0.80**	**0.68-0.94**	**0.008**
CV Death	**1.9**	**1.9**	**0.96**	**0.77-1.19**	**0.68**
Stroke	**0.4**	**0.4**	**0.88**	**0.55-1.41**	**0.59**
CV Death/MI/Stroke	**4.5**	**3.9**	**0.85**	**0.74-0.99**	**0.036**

Clopidogrel: Double vs Standard Dose
Primary Outcome in PCI Patients



Clopidogrel Double vs Standard Dose Bleeding in PCI Population

	Clopidogrel				
	Standard N= 8684	Double N=8548	Hazard Ratio	95% CI	P
TIMI Major[1]	**0.5**	**0.5**	**1.06**	**0.70-1.61**	**0.79**
CURRENT Major[2]	**1.1**	**1.6**	**1.44**	**1.11-1.86**	**0.006**
CURRENT Severe[3]	**0.8**	**1.1**	**1.39**	**1.02-1.90**	**0.034**
Fatal	**0.15**	**0.07**	**0.47**	**0.18-1.23**	**0.125**
ICH	**0.035**	**0.046**	**1.35**	**0.30-6.04**	**0.69**
RBC transfusion ≥ 2U	**0.91**	**1.35**	**1.49**	**1.11-1.98**	**0.007**
CABG-related Major	**0.1**	**0.1**	**1.69**	**0.61-4.7**	**0.31**

[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units

CURRENT

Conclusions
Clopidogrel Dose Comparison

- Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI or stroke) in PCI.
- In patients not undergoing PCI, double dose clopidogrel was not significantly different from standard dose (70% had no significant CAD or stopped study drug early for CABG).
- There was a modest excess in CURRENT-defined major bleeds but no difference in TIMI major bleeds, ICH, fatal bleeds or CABG-related bleeds.

Conclusions
ASA Dose Comparison

- No significant difference in efficacy or bleeding between ASA 300-325 mg and ASA 75-100 mg.

Clopidogrel optimal dose

- Due to difference in design, patient populations, length of treatment and follow-up of these clinical studies, it is not appropriate to make cross-trial comparisons but these clinical studies enable cardiologists to have more scientific discussion about the issue of optimal Clopidogrel regimen.


Thank you
for your attention !