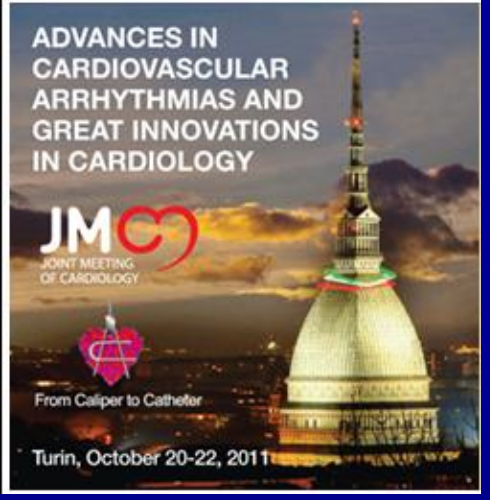

Advances in Cardiovascular Arrhythmias and Great Innovations in Cardiology: PCI UPDATE

Pharmacological management of the stented patient

Leonardo Bolognese
Cardiovascular Department, Arezzo, Italy

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We need a safer ~~DES~~ Life!

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Managing and Resolving the Dual Antiplatelet Conundrum in DES Patients

- Optimal duration of DAPT
- Individual response variability
- Potential drug-interactions
- Managing DAPT in pts undergoing surgical procedures

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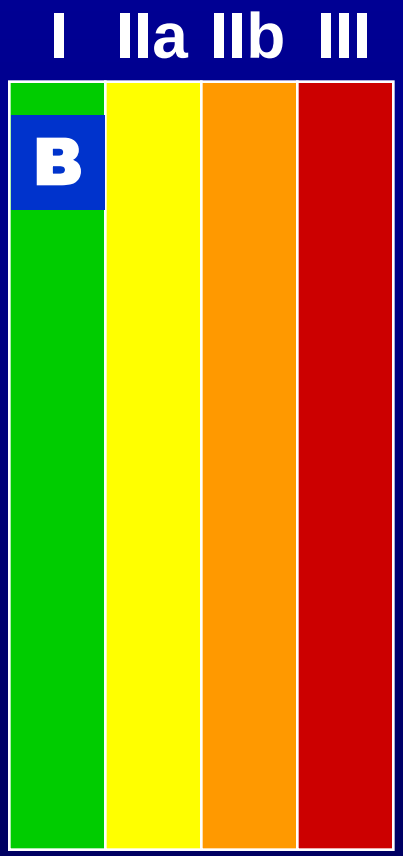
2007 Update of the ACC/AHA/SCAI 2005 Guidelines Update for PCI

Oral Antiplatelet Adjunctive Therapies



For all post-PCI 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).

J Am Coll Cardiol 2008; 51:172

2007 Update of the ACC/AHA/SCAI 2005 Guidelines Update for PCI

Oral Antiplatelet Adjunctive Therapies

Continuation of [illegible]grel therapy b[illegible]year may be [illegible]ed in patients [illegible]going DES placement

Empiric Recommendations!

J Am Coll Cardiol 2008; 51:172

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Against Indefinite Treatment with DAT after DES implantation

Argument # 1

Data supporting prolonged DAT are extrapolated from studies using DAT in different settings with undeniable methodological and selection biases

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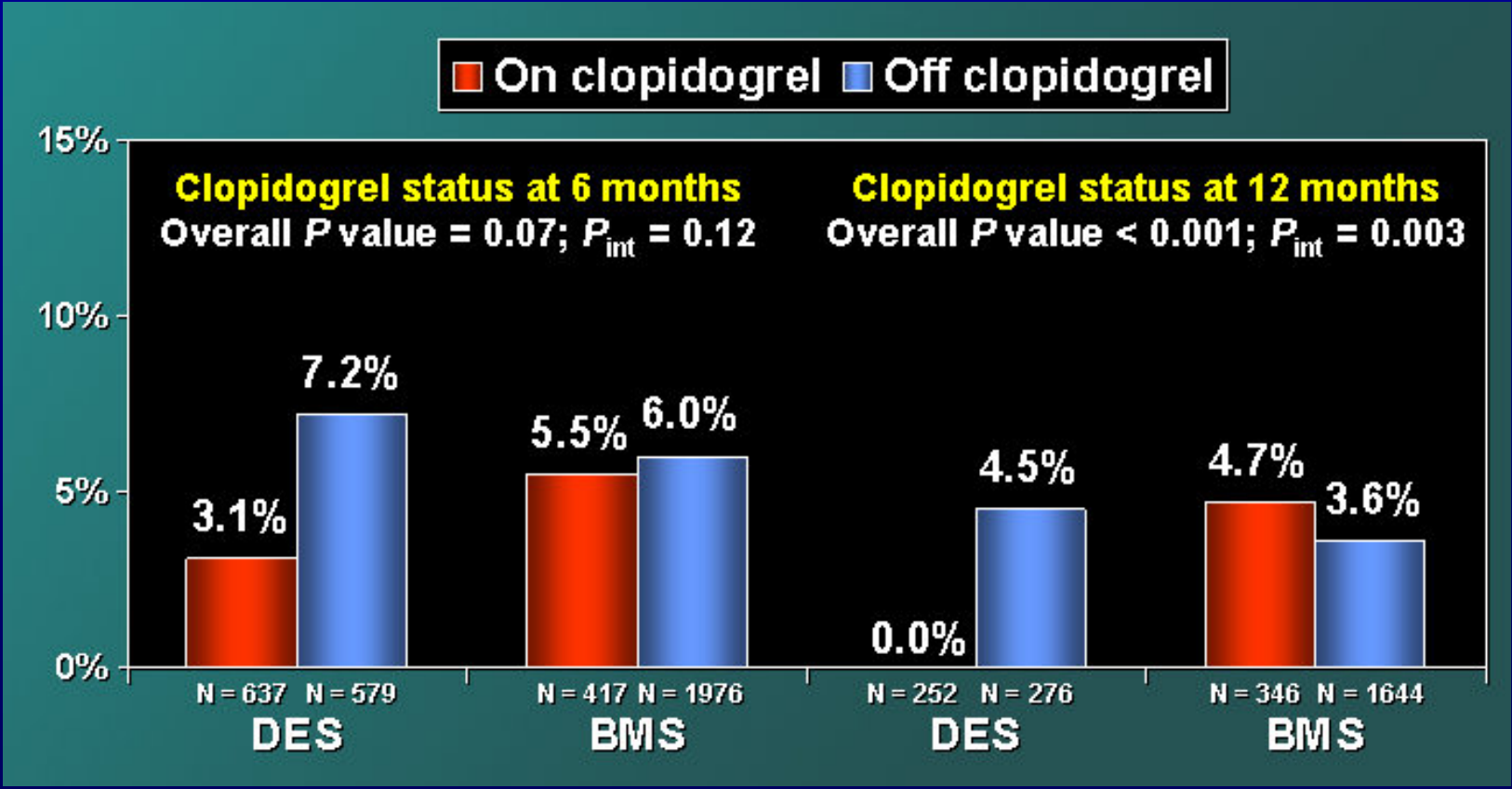
Quoted Registries by Guidelines for prolonged DAPT after DES

Duke database death/MI analysis



Eseinstein EL et al. JAMA 2007; 297:159

Pitfalls of Duke analysis…..

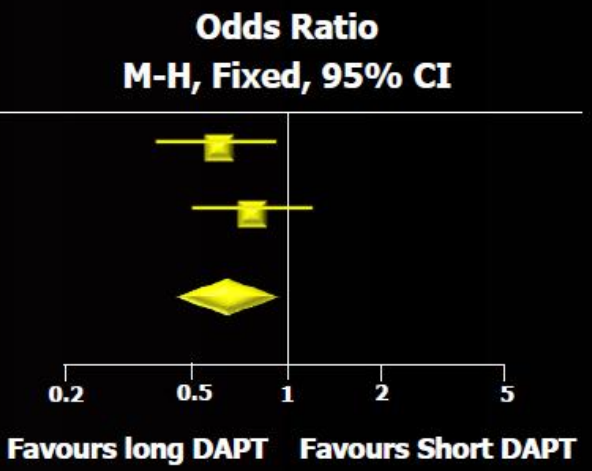
as well as other observational studies

- the number of patients from which the conclusions are drawn is relatively small
- patients' self-reporting of clopidogrel usage
- the observation that clopidogrel did not influence the occurrence of events in patients treated with BMS may in part be explained by the paucity of prescription beyond 30 days or 6 months
- nonrandomized allocation of clopidogrel use
- events were not specifically attributable to the treated vessel
- the observation regarding "net clinical benefit" of extended clopidogrel use in patients with drug-eluting stents is limited by the absence of data on major bleeding

Current Evidence for indication to the Procedure as driver for prolonged DAPT

Study	LONG Events	LONG Total	SHORT Events	SHORT Total	Weight	Odds Ratio M-H, 95% CI
CREDO	35	1053	55	1063	50.2%	0.63 [0.41-0,97]
PCI-CURE	42	1313	55	1345	49.8%	0.78 [0.51-1,17]
Total						**0.70 [0.52-0,95]**

Heterogeneity: Chi2=0.46, P=0.50;I2=0%
Test for overall effect: P=0.02



Pre-treatment effect: potential for bias in both studies

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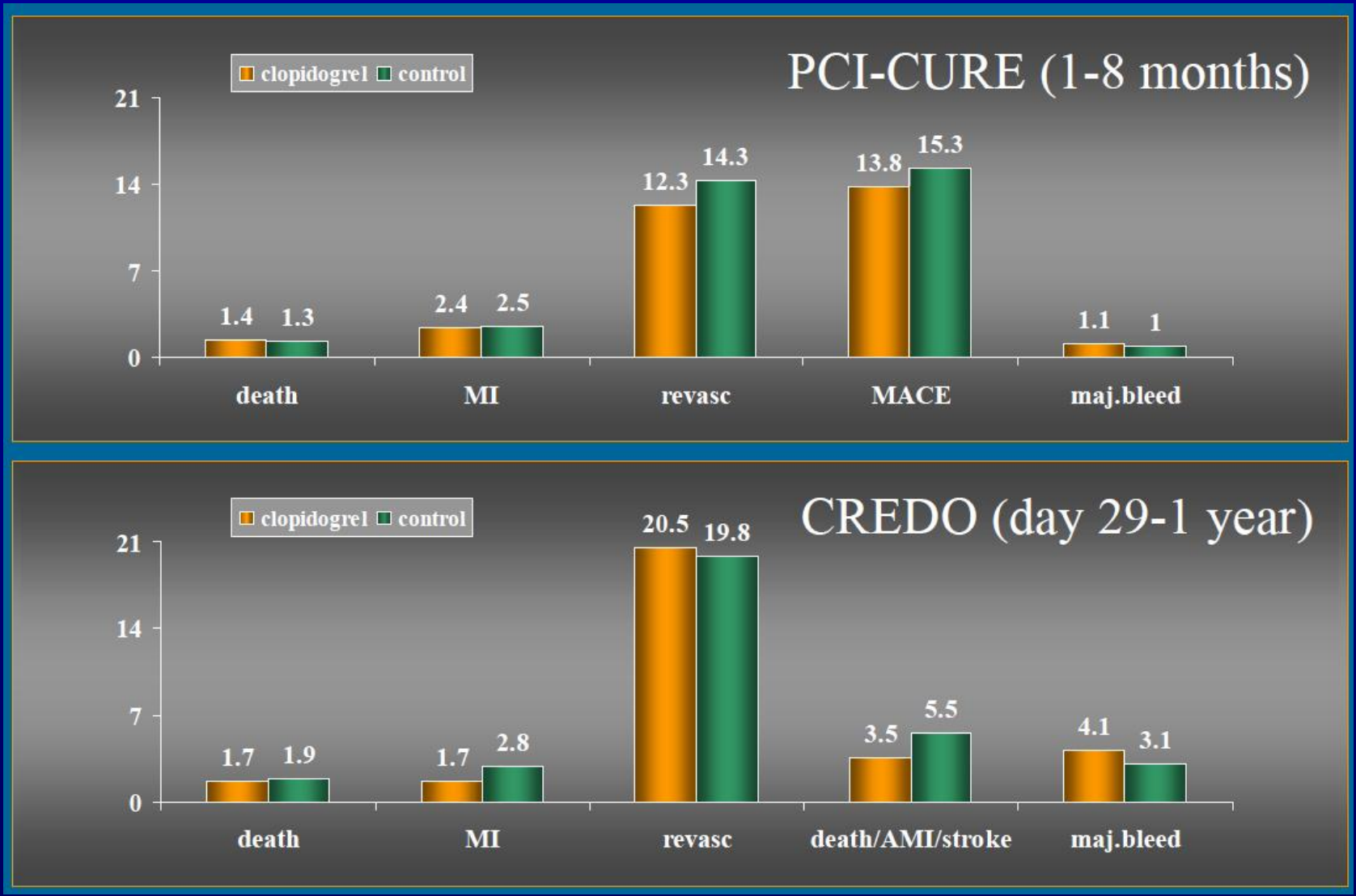
The missing arm

Pretreatment for all +
short vs long-term treatment

Maximum conceivable effects of isolated long-term clopidogrel therapy in PCI-CURE and CREDO



Eriksson P Eur Heart J 2004; 25:720-2

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Against Indefinite Treatment with DAT after DES implantation

Argument # 2

A lot of new set of data are against a prolonged duration of dual antiplatelet therapy

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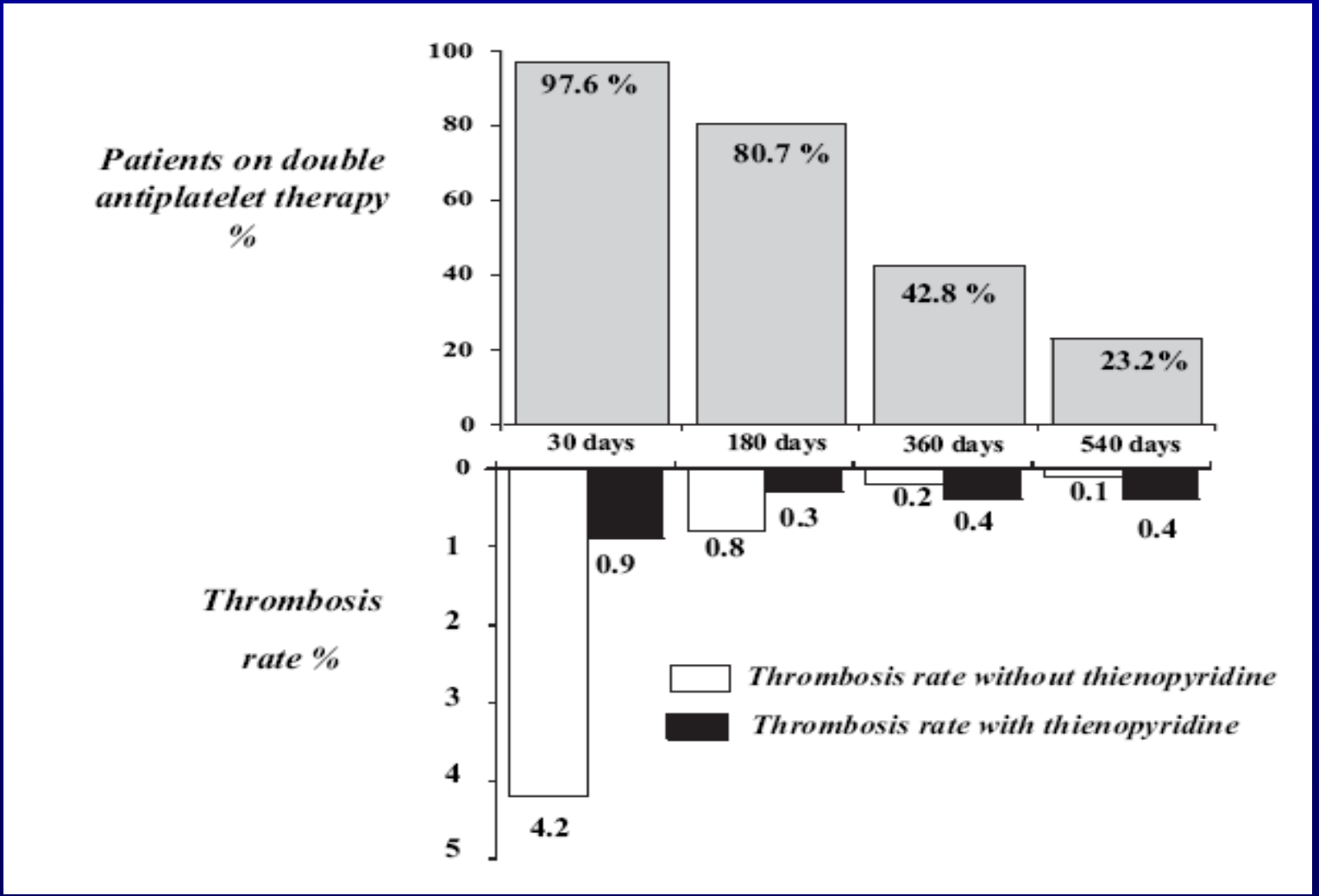
Incidence and Predictors of DES Thrombosis During and After Discontinuation of Thienopyridine Treatment



Airoldi F et al. Circulation 2007; 116:745

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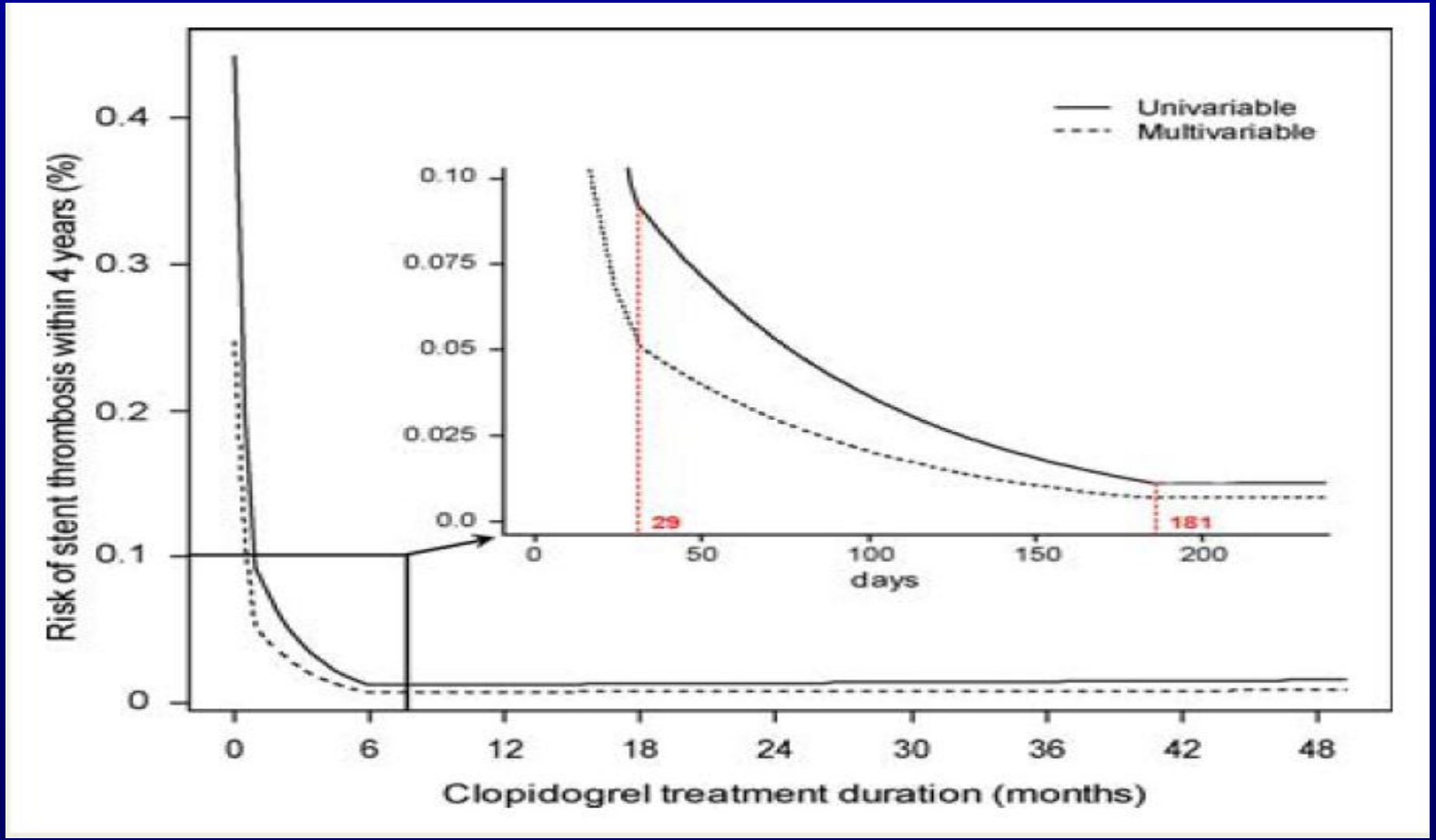
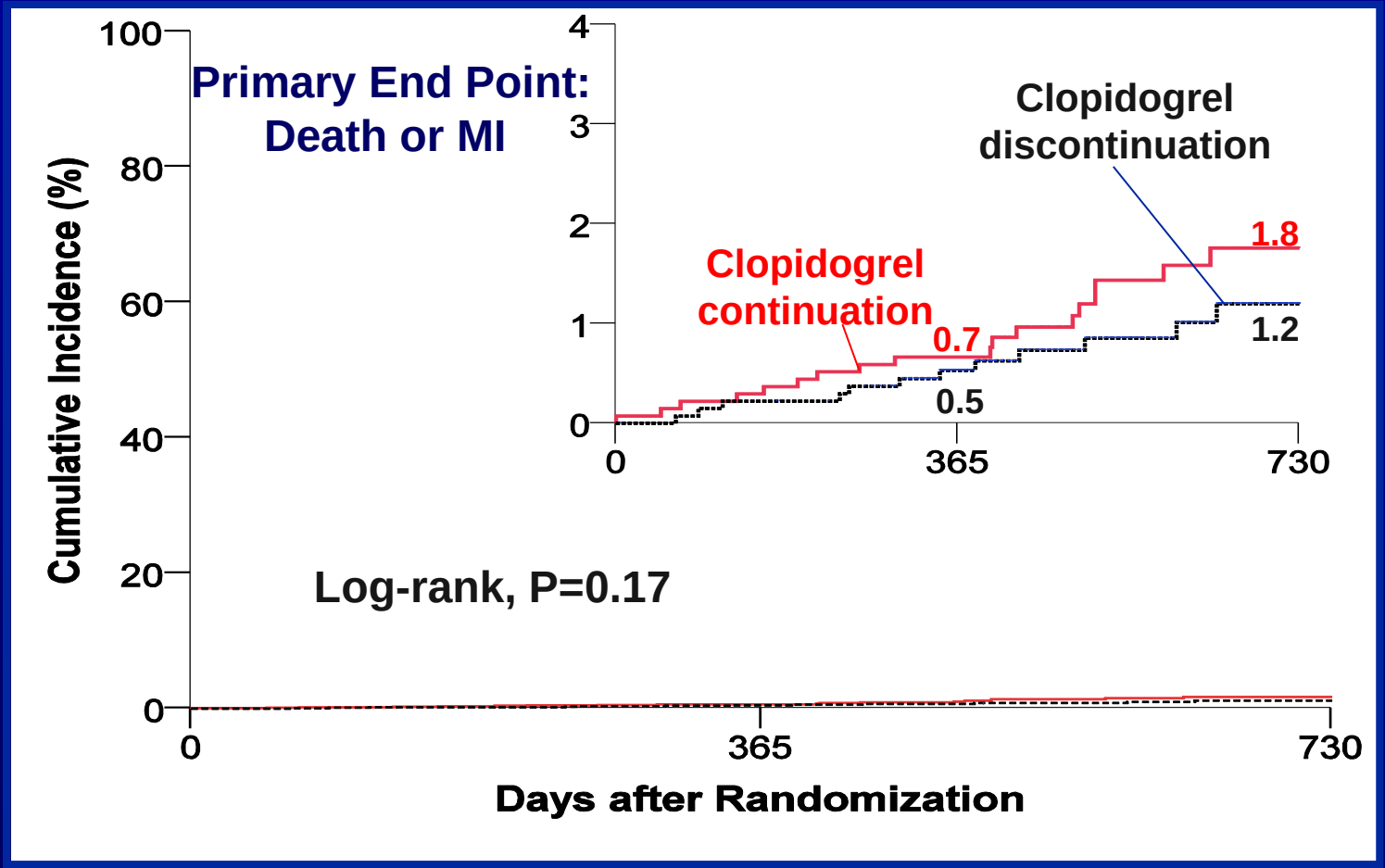
The dependence of ST on discontinuation of clopidogrel therapy seems to be mostly confined to the first 6 months after DES implantation



Schulz S et al. Eur Heart J 2009; 30: 2714–2721

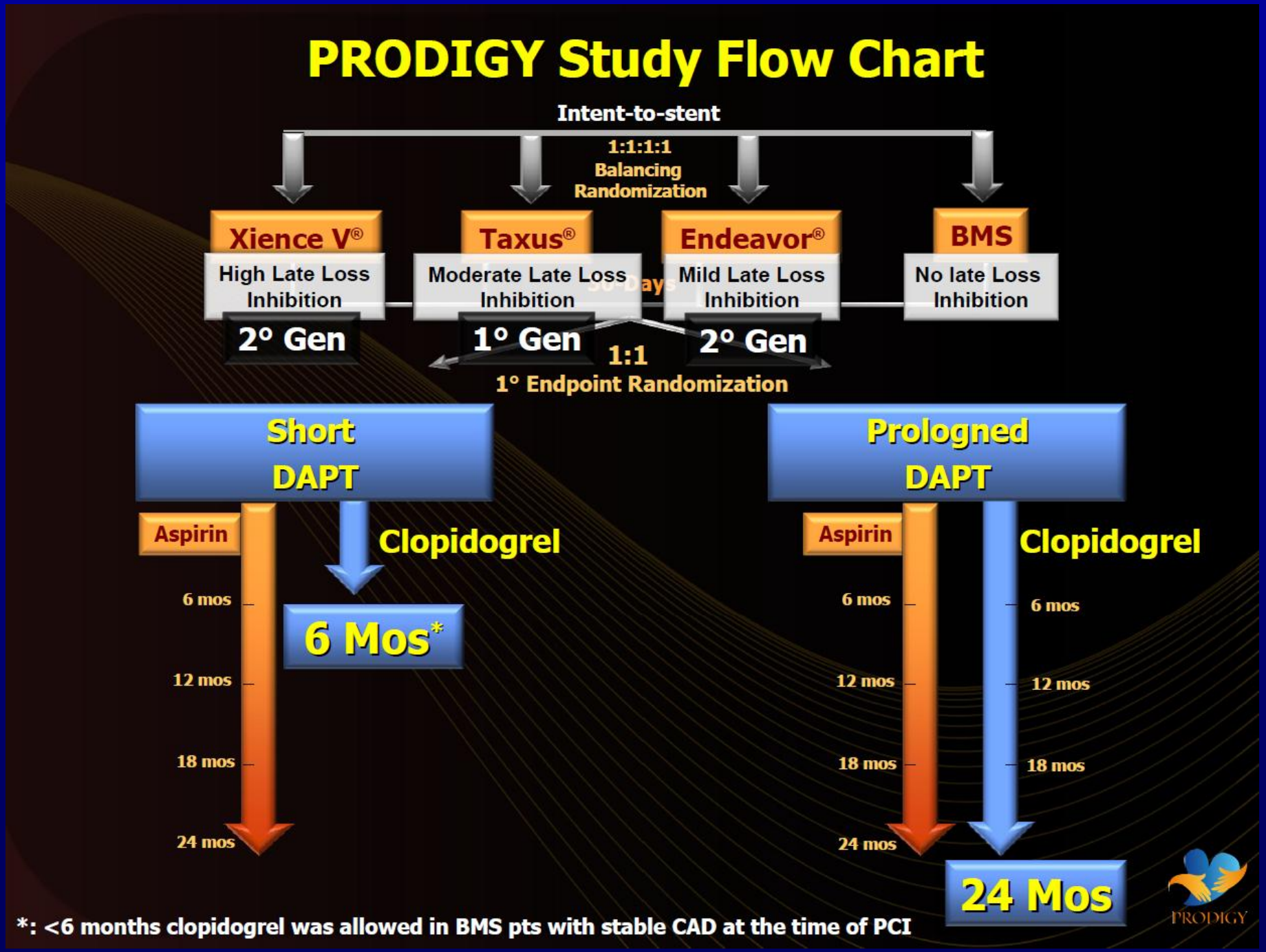
Duration of Dual Antiplatelet Rx After DES Implantation

A Pooled Analysis of the REAL-LATE and the ZEST-LATE Trial



Park SJ et al. New Engl J Med 2010 March 15

PRODIGY Study Flow Chart



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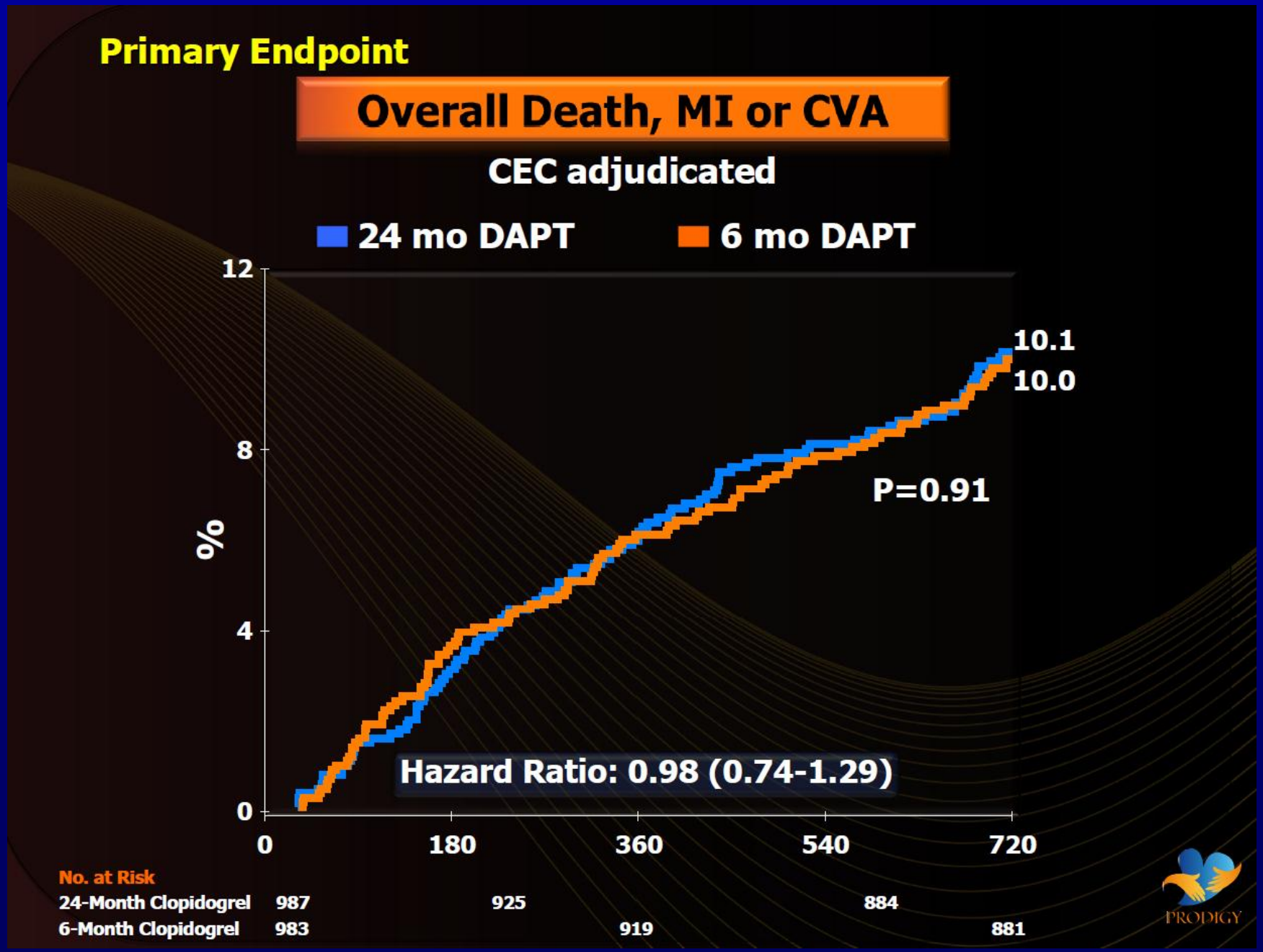
Primary Endpoint

Overall Death, MI or CVA

CEC adjudicated



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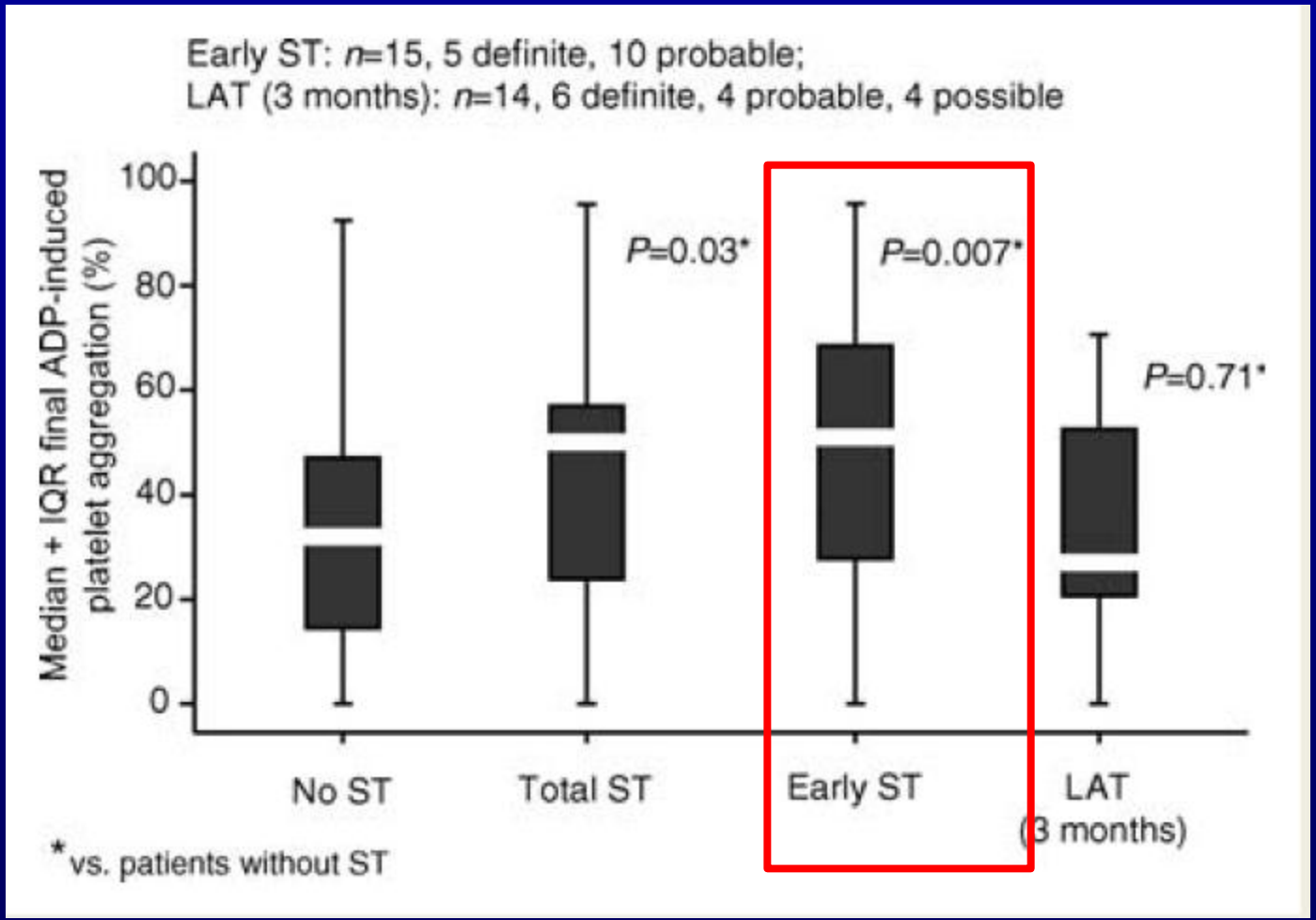
PRODIGY

Early but not late ST is influenced by residual platelet aggregation in patients undergoing coronary interventions



Geisler T et al. Eur Heart J 2010; 31: 59–66

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http://clinicaltrials.gov

Pipeline: RCT on DAPT after stenting

Study	N	Design	Stent	Results
DAPT	24,015	12 vs 30	DES/BMS	?
ISAR SAFE	6,000	6 vs 12	DES	2014
ITALIC	3,200	6 vs 12	Xience	?
PRODIGY	2,002	6 vs 24	DES/BMS	2011
OPTIDUAL	1,966	12 vs 30	DES	2013
DES LATE	5,000	12 vs 24	DES	2013
SCORE	280	12 vs 24	DES	no update
OPTIMAZE	3,120	3 vs 12	Endeavor	2012
ZEUS	1,600	1 mo allowed	Endeavor	2013
ARCTIC	2,500	12 vs. 18	DES	2012
SECURITY	4,000	6 vs 12	2 gen DES	?
EASTS	3,792	12 vs. 24*	SES	2014
ISAR-Caution	3,000	*tapering	DES	2011
FDI-DAPT-ZES	75	RUTTS <30%	Endeavor	2012

Pipeline on DAPT studies:

- Ongoing studies have to let us know the following key points:
  - Is DAPT necessary for DES safety?
  - If so, for how long?
  - If so, is DES type specific?
  - If so, at what price in terms of side effects?

Against Indefinite Treatment with DAT after DES implantation

Argument # 3

Prolungation of DAT is associated with significant harm. Thus, the net clinical benefit, if any, is at the best marginal

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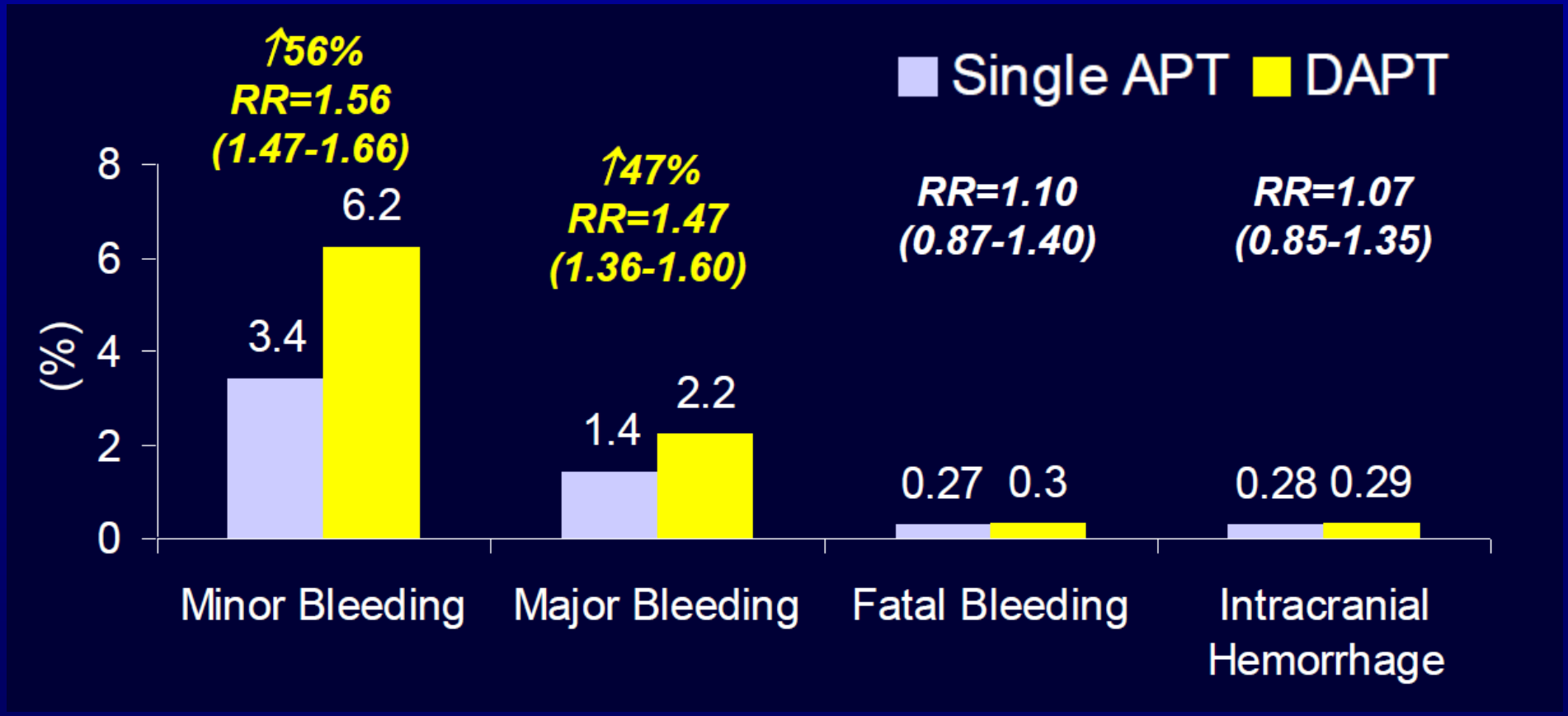
Risk of Bleeding with DAPT

18 RCTs with 129,314 Patients Comparing Single vs Dual Antiplatelet Rx

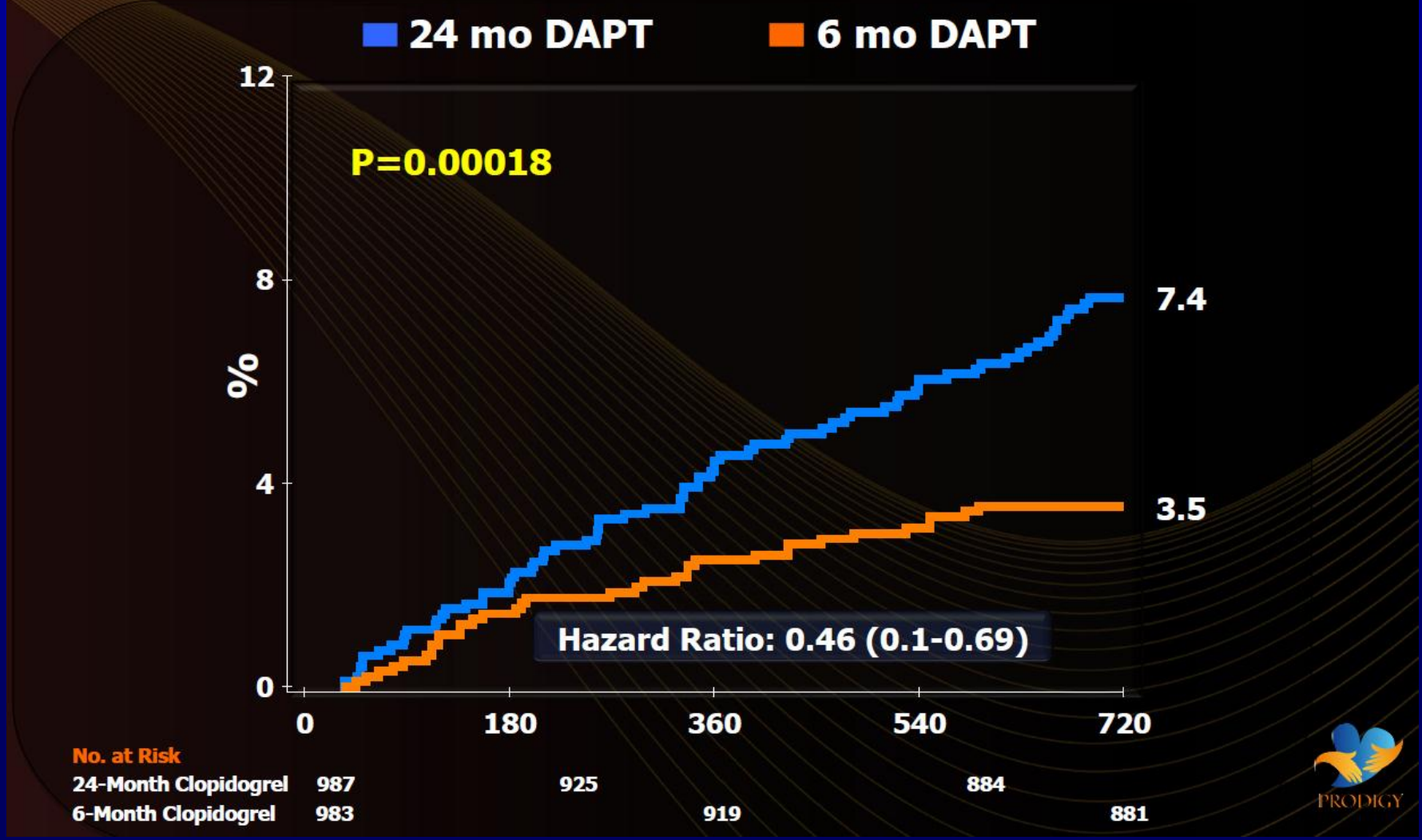


Serebruany VL et al. Fund & Clin Pharmacology 2008;22:315

Key Safety Endpoint

Type II, III or V BARC bleeding

CEC adjudicated



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PRODIGY

(b) Recommended duration of dual antiplatelet therapy

After percutaneous coronary intervention

- 1 month after BMS implantation in stable angina;[55,60,94]
- 6–12 months after DES implantation in all patients;[60,94]
- 1 year in all patients after ACS, irrespective of revascularization strategy.

Data suggest that certain patient populations (e.g. high risk for thromboembolic events, patients after SES or PES implantation), may benefit from prolonged DAPT beyond 1 year. The downside of this strategy is the increased rate of severe bleeding complications over time. Recent data suggest that DAPT for 6 months might be sufficient because late and very late stent thrombosis correlate poorly with discontinuation of DAPT.

55. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;**26**:804–847.

60. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1598–1660.

94. Van De Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Silber S, Aguirre FV, Al-Attar N, Alegria E, Andreotti F, Benzer W, Breithardt O, Danchin N, Di Mario C, Dudek D, Gulba D, Halvorsen S, Kaufmann P, Kornowski R, Lip GY, Rutten F. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; **29**:2909–2945.

Managing and Resolving the Dual Antiplatelet Conundrum in DES Patients

- Optimal duration of DAPT
- **Individual response variability**
- Potential drug-interactions
- Managing DAPT in pts undergoing surgical procedures

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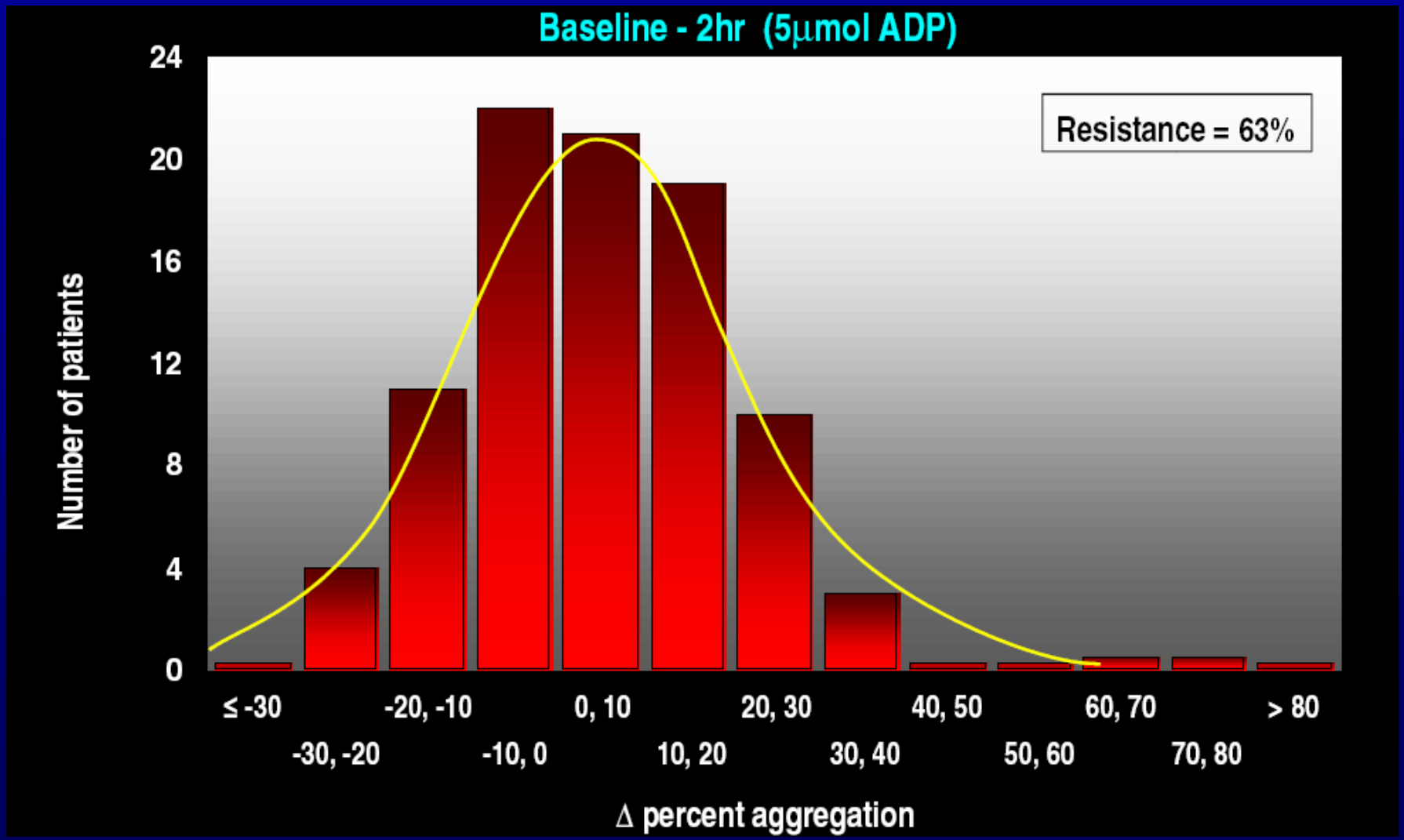
Clopidogrel Response Variability



Gurbel PA et al. Circulation 2003; 107:2908

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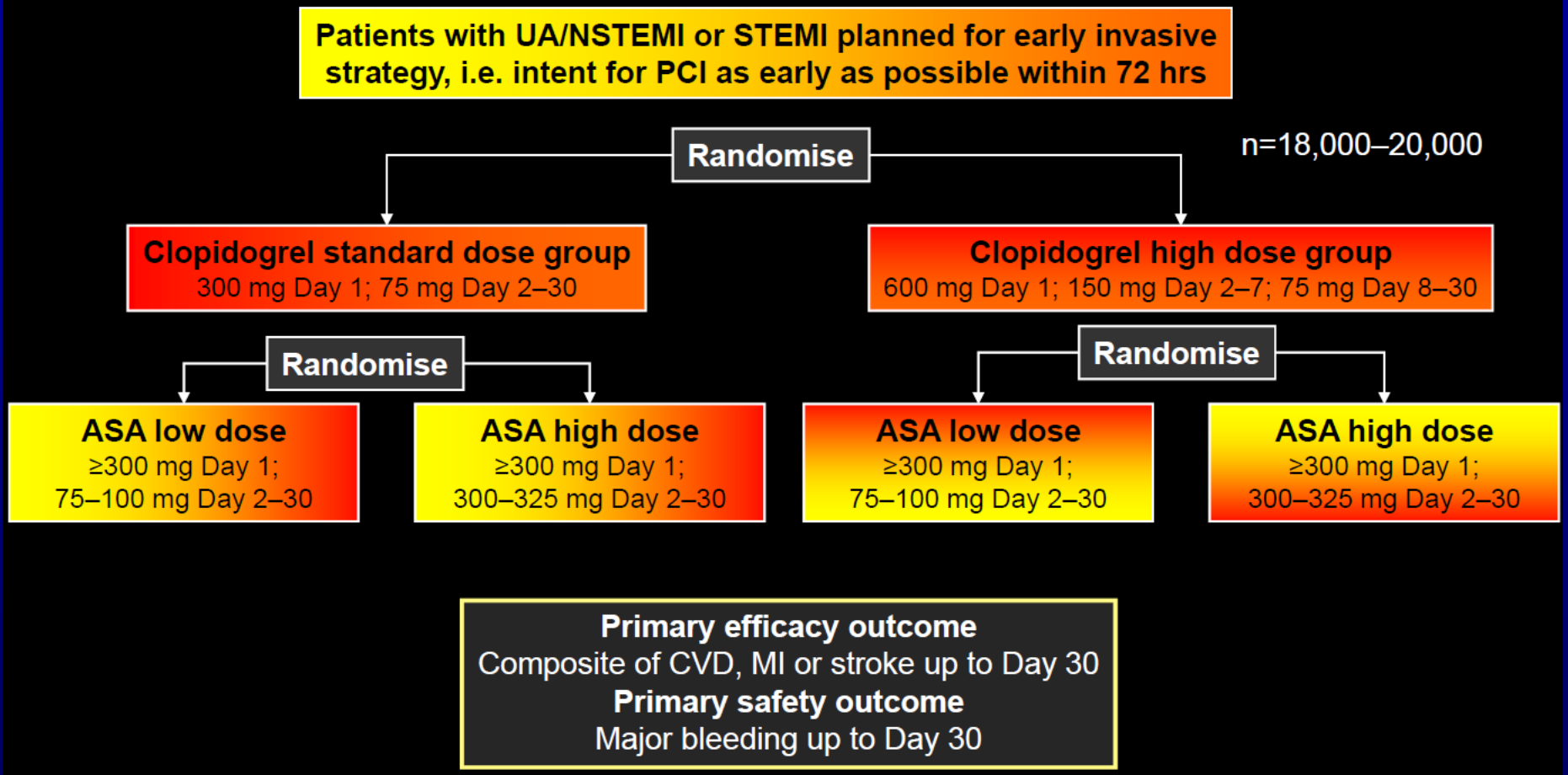
Tailored Antiplatelet Drug Selection to Prevent Ischemic and Thrombotic Events after PCI: Current and Future Therapeutic Alternatives

High-dose clopidogrel

Prasugrel

Ticaglegor

CURRENT-OASIS 7 *study design*



Mehta et al. Am Heart J 2008;156:1080–88

CURRENT OASIS 7 trial

Primary hypothesis

In patients with ST and non-ST-segment elevation acute coronary syndromes, to determine whether a high dose regimen of clopidogrel (600 mg loading dose followes by 150 once daily from days 2 to 7, then 75 mg daily) is superior to a standard dose regimen of clopidogrel (300 mg loading dose followed by 75 mg once daily) in preventing the composite of cardiovascular death, myocardial infarction, or stroke at 30 days.

Results

CV Death/MI/Stroke	Standard	Double	HR	95% CI	P
Overall (2N=25,087)	**4.4**	**4.2**	**0.95**	**0.84-1.07**	**0.370**

Error α > 5%

Clopidogrel 300 mg +75 mg = Clopidogrel 600 mg +75 mg

Null hypotesis can not be rejected

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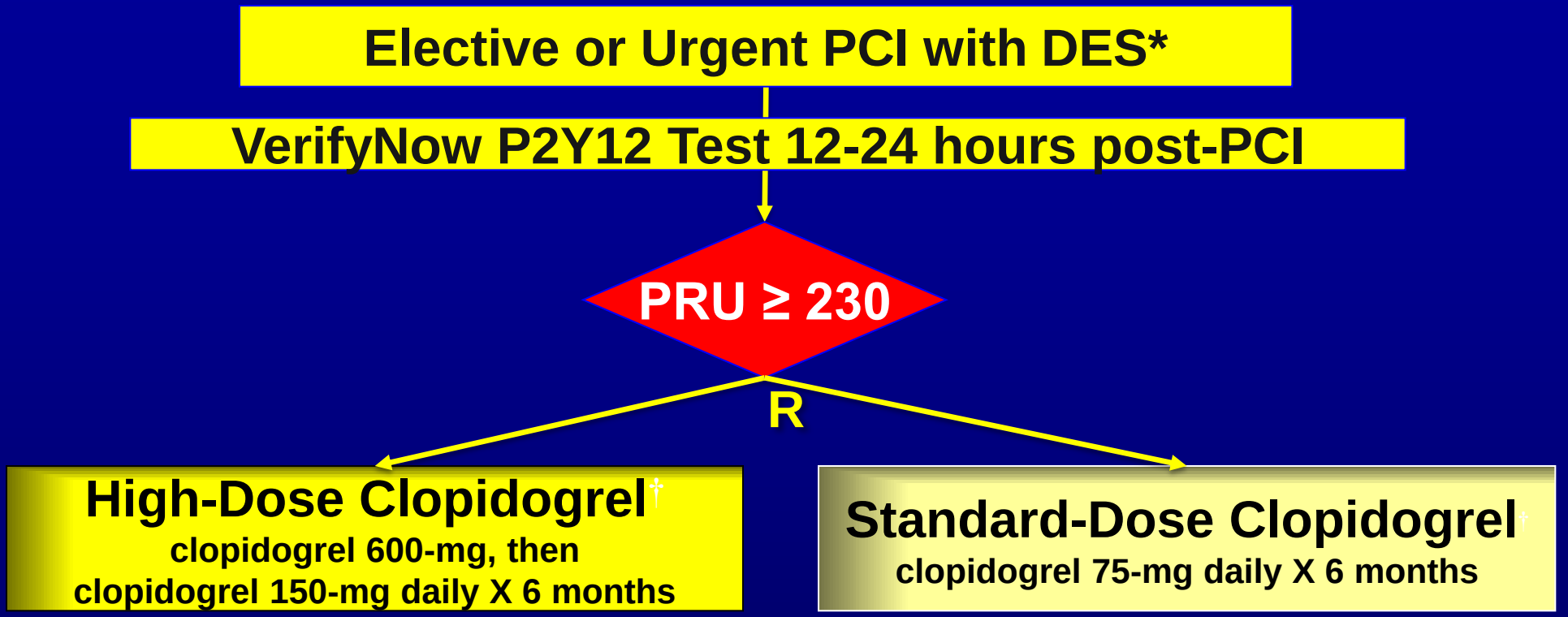
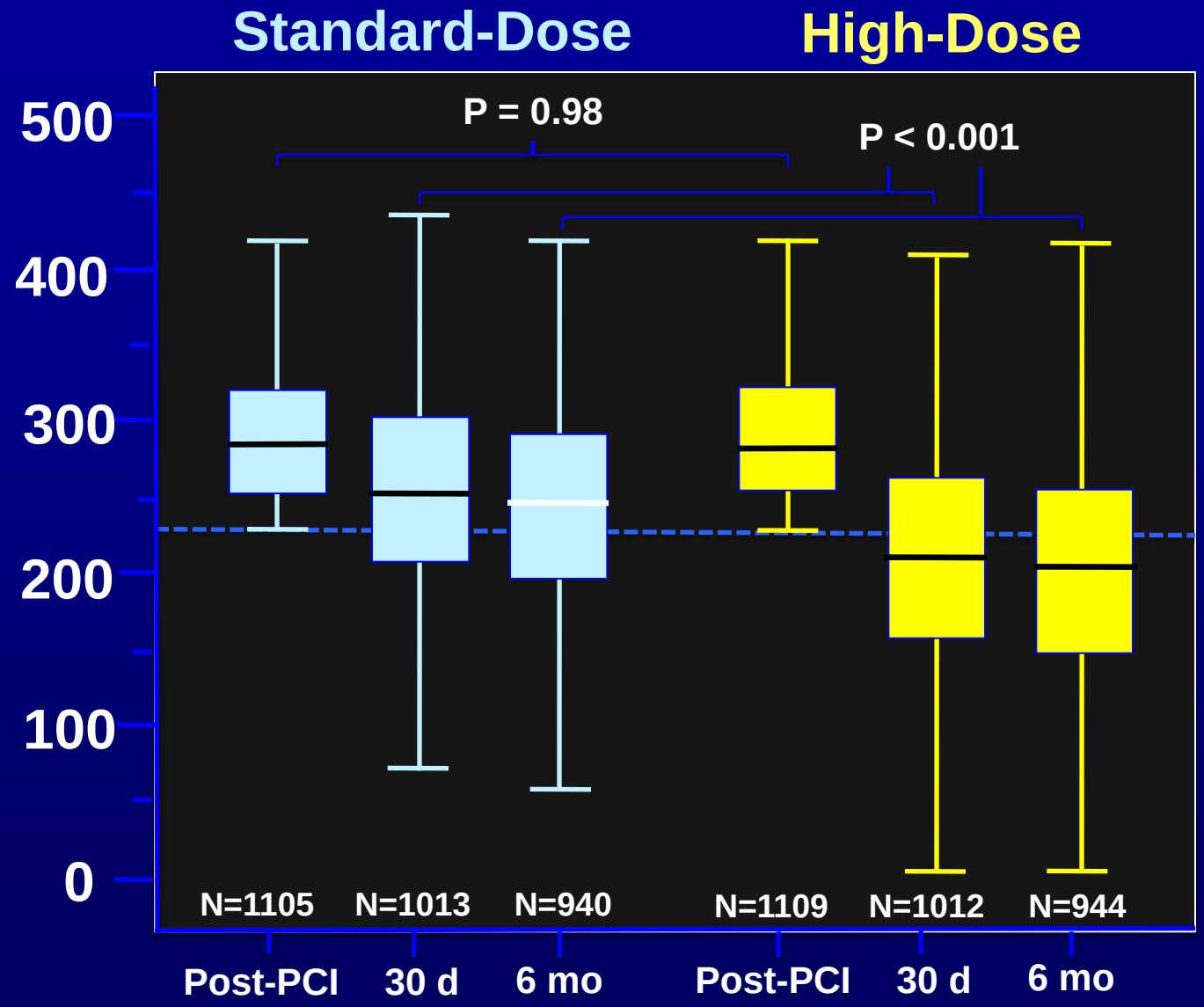
GRAVITAS Study Design



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

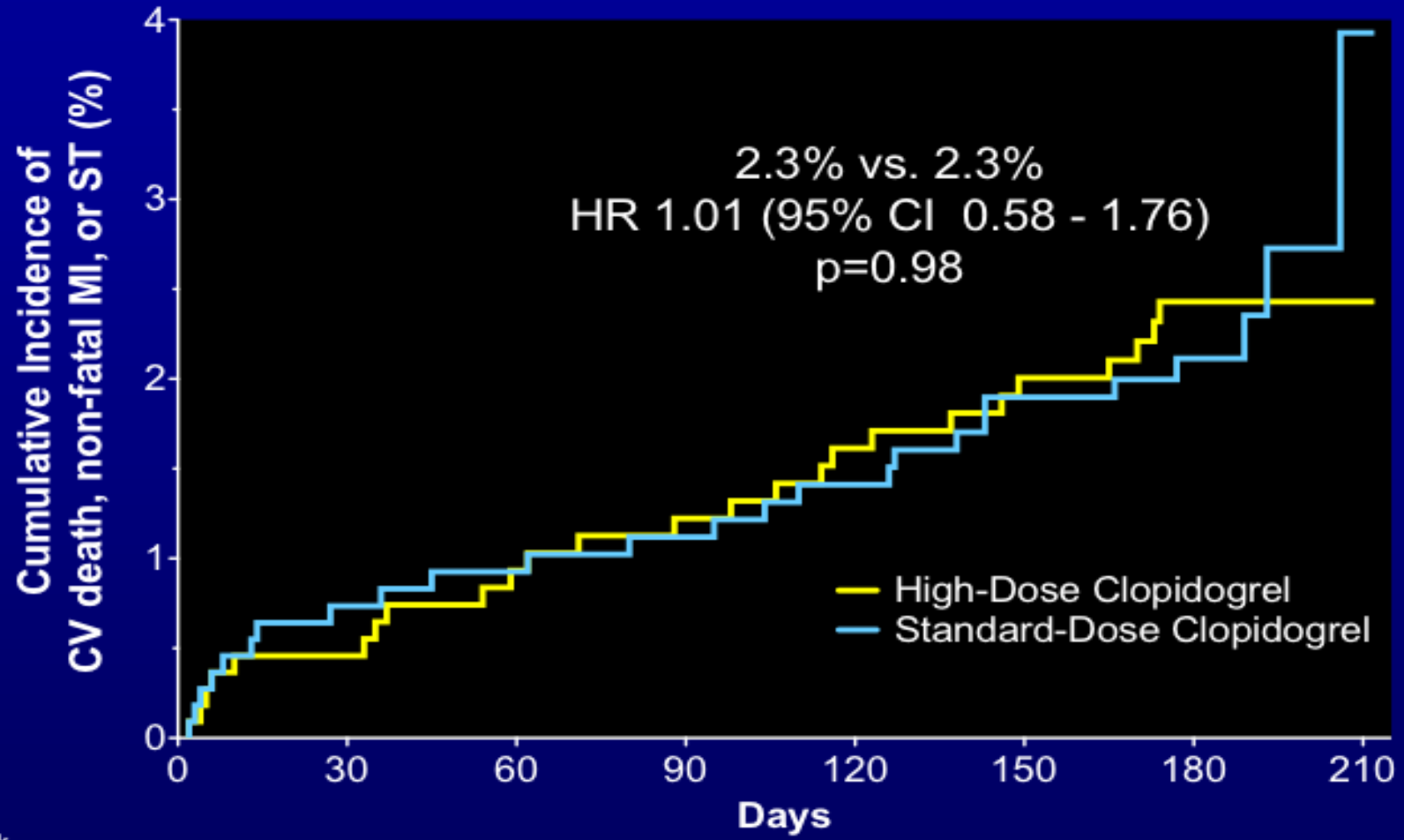
Pharmacodynamics: Effect of SD vs HD Clopidogrel



Persistently high reactivity @ 30 days: 62% vs 40%, p<0.001

Price MJ et al. Circulation 2011; 124:1132-7

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

Price MJ et al. Circulation 2011; 124:1132-7

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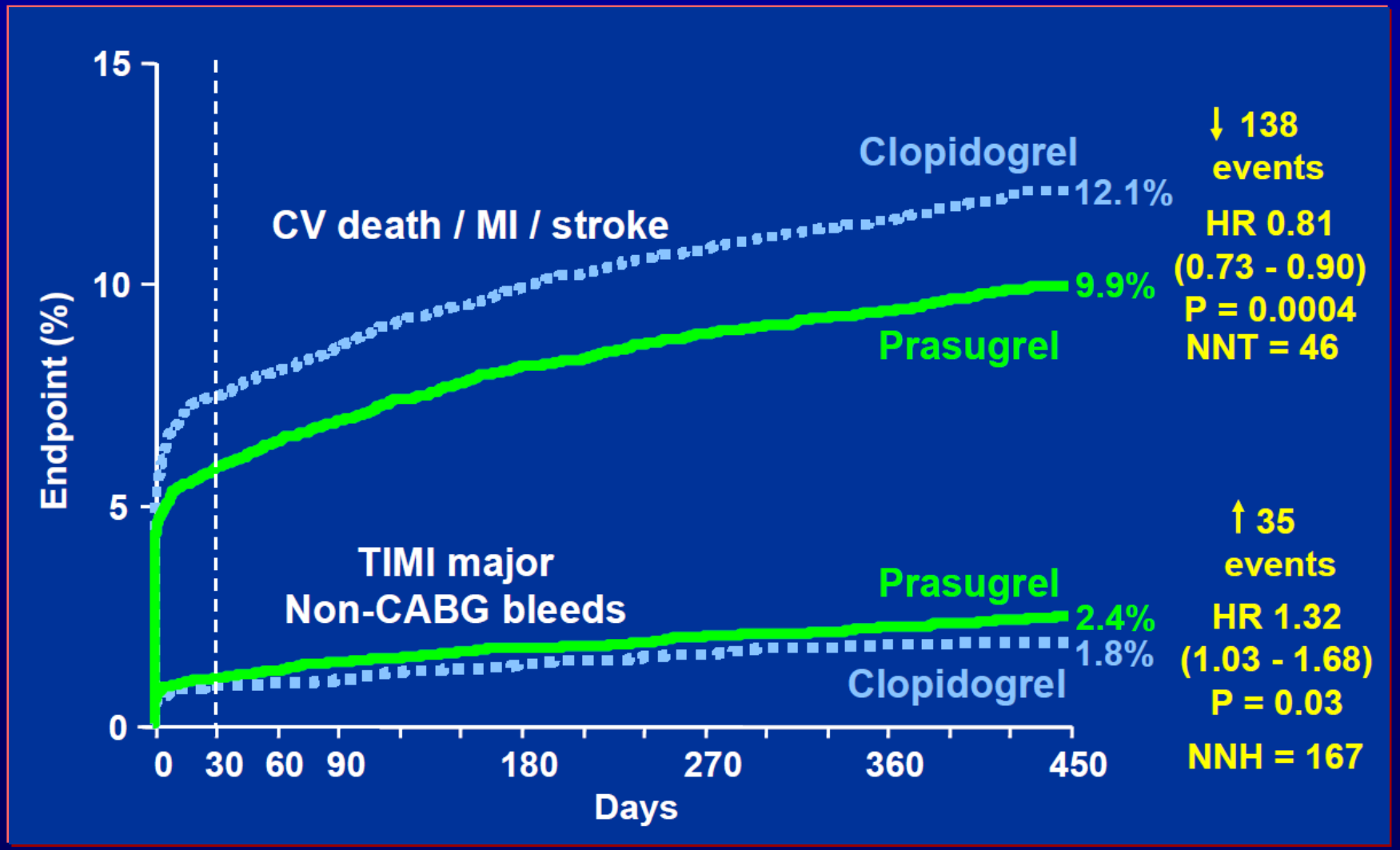
TRITON TIMI-38

Balance of Efficacy and Safety



Wiviott SD et al. N Engl J Med 2007; 2001

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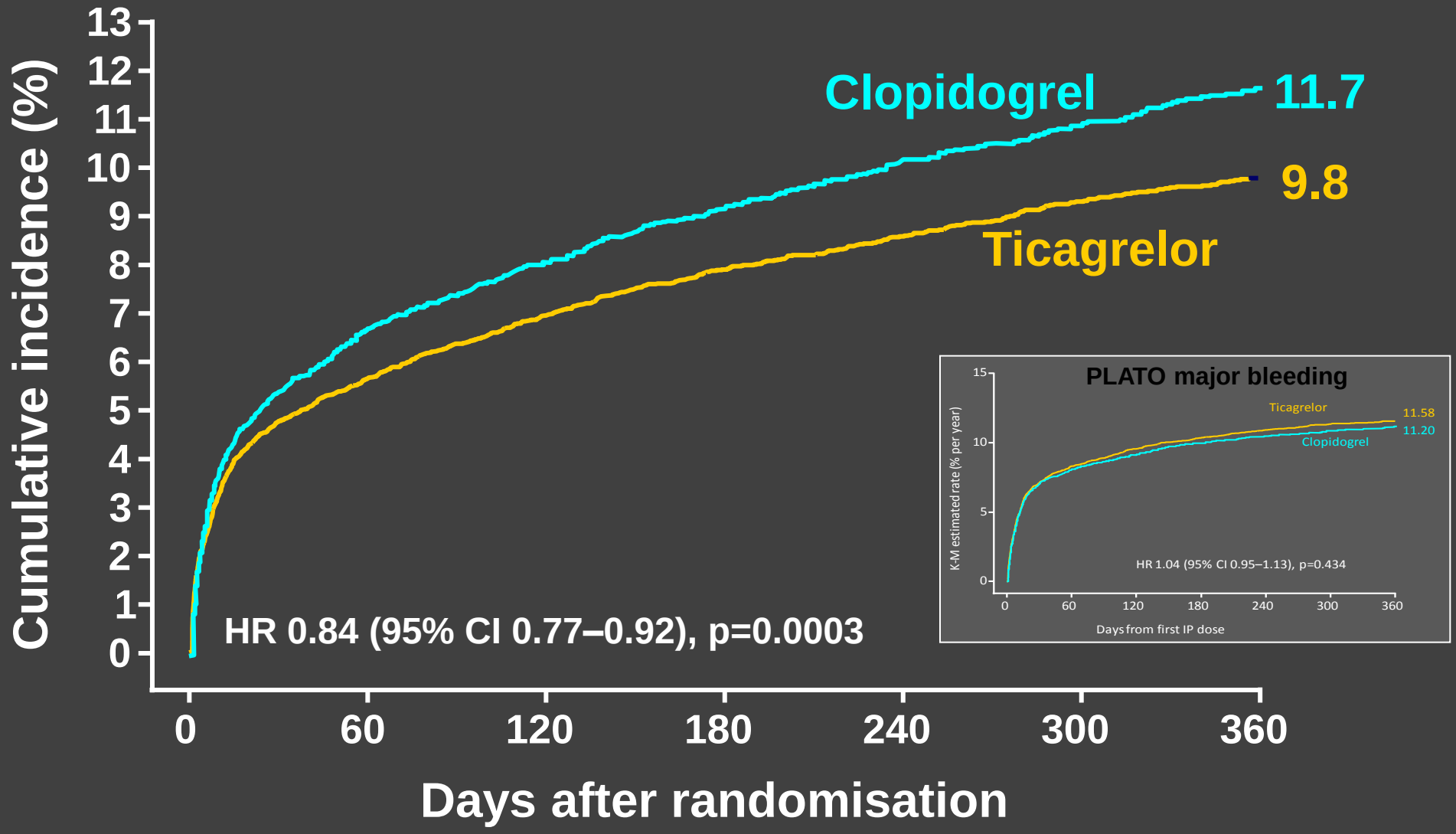
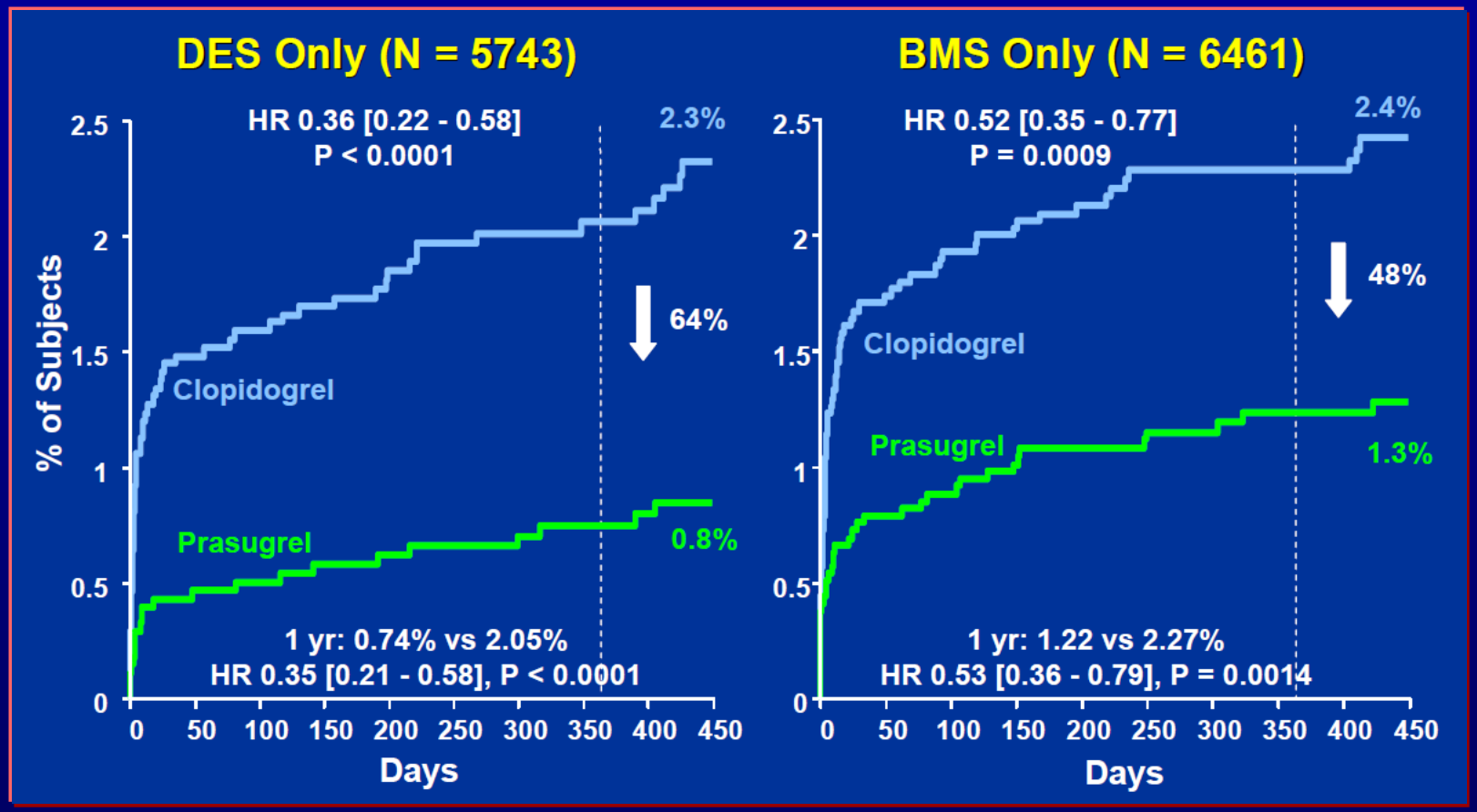
PLATO, primary efficacy endpoint composite of CV death, MI or stroke



Wallentin L et al. NEJM 2009; 361:1045-57

CEC Adjudicated Stent Thrombosis
Definite/Probable



Wiviott SD et al. Lancet 2008;371:1

PLATO
Invasive

Stent thrombosis

	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)	HR for ticagrelor (95% CI)	p value*
Stent thrombosis, %				
Definite	1.0	1.6	0.62 (0.45–0.85)	0.003
Probable or definite	1.7	2.3	0.72 (0.56–0.93)	0.01
Possible, probable, or definite	2.2	3.1	0.72 (0.58–0.90)	0.003

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¶ Evaluated in patients with any stent during the study

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

* By univariate Cox model

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- Managing DAPT in pts undergoing surgical procedures

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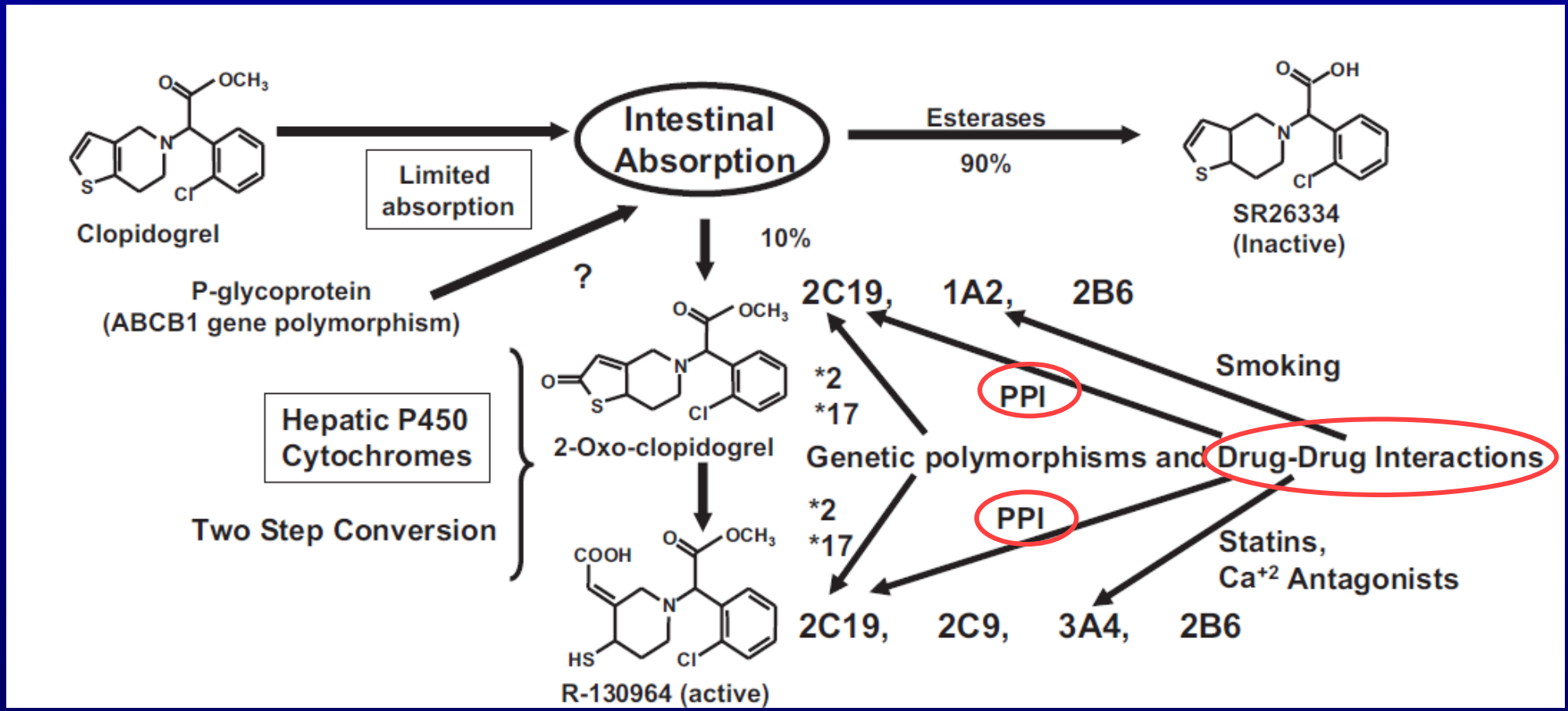
Clopidogrel response variability; the role of drug-drug interactions



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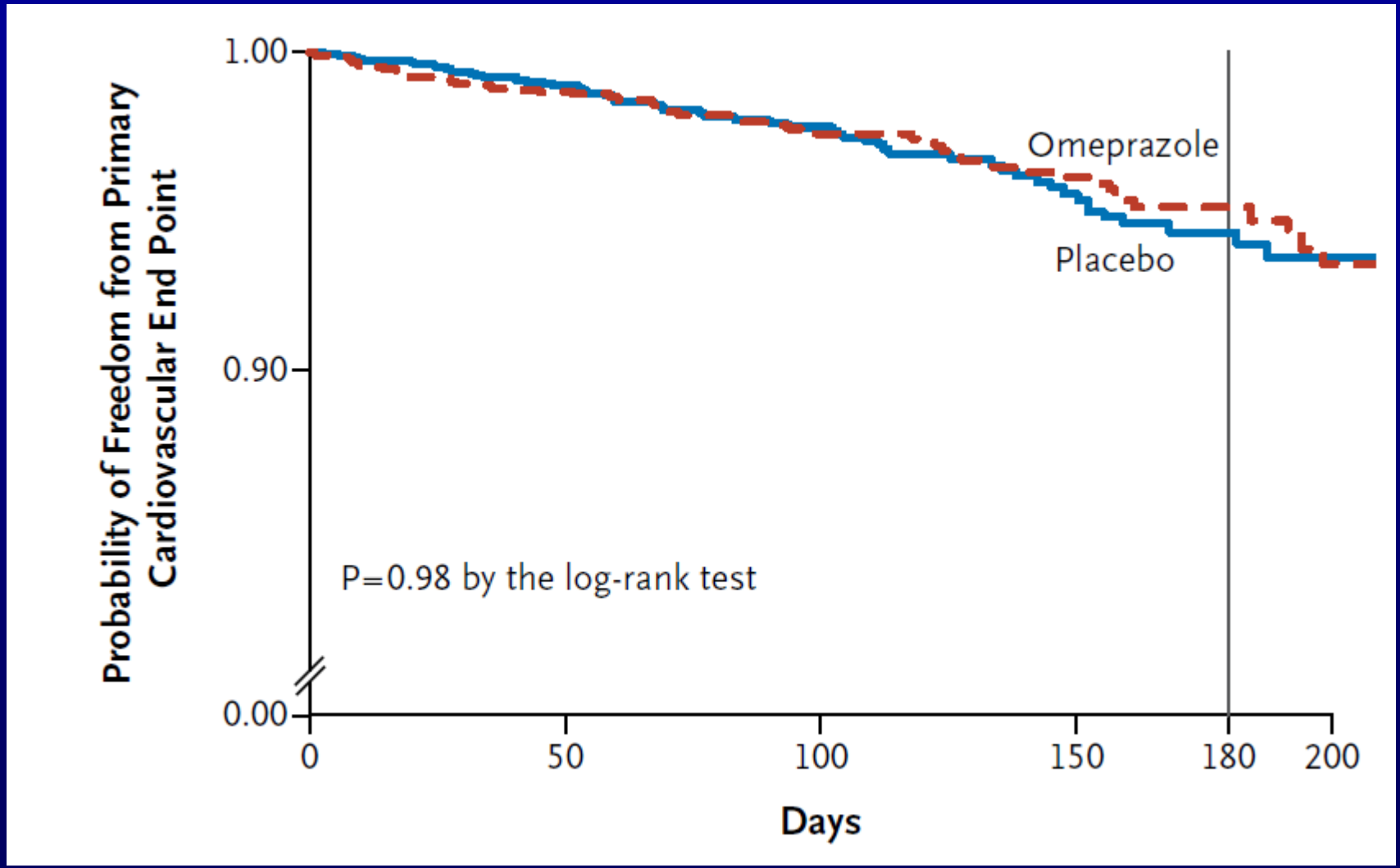
The COGENT Trail: Survival Curves for PPI Treated vs Placebo

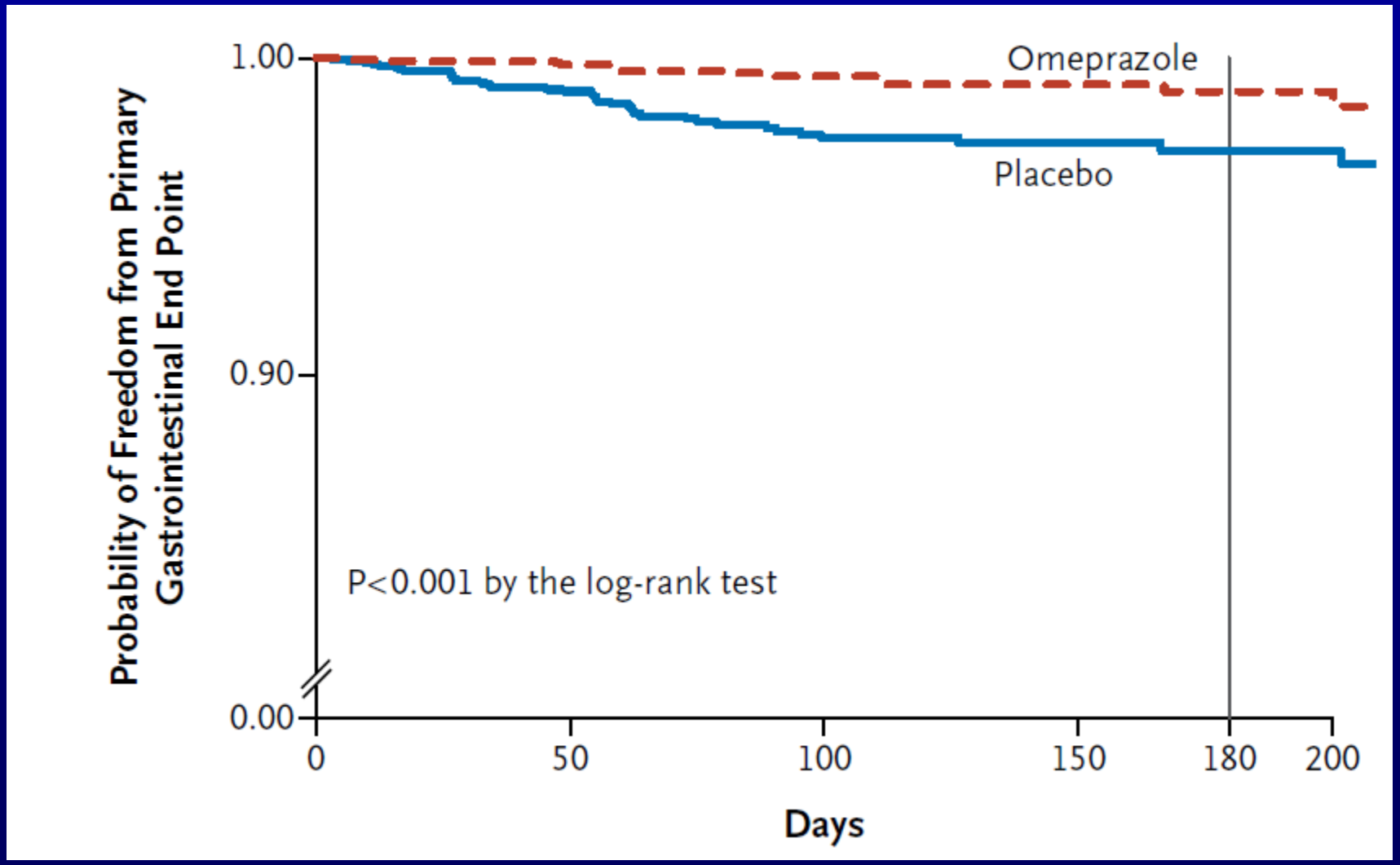
Primary Cardiovascular Events



Bhatt DL et al. N Engl J Med 2011; 364:681 - 683

The COGENT Trial: Survival Curves for PPI Treated vs Placebo

Primary Gastrintestinal Events



Bhatt DL et al. New Engl J Med Online October 6 2010

European Heart Journal
doi:10.1093/eurheartj/ehr236

ESC GUIDELINES

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Recommendations for oral antiplatelet agents

Recommendations	Class [a]	Level [b]	Ref [c]
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A	125–127

European Heart Journal
doi:10.1093/eurheartj/ehr236

Managing and Resolving the Dual Antiplatelet Conundrum in DES Patients

- Optimal duration of DAPT
- Individual response variability
- Potential drug-interactions
- **Managing DAPT in pts undergoing surgical procedures**

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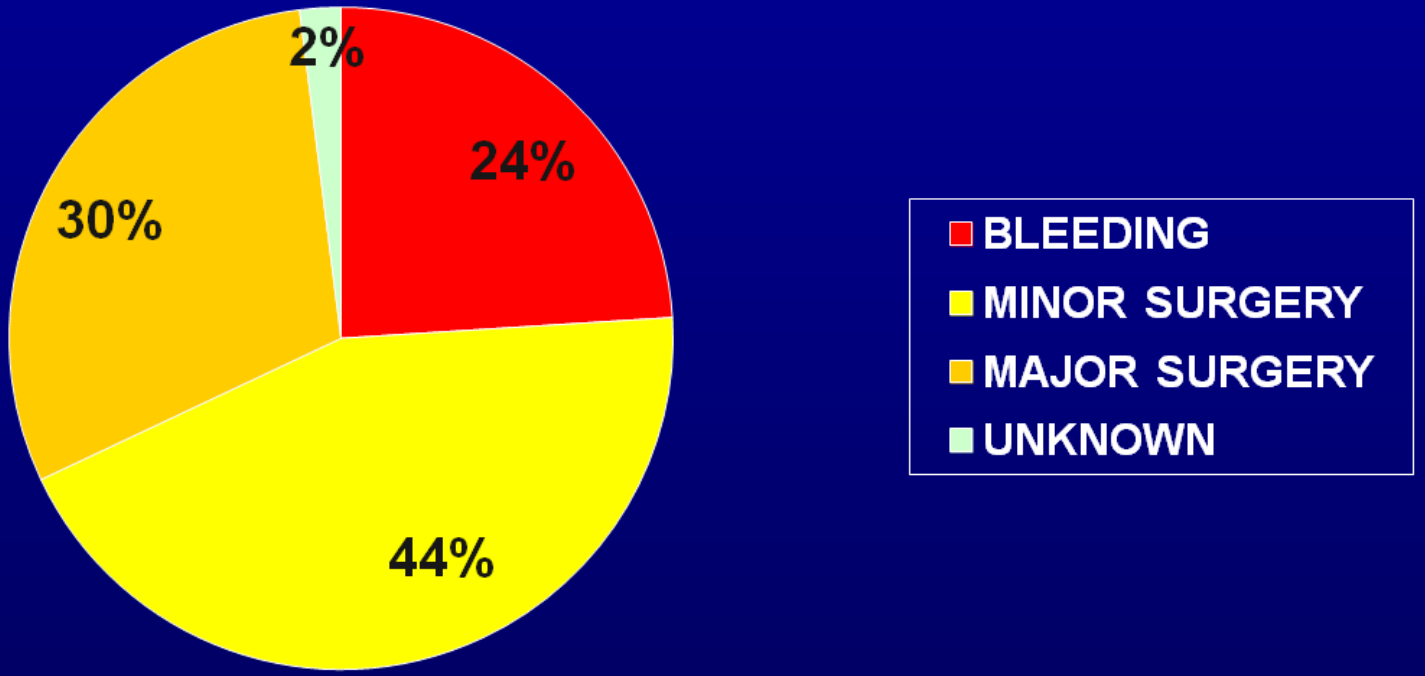
Interventional Cardiology

Background, Incidence, and Predictors of Antiplatelet Therapy Discontinuation During the First Year After Drug-Eluting Stent Implantation

Ignacio Ferreira-González, MD, PhD; Josep R. Marsal, BSc; Aida Ribera, PhD; Gaietà Permanyer-Miralda, MD, PhD; Bruno García-Del Blanco, MD; Gerard Martí, MD; Purificación Cascant, RN; Victoria Martín-Yuste, MD; Salvatore Brugaletta, MD; Manuel Sabaté, MD, PhD; Fernando Alfonso, MD, PhD; Mari L. Capote, MD; Jose M. De La Torre, MD, PhD; Marta Ruíz-Lera, MD; Dario Sanmiguel, MD; Mérida Cárdenas, MD; Beth Pujol, RN; Jose A. Baz, MD; Andrés Iñiguez, MD; Ramiro Trillo, MD; Omar González-Béjar, MD; Juan Casanova, MD; Joaquín Sánchez-Gila, MD; David García-Dorado, MD, PhD

N=1622 Patients on dual antiplatelet therapy



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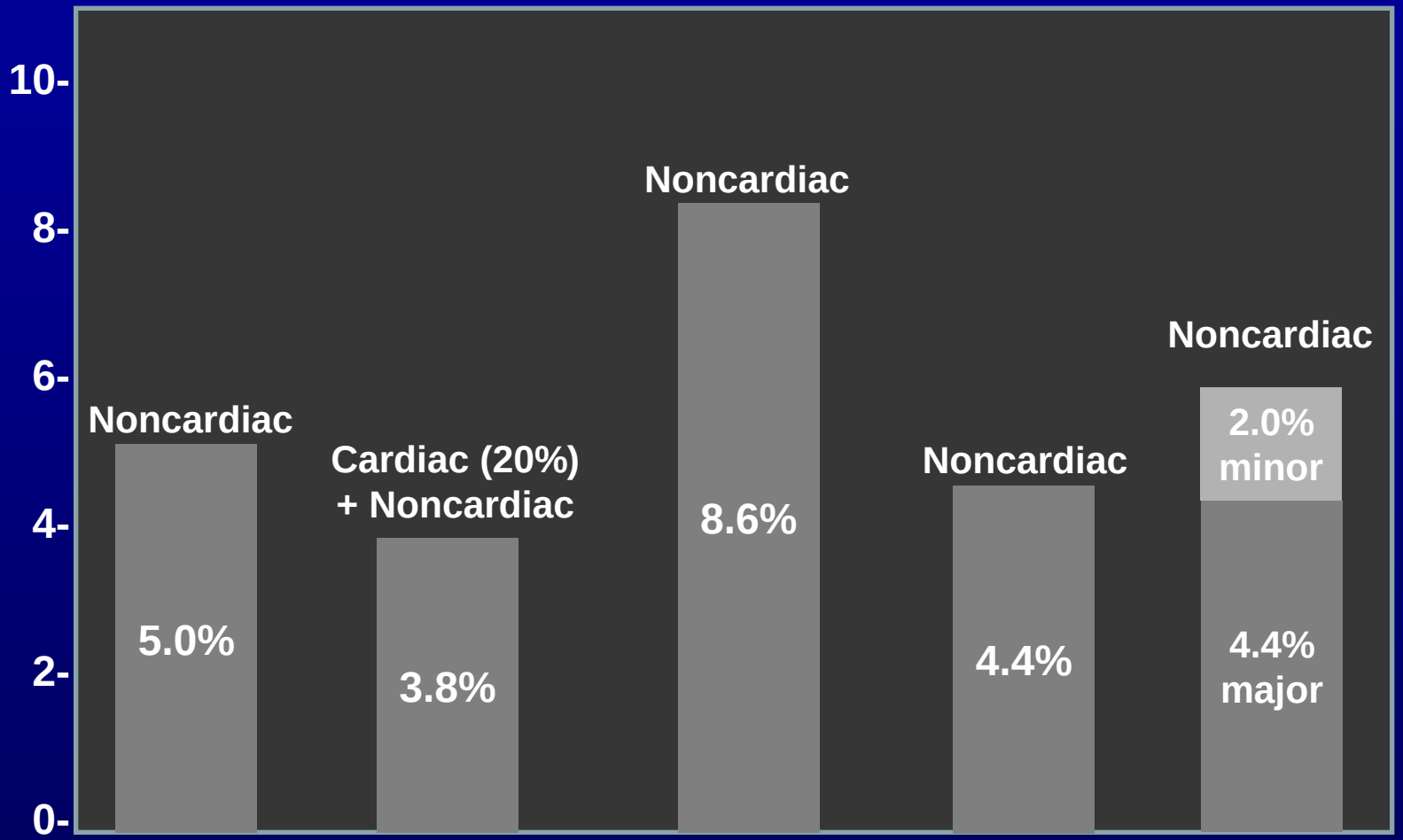
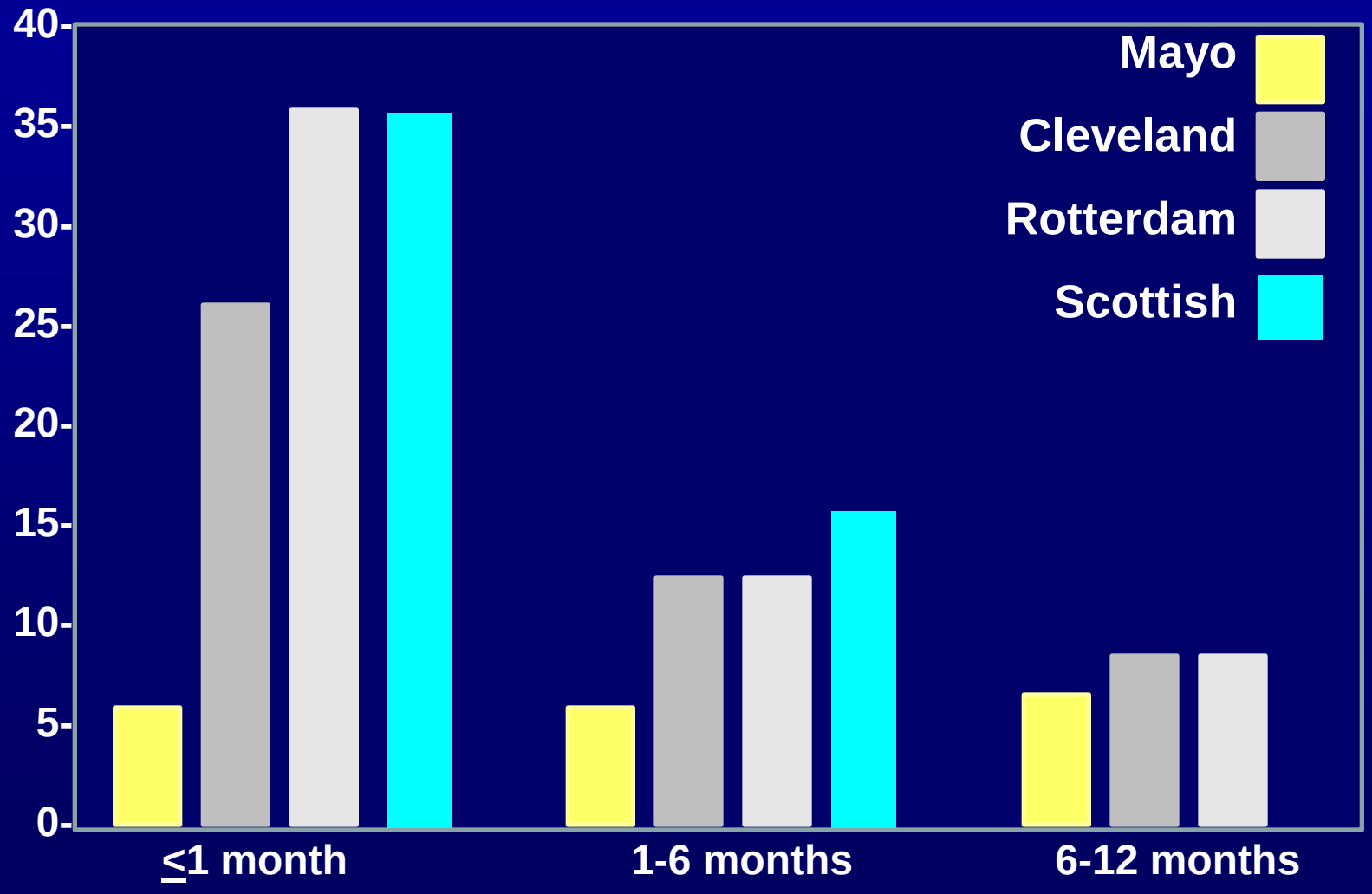
Circulation 2010, 122:1017-1025

Incidence of surgery within 1 year after coronary stenting



Rates of MACE (Death+MI+Stent Thrombosis) In relation to time interval between DES and surgery



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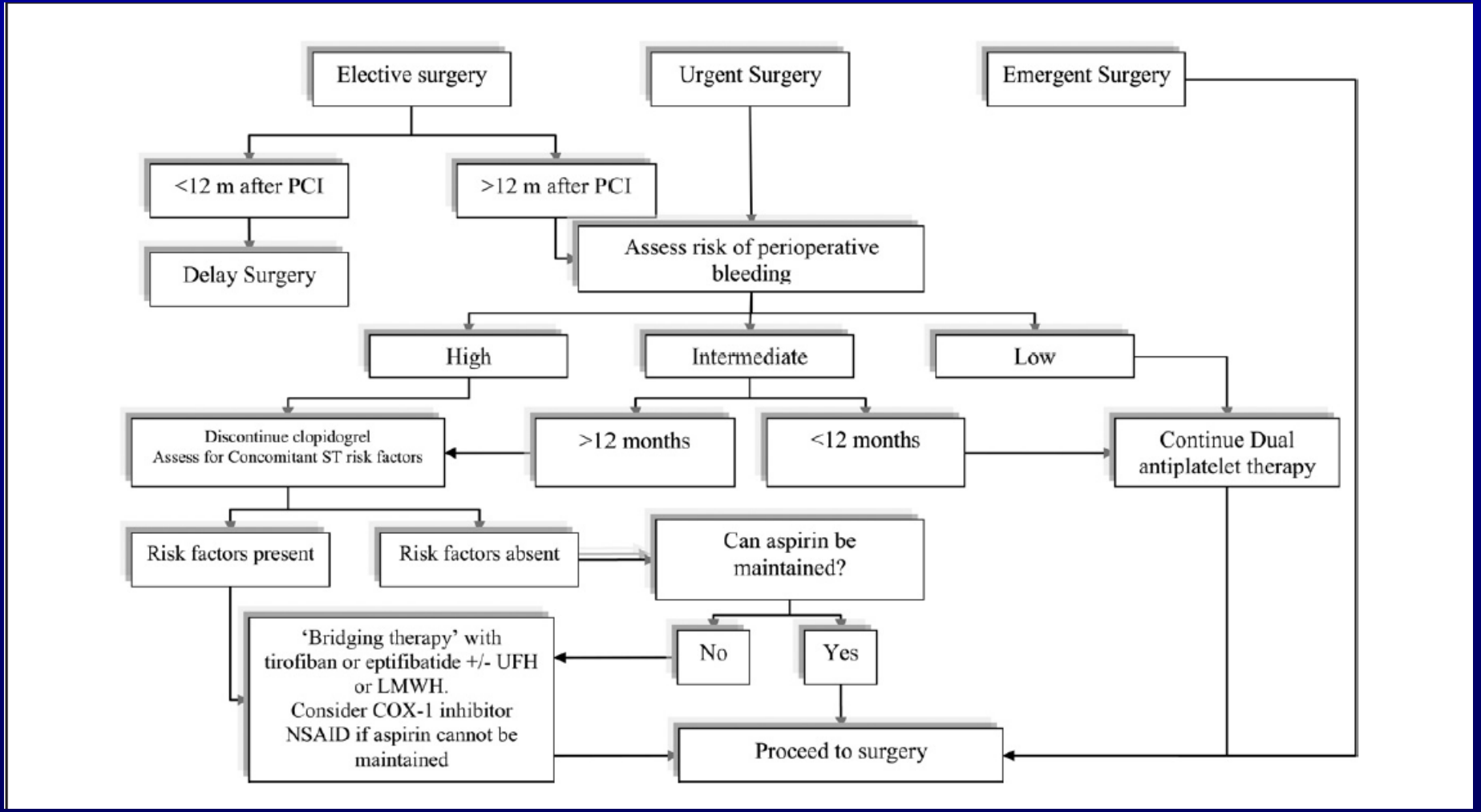
Hemorrhagic Risk in Noncardiac Surgery

Surgical Hemorrhagic Risk	Blood Transfusion Requirement	Type of Surgery
Low	Usually not required	Peripheral, plastic, and general surgery, biopsies; minor orthopedic, otolaryngology, and general surgery; endoscopy; eye anterior chamber; dental extraction and surgery
Intermediate	Frequently required	Visceral surgery; cardiovascular surgery; major orthopedic, otolaryngology, urologic reconstructive surgery
High	Possible bleeding in a closed space	Intracranial neurosurgery; spinal canal surgery; eye posterior chamber surgery

Abualsaud AO, Eisenberg MJ, J Am Coll Cardiol Intv 2010;3:131

Algorithm of Perioperative Management of Pts With DES



Abualsaud AO, Eisenberg MJ, J Am Coll Cardiol Intv 2010;3:131

Guidelines

The Cardiac Society of Australia and New Zealand

Guidelines for the Management of Antiplatelet Therapy in Patients With Coronary Stents Undergoing Non-Cardiac Surgery

Table 3. *Perioperative Antiplatelet Therapy Tailored to Risk.*

	ST risk high	ST risk lower
Bleeding complication risk high: •*Intracranial* •*Spinal* •*Extraocular* •*TURP*	Stop antiplatelet therapy* and if on DAP, consider bridging therapy	Stop antiplatelet therapy*
Bleeding complication risk not high	Continue antiplatelet therapy	Continue antiplatelet therapy

* Stopping DAP five days before surgery is adequate to prevent bleeding complications [43]. Antiplatelet therapy should be recommenced as soon as possible after the procedure.

Phase 2 bridge study for urgent surgery early after DES

Inclusion criteria

Patients within 6-12 months of DES implantation

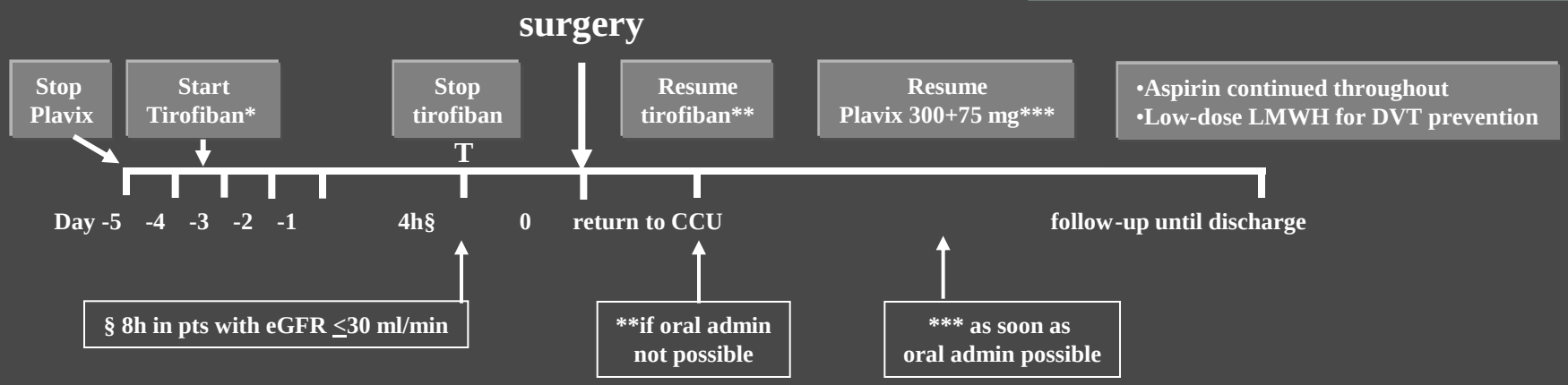
+

high-risk for surgical bleeding, "so that the surgeon would not operate on clopidogrel"

12 months in the case of high-risk of ST:
- stent implantation due to an ACS
- diabetes
- renal insufficiency
- severe LV dysfunction
- DES in LMCA, proximal LAD, bifurcation

Exclusion criteria

- Allergy to tirofiban – eptifibatide
- Thrombocytopenia <100.000
- Stroke < 30 days or prior ICH
- Intracranial disease
- Uncontrolled hypertension
- Unable to sign consent form



Primary EP: the composite of
Death, MI, stent thrombosis, haemostatic reoperation

*Tirofiban:0.4 mg/kg/min over 30', followed by 0.1 mg/kg/min
Or 0.05 mg/kg/min if eGFR <30 ml/min

Dipartimento Cardiologico A. De Gasperis
Azienda Ospedaliera Niguarda Ca' Granda

Phase 2 bridge study
For urgent surgery early after DES: current status

PATIENTS ENROLLED		**58**
	cardiac	20
	urinary tract	7
	gastrointestinal	19
	mixed surgery	12
PRIMARY ENDPOINT*		0 (97.5% C.I. 6.1%)
BLEEDING EVENTS**	major	2
	minor	3
	transf.	13
SEVERE§ THROMBOCITOPENIA		1

* The composite of death+MI+stent thrombosis+haemostatic reoperation
**Bleeding according to TIMI criteria: major means Hb decrease >5 g/dL, minor means Hb decrease ≥3 but <5 g/dL, after correction for transfusion (1 g ofHb for each U transfused); § platelet count <20,000.

Savonitto S. et al J Thromb Haemost 2011, in press

Managing and Resolving the Dual Antiplatelet Conundrum in DES Patients

- **Optimal duration of DAPT** — *1 year reasonable; even less in low-risk pts*
- **Individual response variability** — *new antiplatelet agents might be the answer*
- **Potential drug-interactions** — *?no enough evidence?*
- **Managing DAPT in pts undergoing surgical proceures** — *individual basis; multidisciplinary approach*

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