Parma, 18 marzo 2014 – Ordine dei Medici di Parma

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA Azienda Ospedaliero - Universitaria di Parma	GESTIONE DELLA TERAPIA ANTITROMBOTICA NEI PAZIENTI CANDIDATI A PROCEDURE DI ENDOSCOPIA DIGESTIVA	PROCEDURA INTERDIPARTIMENTALE P01 E24A, B58A, B62A, B64A
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA Azienda Ospedaliero - Universitaria di Parma	GESTIONE DELLA TERAPIA ANTITROMBOTICA NEI PAZIENTI CANDIDATI A PROCEDURE DI ENDOSCOPIA TORACICA	PROCEDURA AZIENDALE

La terapia antiaggregante piastrinica: indicazioni, durata e rischi della sospensione

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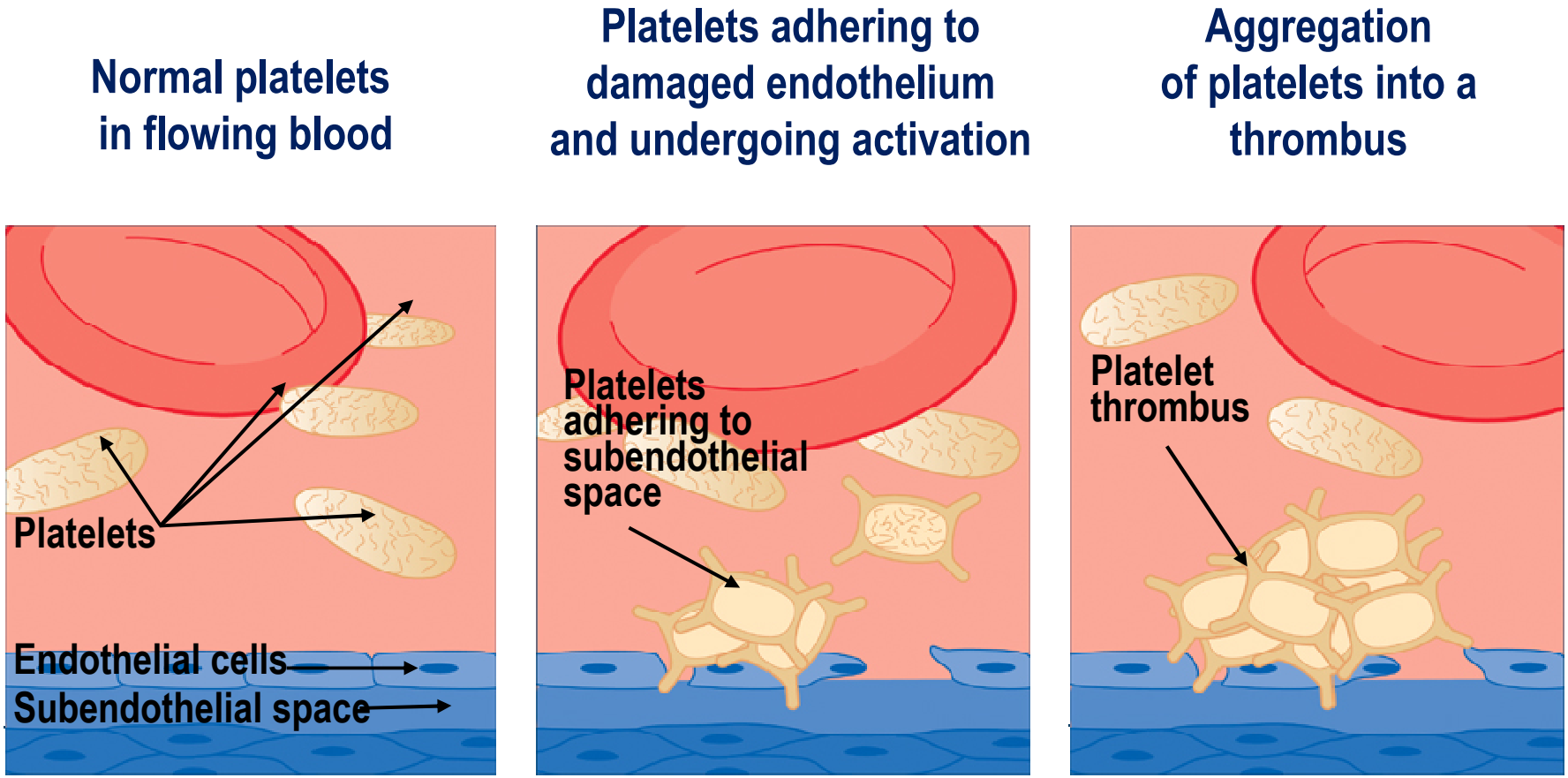
Azienda Ospedaliero-Universitaria di Parma

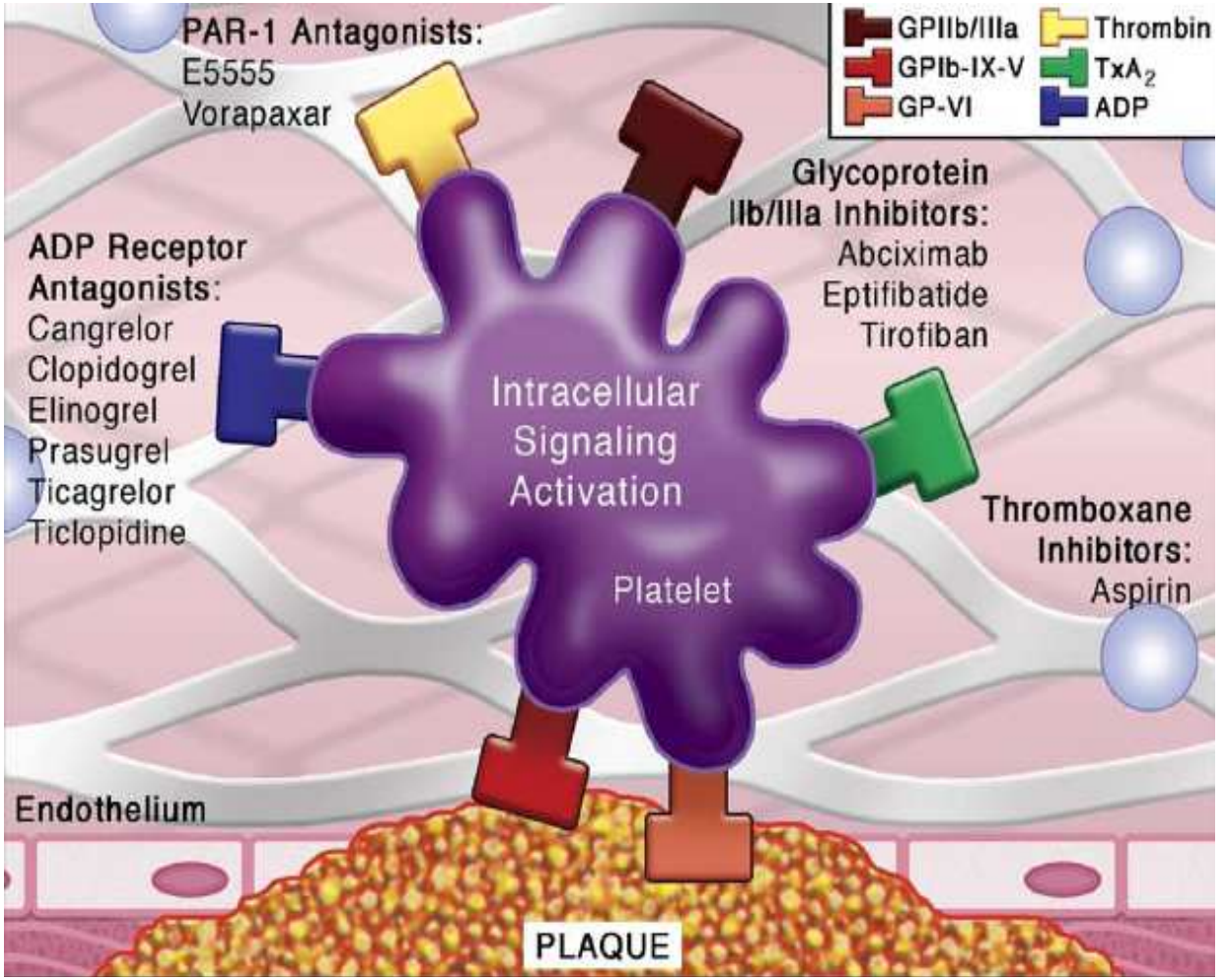
Platelet and Thrombus formation



Adapted from: Ferguson JJ. The Physiology of Normal Platelet Function.

In: Ferguson JJ, Chronos N, Harrington RA (Eds). Antiplatelet Therapy in Clinical Practice. London: Martin Dunitz; 2000: pp.15–35.

Multiple pathways of platelet inhibition



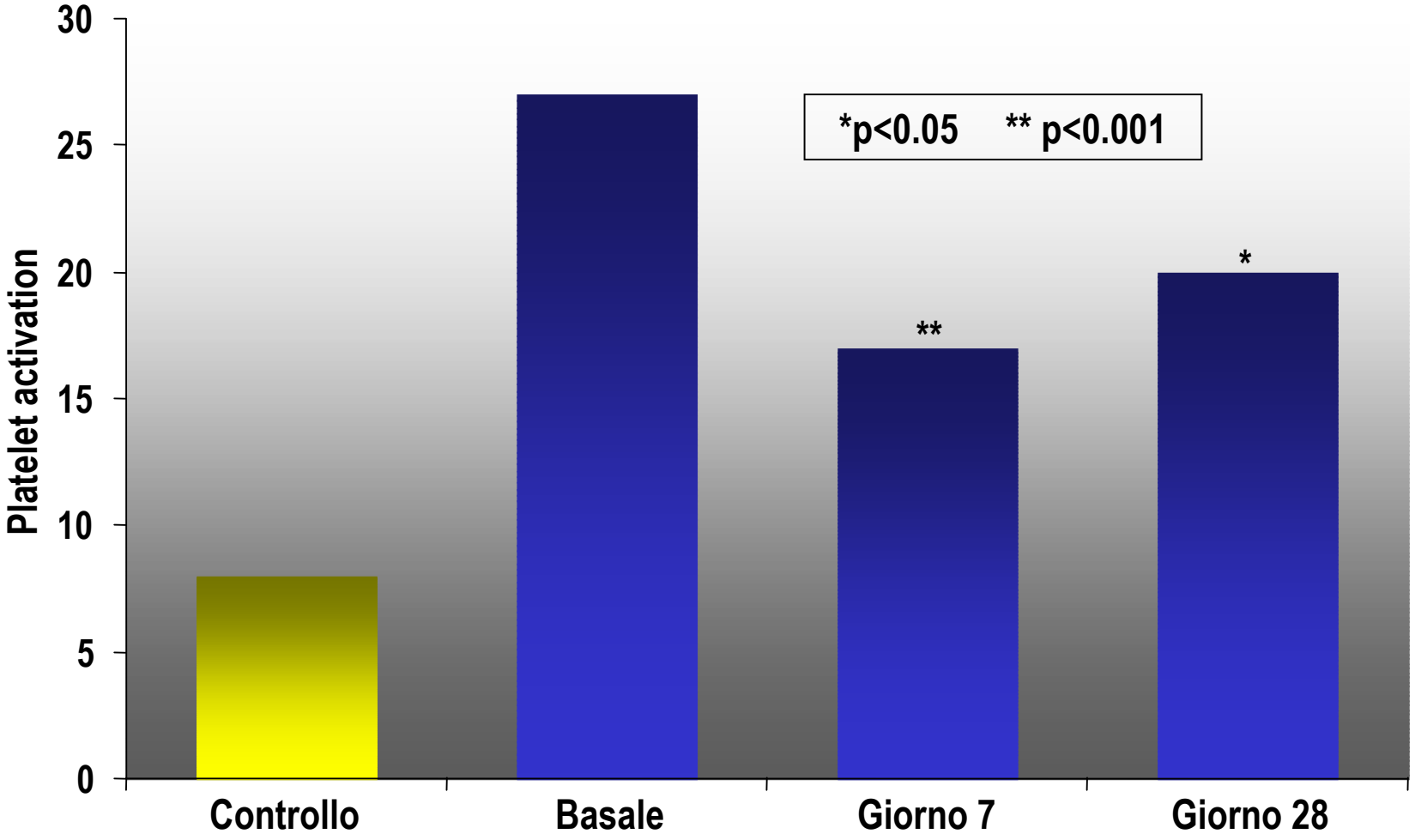
Deasai NR and Bhatt DL JACC Intv 2010;3:571-83

Recommendations for oral antiplatelet agents (1)

Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
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
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.	I	B

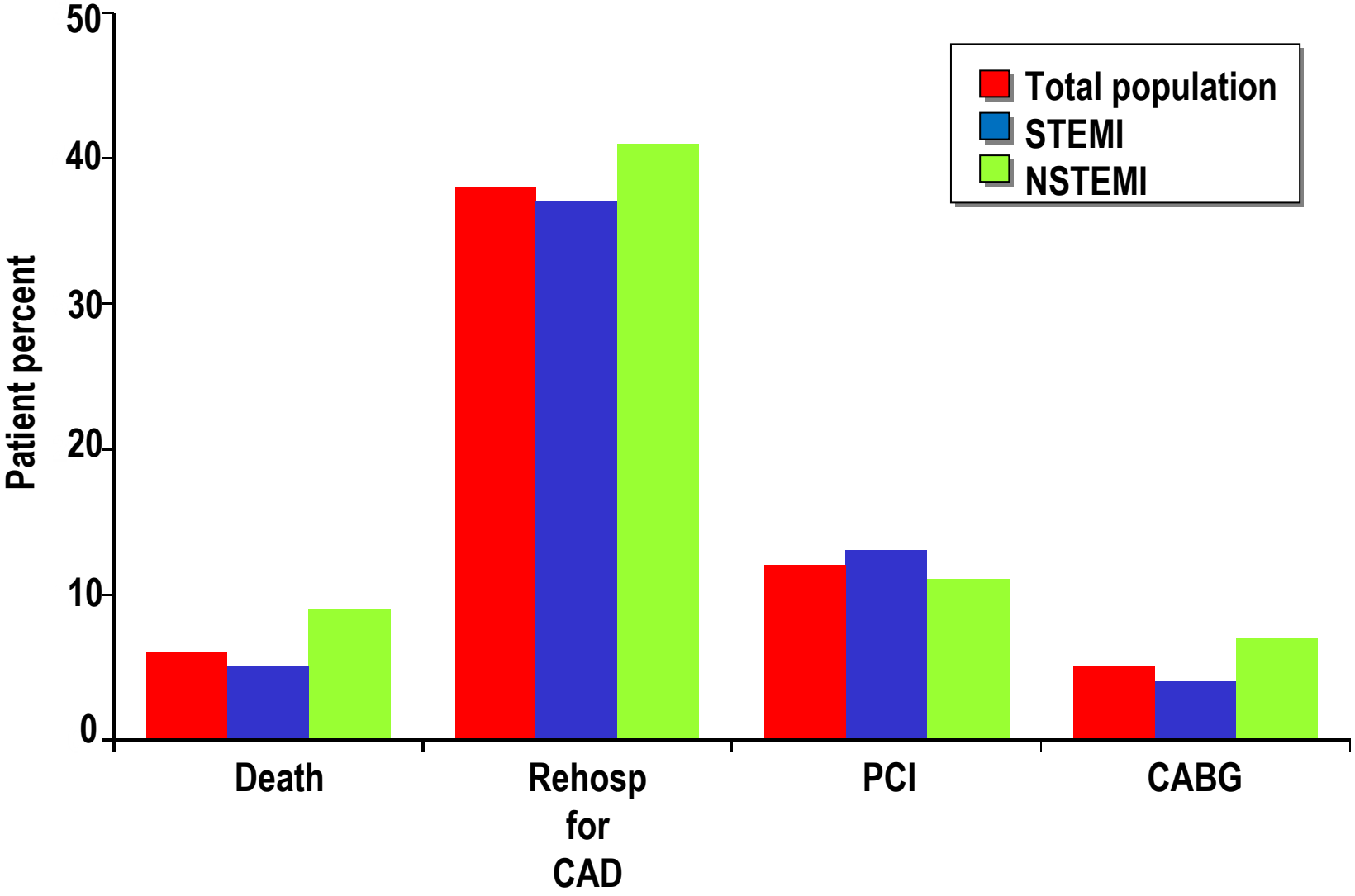
European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

Persistent platelet hyperactivity after ACS



Ault K. et al. J Am Coll Cardiol 1999; 33: 634-639

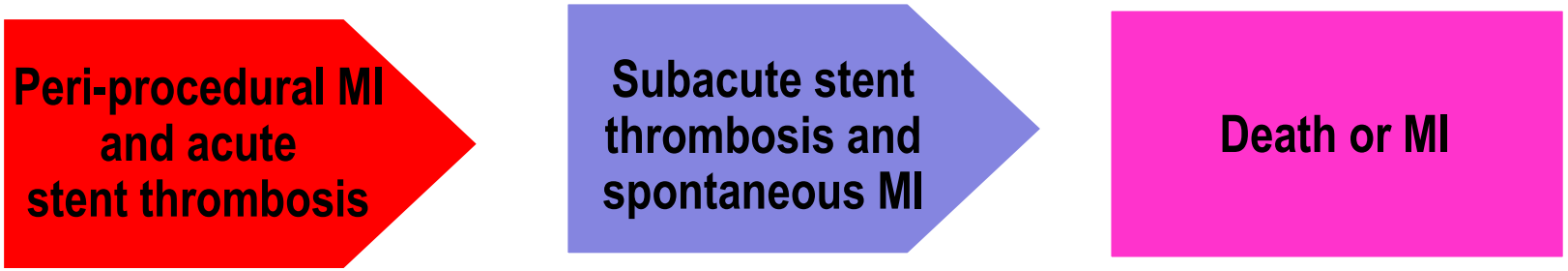
Acute Coronary Syndromes
Clinical outcomes at 1 year post-discharge



Montalescot G. et al,. Eur Heart J 2007; 28: 1409-1417

Antiplatelet therapy in PCI

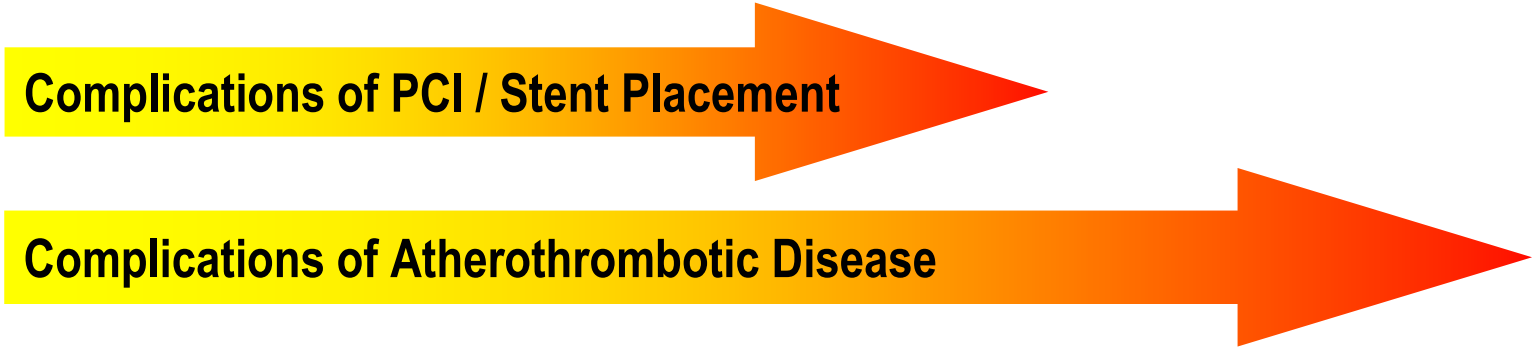
Early and Long-Term Risk of Ischemic Events



- Within 48 hours
- Incidence: 6-8%

- Within 30 days
- Incidence: 6.5-8.5%

- 1 year
- Incidence: 10-12%



EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES
MYOCARDIAL REVASCULARIZATION 2010

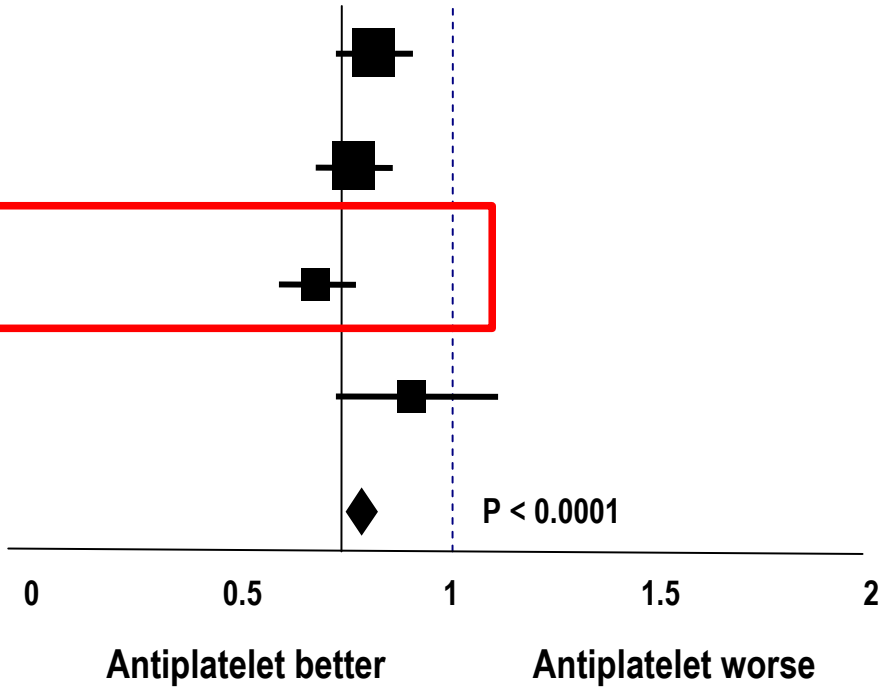
Recommended duration of dual antiplatelet therapy after percutaneous coronary intervention:

a) 1 month after BMS implantation in stable angina;
b) 6–12 months after DES implantation in all patients.

ASPIRIN
Dose and Efficacy

Indirect comparisons of aspirin doses in high-risk patients

Aspirin dose	No. of trials	Percent
500 - 1500 mg	34	9
160 - 325 mg	19	26
75 - 150 mg	12	32
< 75 mg	3	13
Any aspirin	65	23



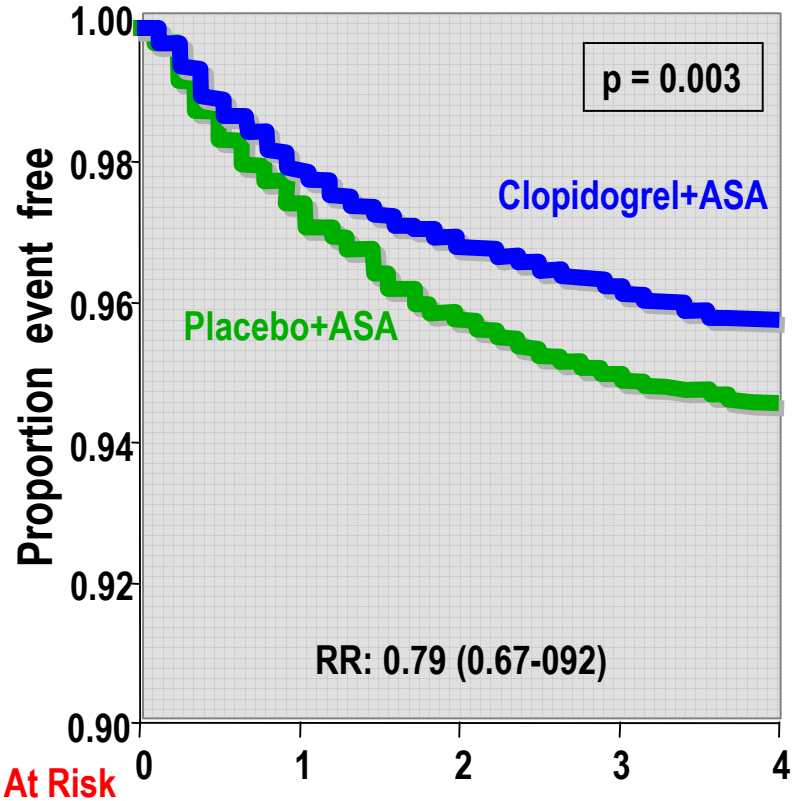
Antithrombotic Trialist Collaboration BMJ 2002; 324:71-86

CURE

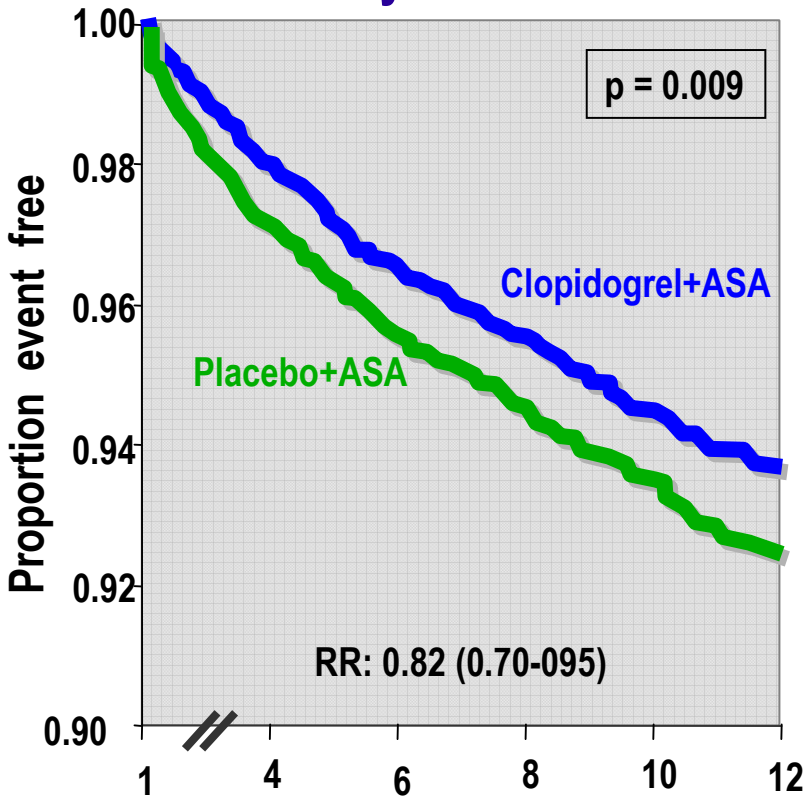
Early and Late Effects of Clopidogrel

12,562 patients hospitalized for NSTE-ACS, with hig risk profile
Primary End Point (MI/IS/CV Death)

0-4 days



31 days to 12 months



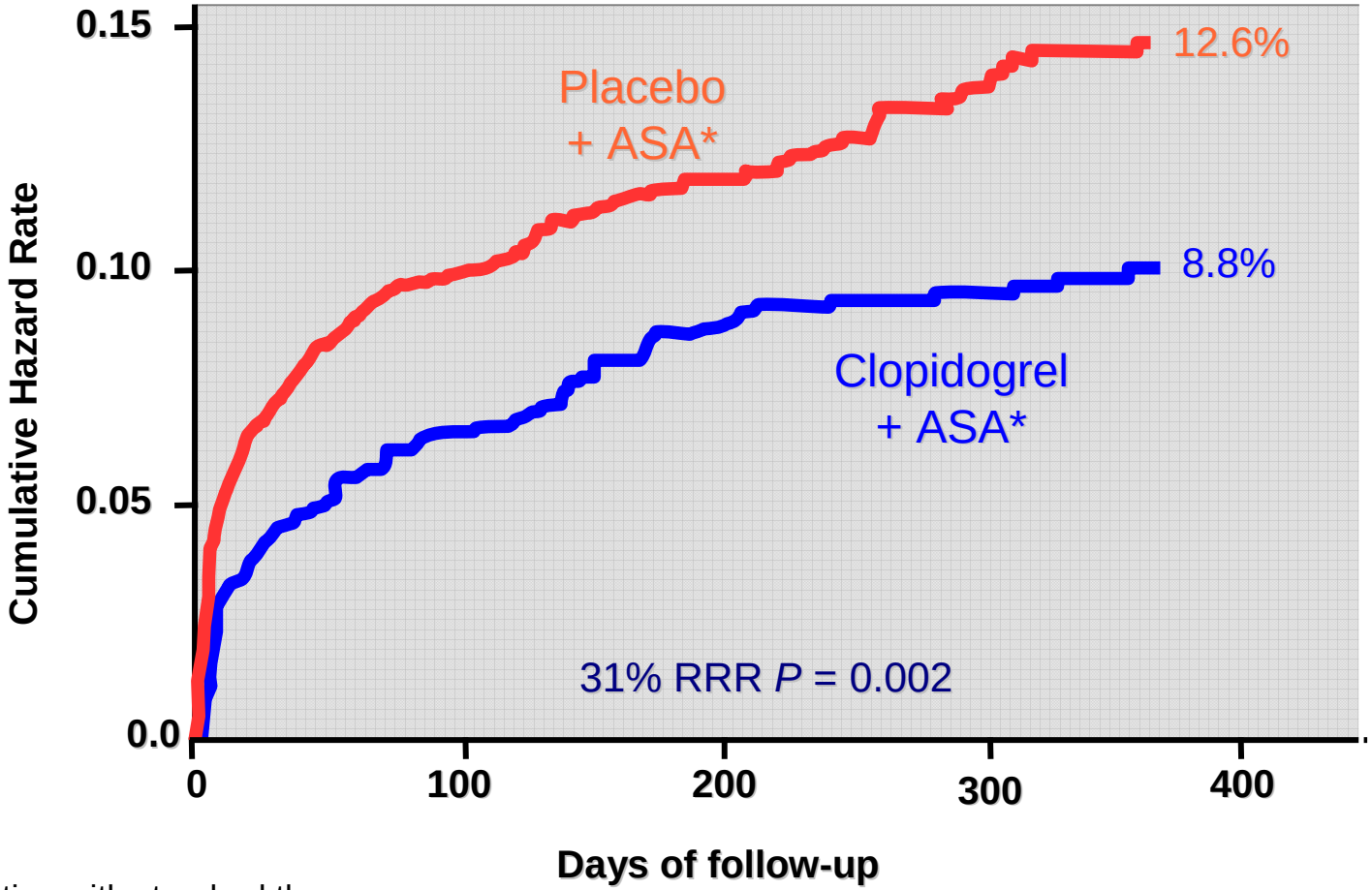
No. At Risk												
Clopidogrel	6259	6145	6070	6026	5990	5981	5481	4742	4004	3180	2418
Placebo	6303	6159	6048	5993	5965	5954	5390	4639	3929	3159	2388

The CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.

PCI - CURE

Early and Late Effects of Clopidogrel

N = 2658 subgroup of CURE, recieving PCI
Primary Endpoint (CV Death or MI from PCI to end of follow-up)



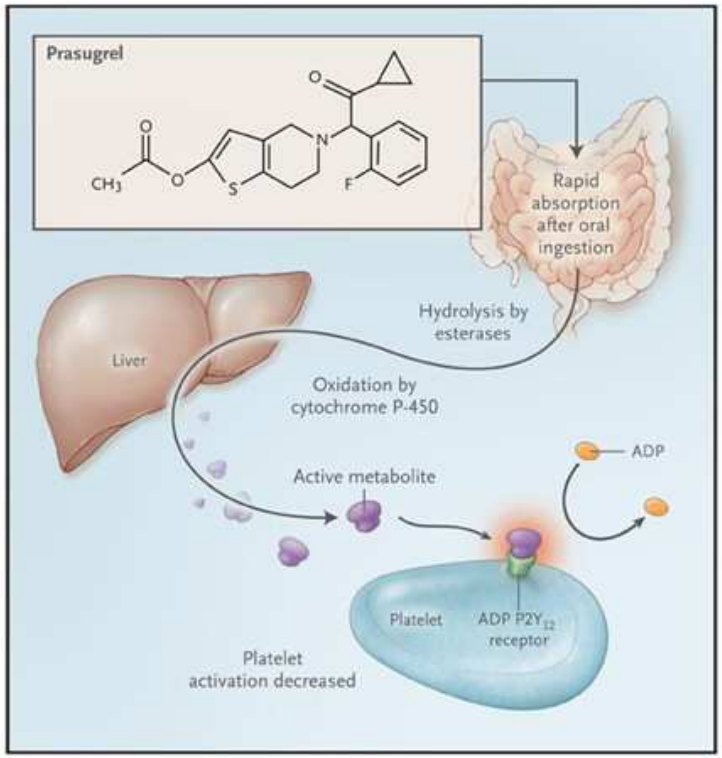
* In combination with standard therapy

Mehta, SR. et al for the CURE Trial Investigators. *Lancet.* August 2001.

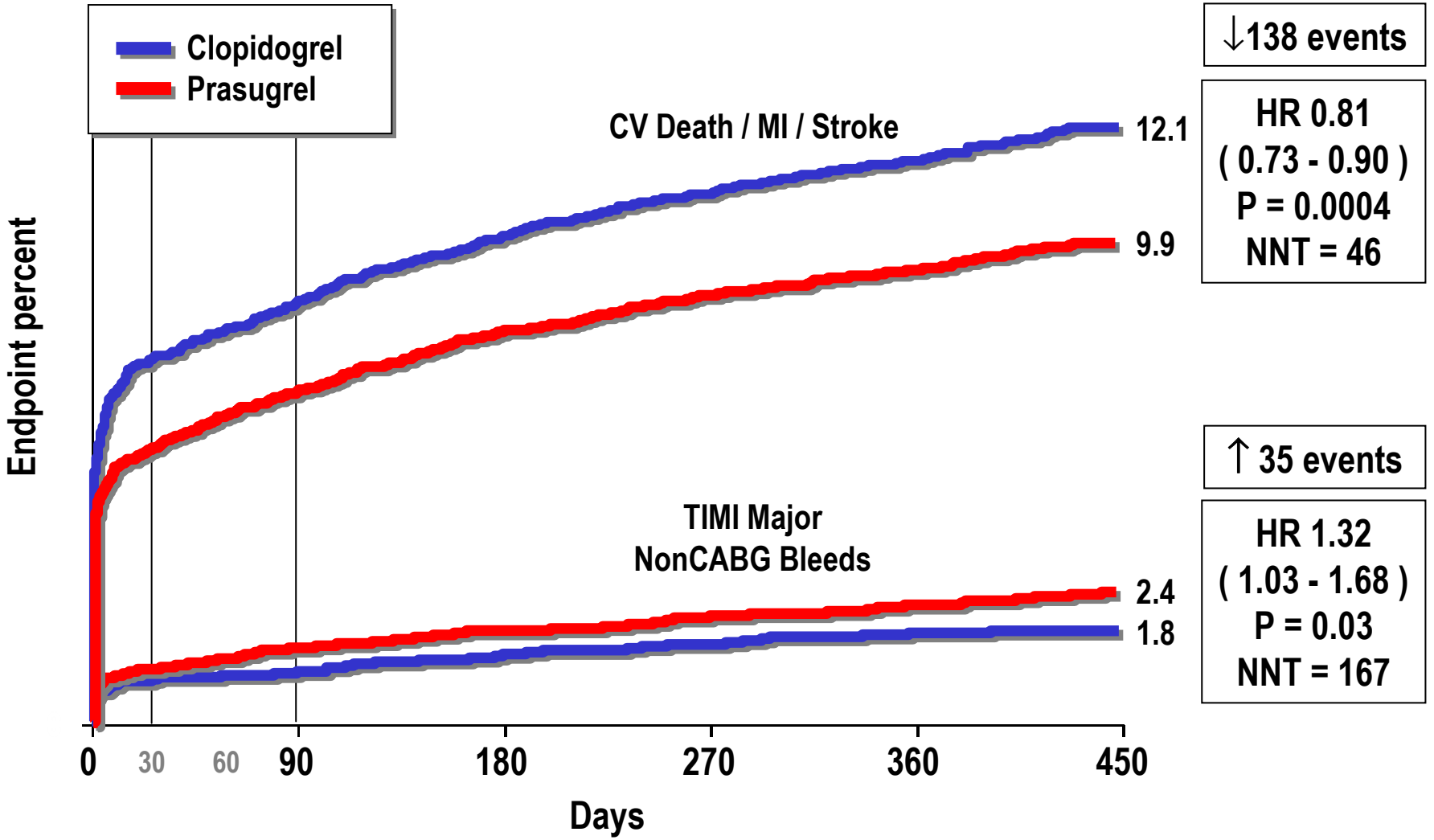
Prasugrel

Metabolism and mechanism of action

- ✓ **Pro-drug, no resistance or variability in response**
- ✓ **Rapid onset of antiplatelet effect**
- ✓ **Irreversible effect with slow offset of antiplatelet effect**
- ✓ **Efficacy endpoint (more potent than clopidogrel)**
- ✓ **Safety endpoint**



The TRITON-TIMI 38 trial
Prasugrel vs clopidogrel in ACS undergoing PCI



Wiviott SD et al. N Engl J Med 2007; 357:2001-2015

Ticagrelor

Metabolism and mechanism of action

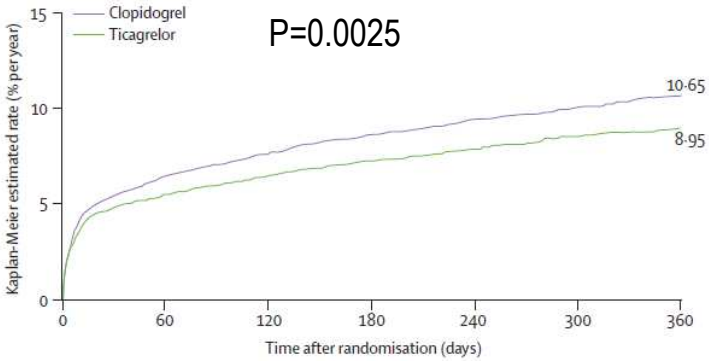
- ✓ **Active drug, no resistance or variability in response**
- ✓ **Rapid onset and offset of antiplatelet effect**
- ✓ **Reversible effect**
- ✓ **Efficacy endpoint**
- ✓ **Safety endpoint**

Nature Review Cardiology 2009;6:737-8

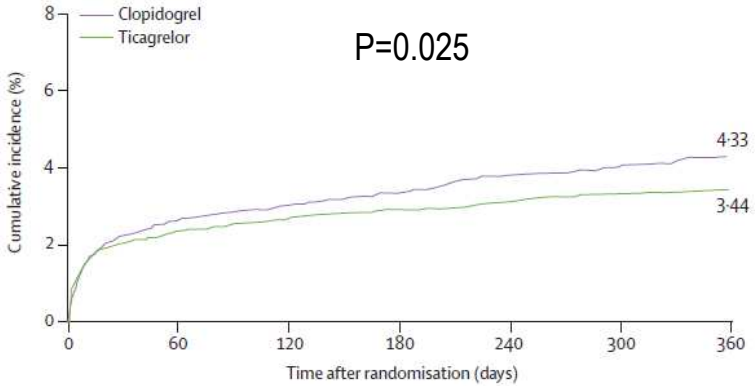
The PLATO trial

Ticagrelor vs clopidogrel in ACS with a planned invasive strategy

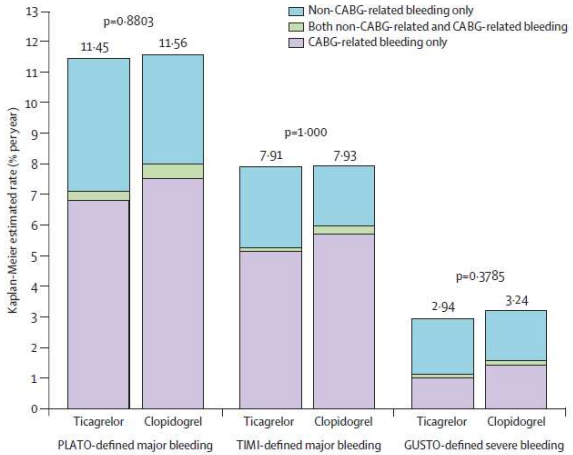
Primary endpoint: CV death, MI or stroke



Secondary endpoint: CV death

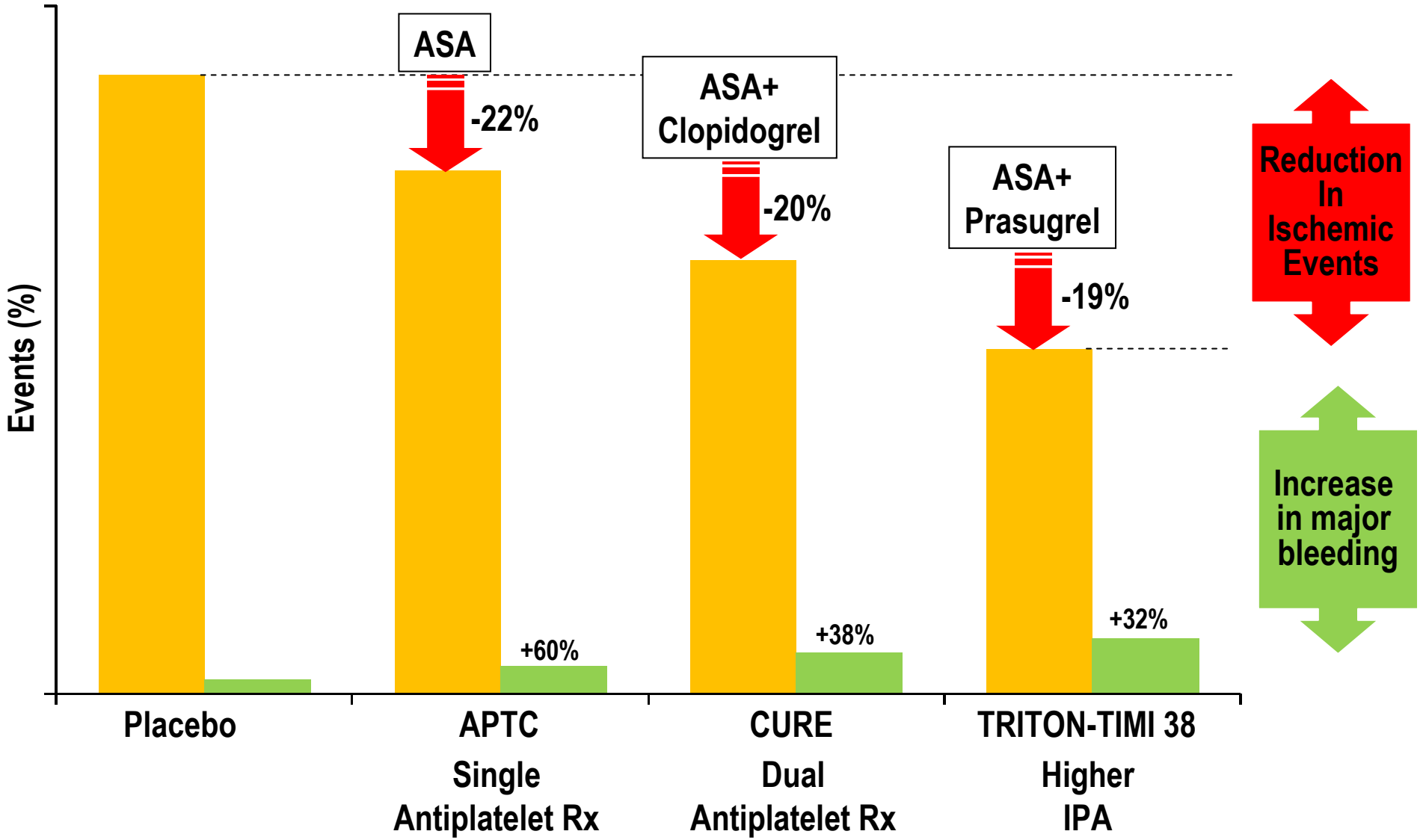


Rates of major bleeding



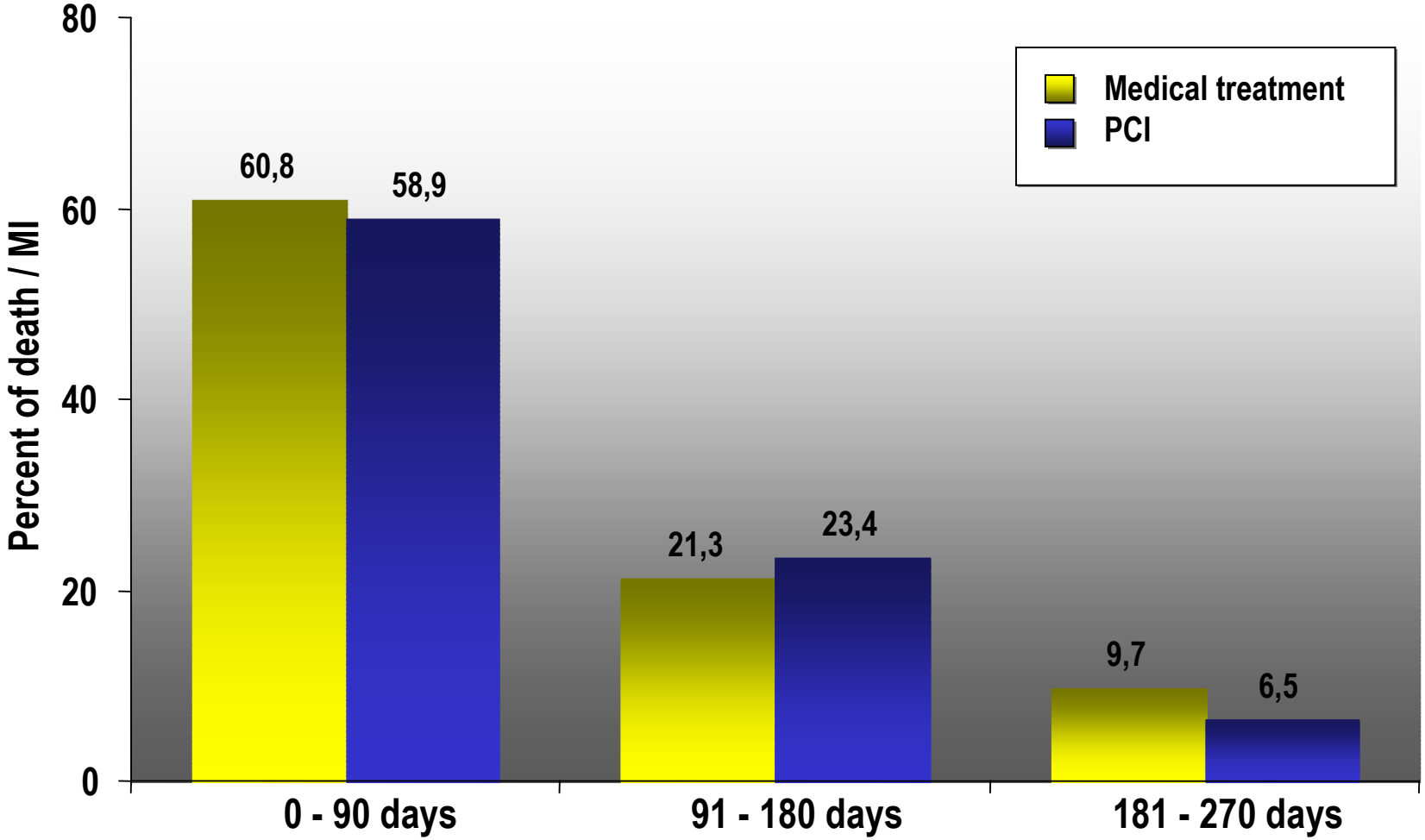
Cannon CP., et al. Lancet 2010;375:283-93

Antiplatelet Therapy in ACS



Adverse Events after Stopping Clopidogrel after Acute Coronary Syndrome

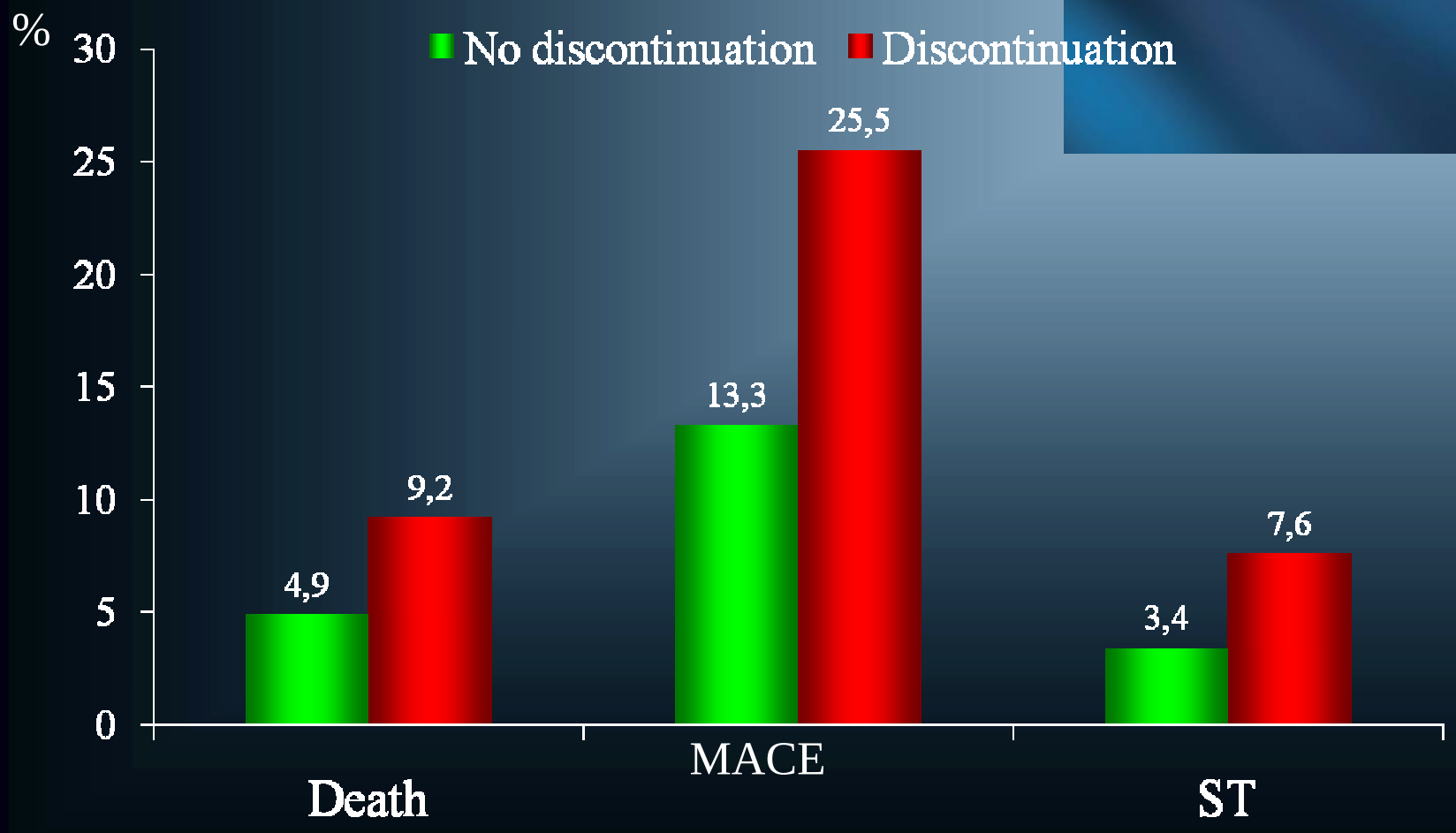
Time distribution of death or MI in 268 of 3137 patients after stopping DAT (mean DAT duration 302 ±151 days)



HO PM et al. JAMA 2008; 299 (5): 532-539

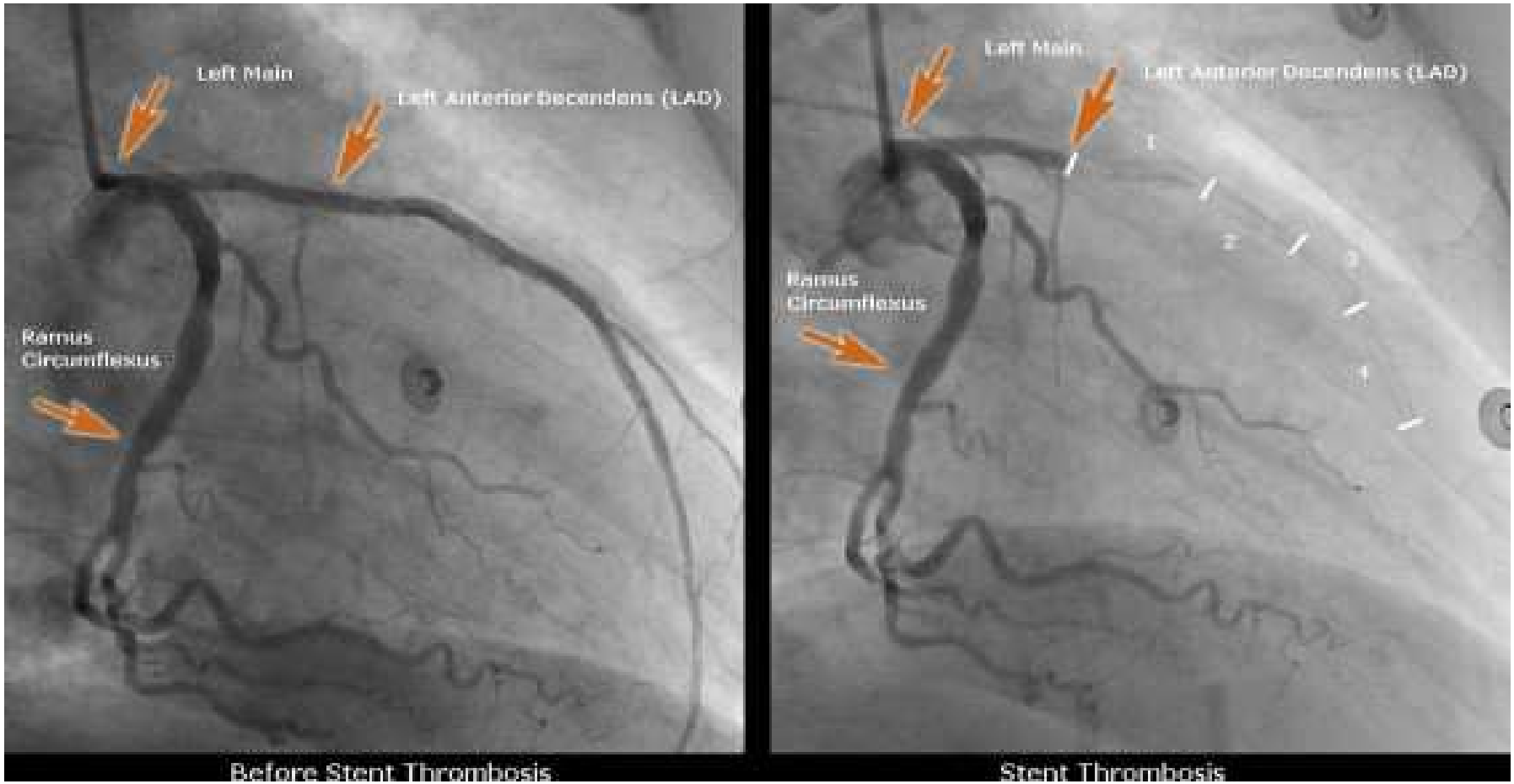
Discontinuation of antiplatelet therapy after coronary stenting and Prognosis

Pts who discontinued antiplatelet therapy had a higher incidence of death, MACE and stent thrombosis

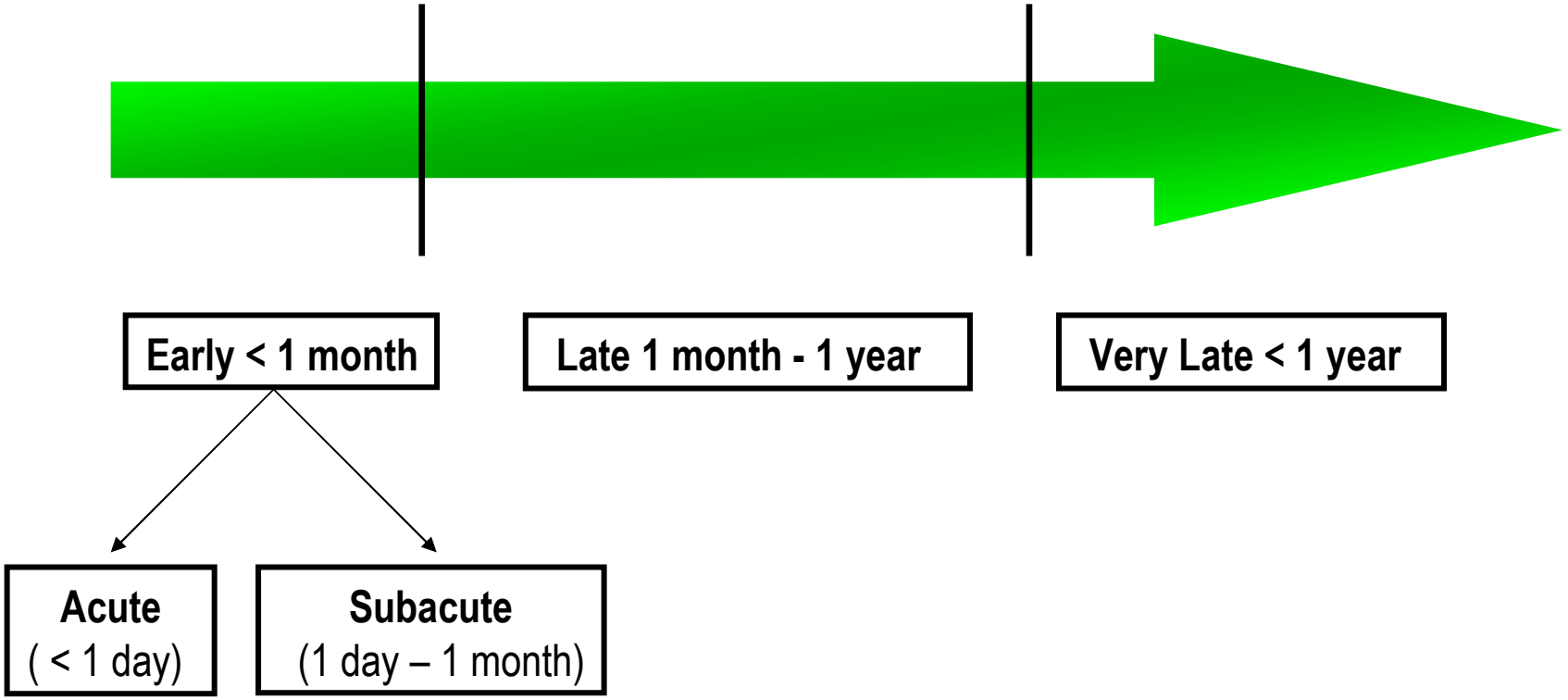


Rossini R et al. Am J Card 2011, 107: 186-194

Coronary Stent Thrombosis

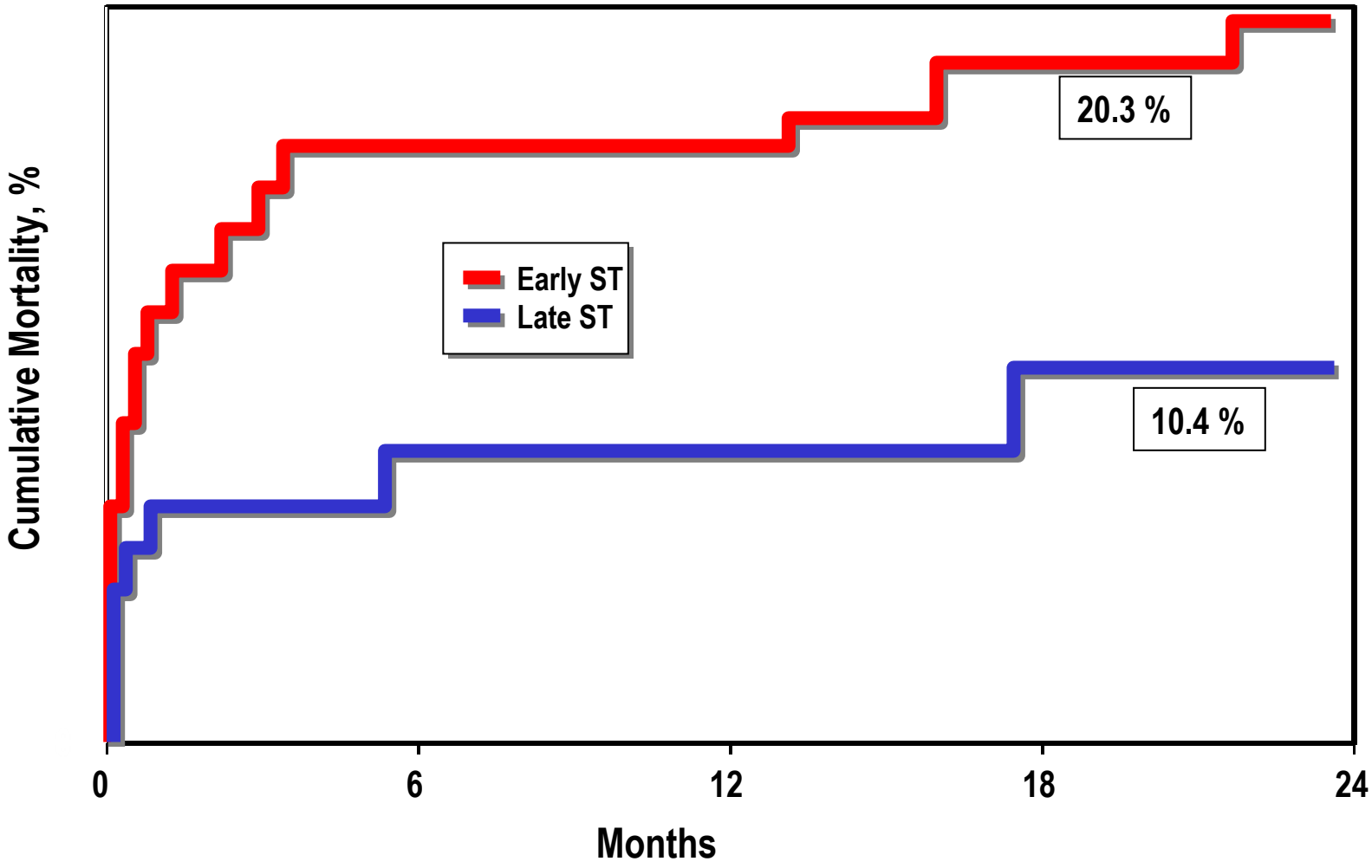


Time Frame of Stent Thrombosis



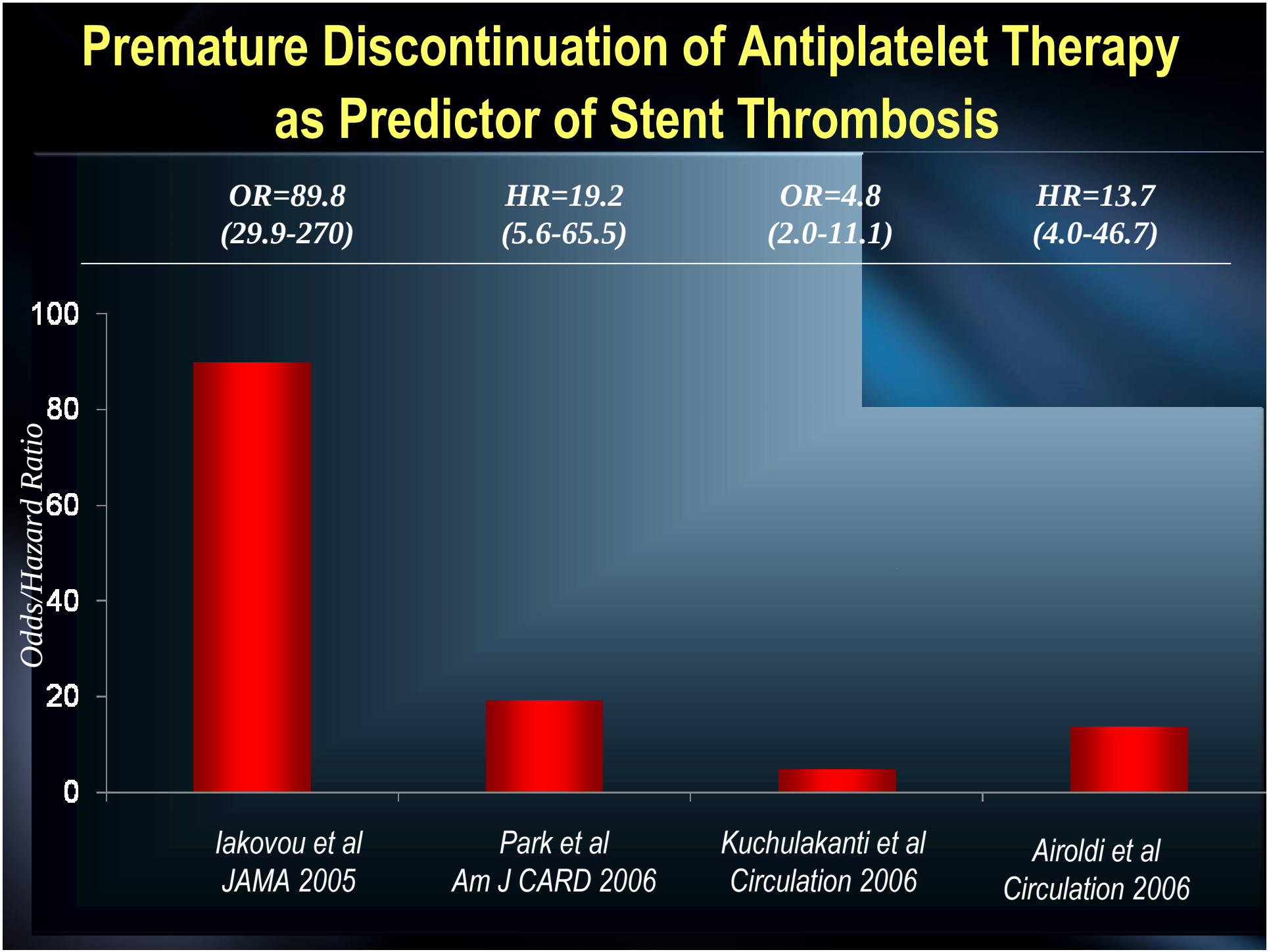
Adapted from Windecker, Circulation 2007;116:1952-1965

Cumulative Mortality after Stent Thrombosis



Wenaweser P. et al JACC 2008; 52: 1134-40

Premature Discontinuation of Antiplatelet Therapy as Predictor of Stent Thrombosis

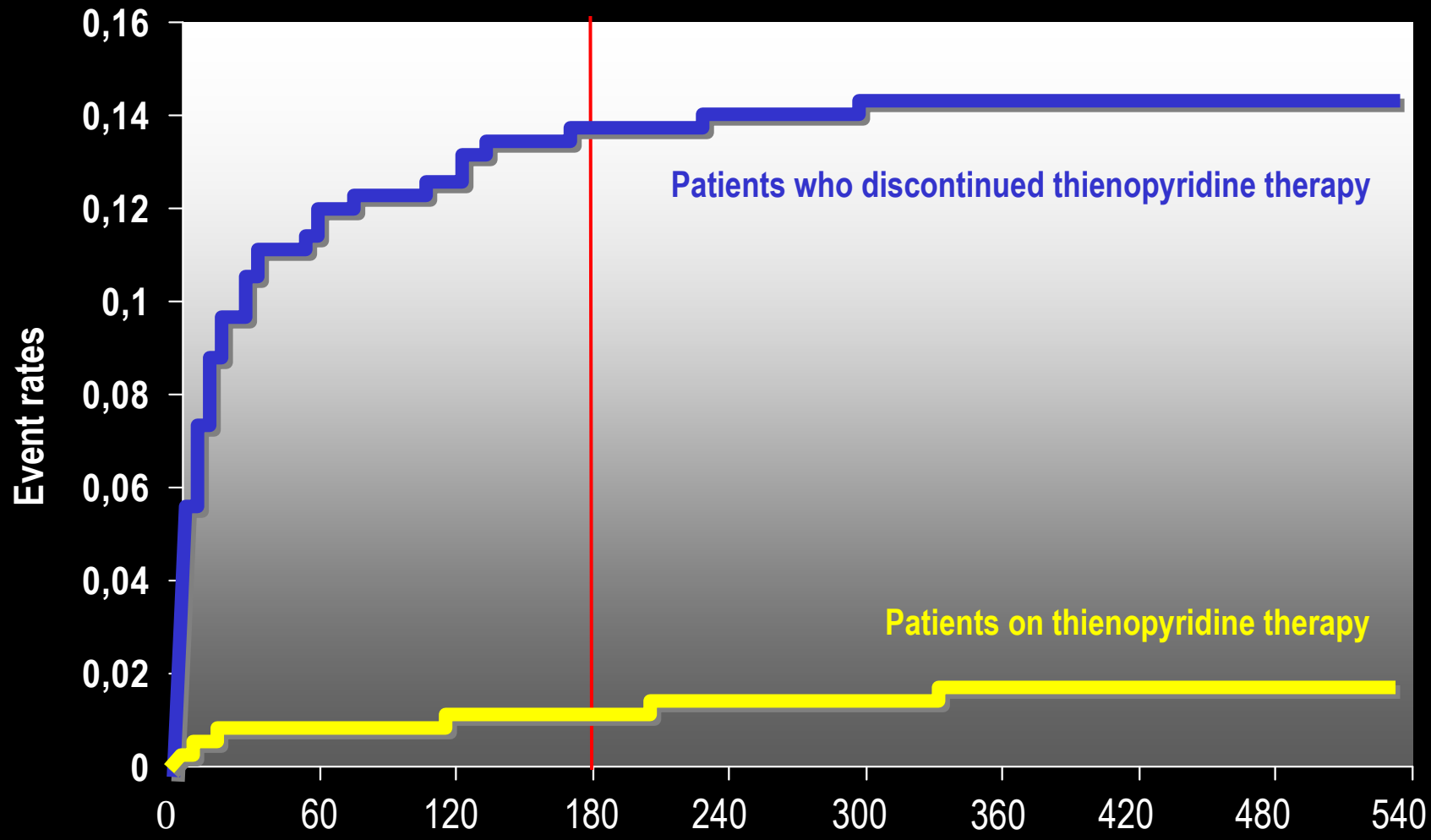


Predictors of Stent Thrombosis

	HR (95% CI)	P value
Premature antiplatelet discontinuation	**161.17 (26.03-997.94)**	**<0.001**
Renal failure	10.06 (3.13-32.35)	<0.001
Bifurcation lesion	5.96 (1.90-18.68)	0.002
Diabetes	5.84 (1.74-19.55)	0.004
LVEF per 10% decrease	1.12 (1.06-1.19)	<0.001
Stent lenght, per 1 mm increase	1.03 (1.00-1.05)	0.01

Lakovou I et al JAMA, 2005;296:2126-30

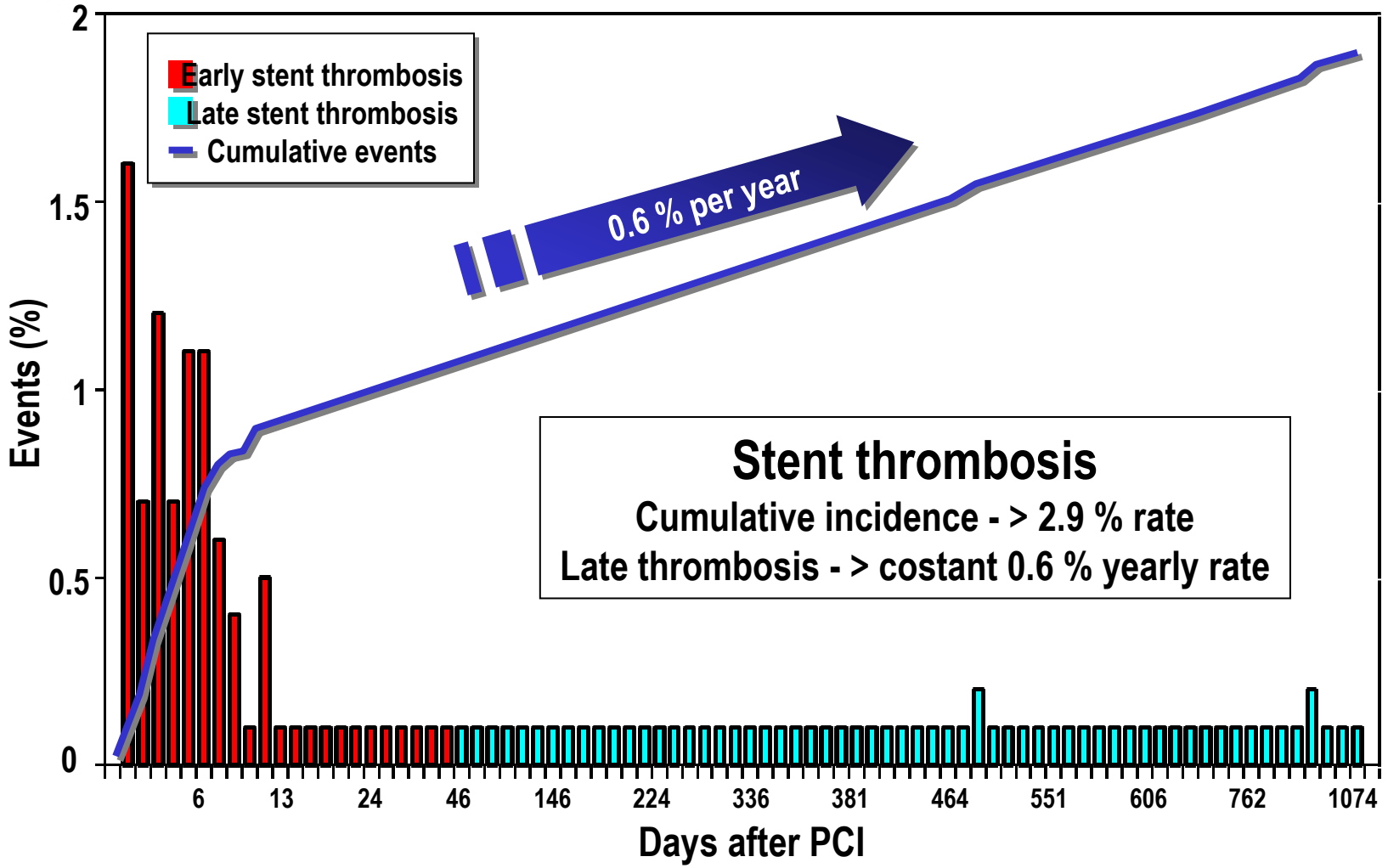
Cumulative Risk in patients on Dual-Antiplatelet Therapy and in patients who discontinued



Airoldi F et al. Circulation 2007; 116:745-754.

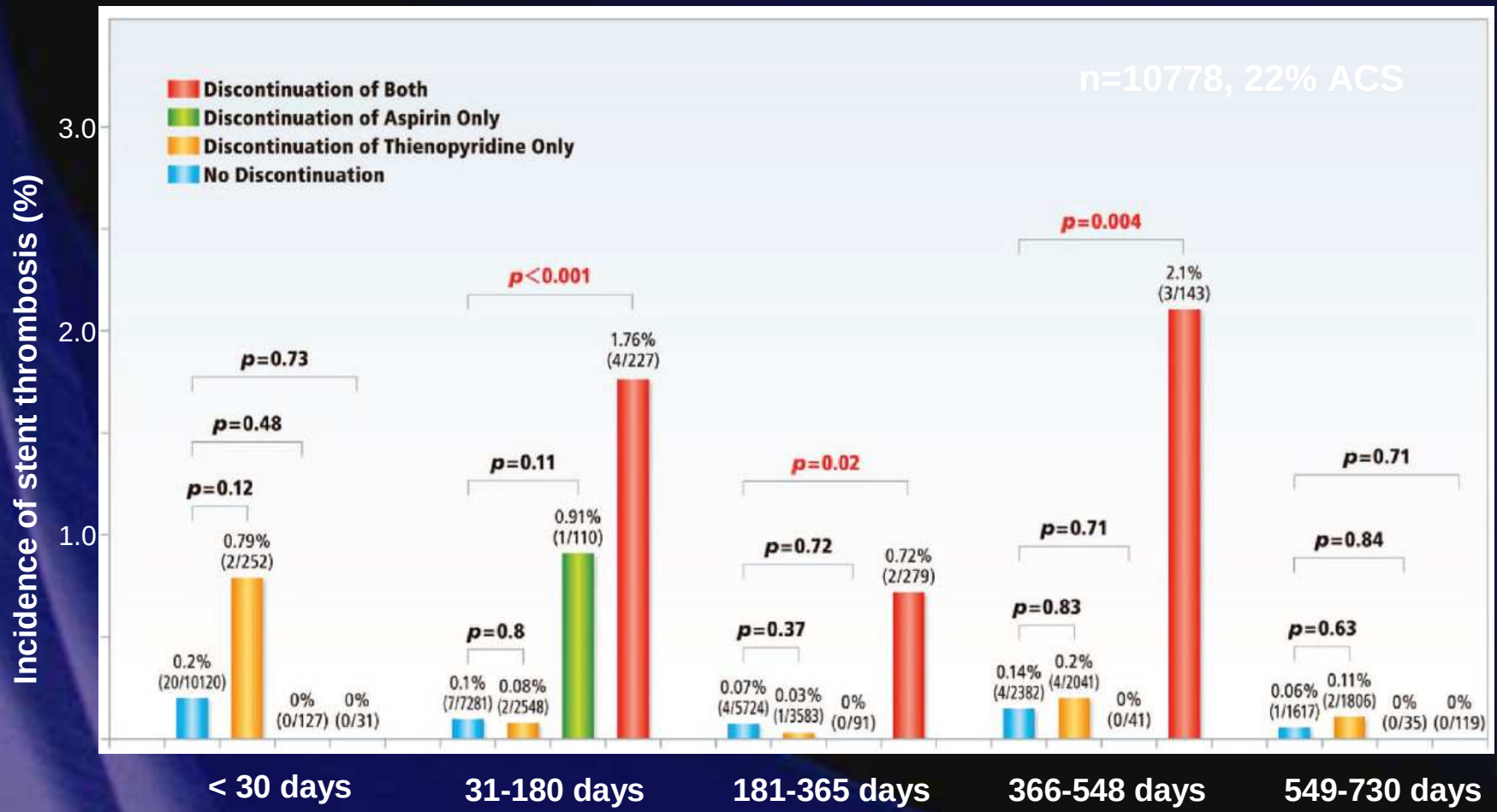
Rotterdam-Bern Registry
Long-term incidence of DES thrombosis

8146 patients treated with DES (sirolimus or paclitaxel-eluting stents) followed for a mean of 1.7 years (up to 3)



Daemen J. et al. Lancet 2007; 369: 667-678

Incidence of ST and Discontinuation of Thienopyridine or ASA up to 2 yrs post SES



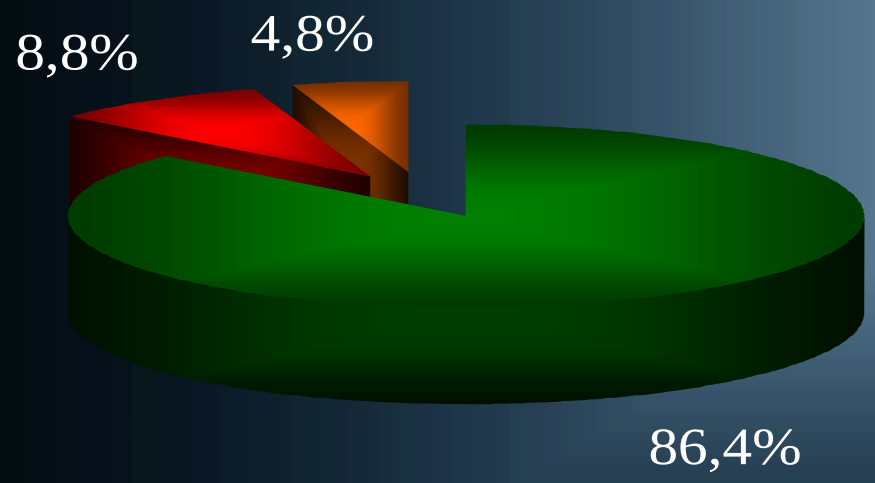
APT = antiplatelet therapy
SES = sirolimus eluting stent

Kimura T et al. Circulation 2009;119:987-995

Prevalence, Predictors, and Long-Term Prognosis of Premature Discontinuation of Oral Antiplatelet Therapy After Drug Eluting Stent Implantation

Roberta Rossini, MD, PhD[a,*], Davide Capodanno, MD[b], Corrado Lettieri, MD[c], Giuseppe Musumeci, MD[a], Tamar Nijaradze, MD[a], Michele Romano, MD[c], Nikoloz Lortkipanidze, MD[a], Nicola Cicorella, MD[c], Giuseppe Biondi Zoccai, MD[d], Vasile Sirbu, MD[a], Antonio Izzo, MD[c], Giulio Guagliumi, MD[a], Orazio Valsecchi, MD[a], Antonello Gavazzi, MD[a], and Dominick J. Angiolillo, MD, PhD[b]

- *1358 consecutive pts treated with DES discharged on ASA (100 mg/day) + clopidogrel (75 mg/day)*
- *Clopidogrel was to be maintained for 12 months*
- *Pts were followed-up for 32.4 ±11.3 months*

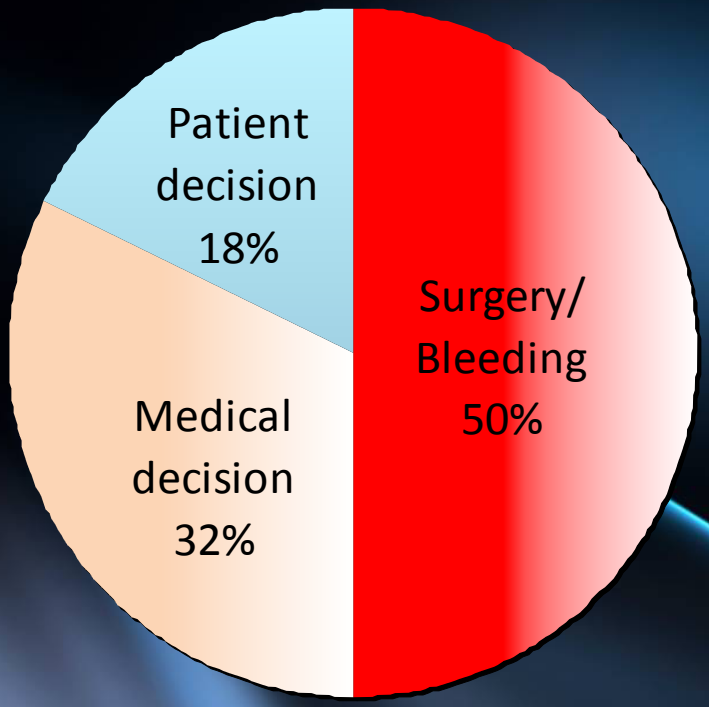


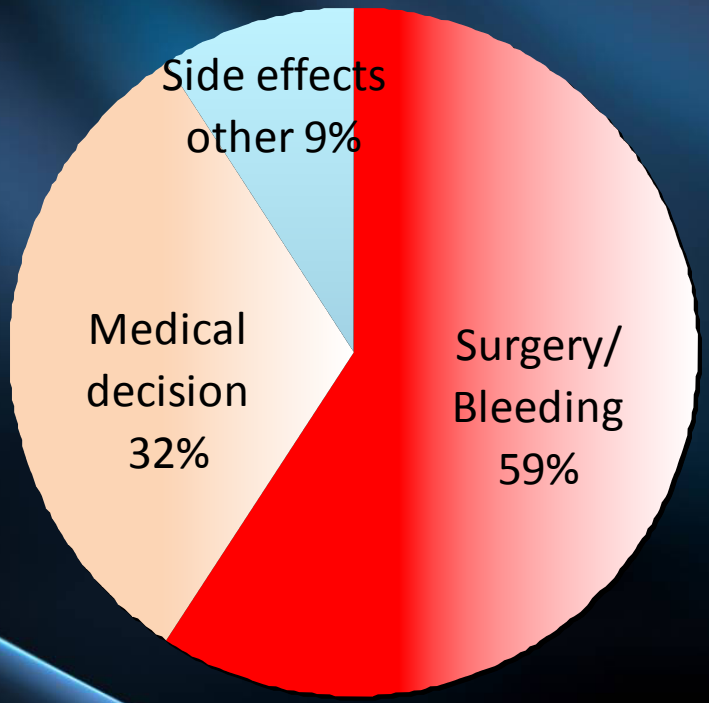
Discontinuation Causes:

- Surgery 34.5%
- Bleeding 21%
- Medical decision 17.6%
- Dental interventions 7.6%
- Economic/burocratic reasons 5.9%
- Anticoagulant therapy 5.0%

Rossini R et al. Am J Card 2011, 107: 186-194

Causes of premature antiplatelet discontinuation

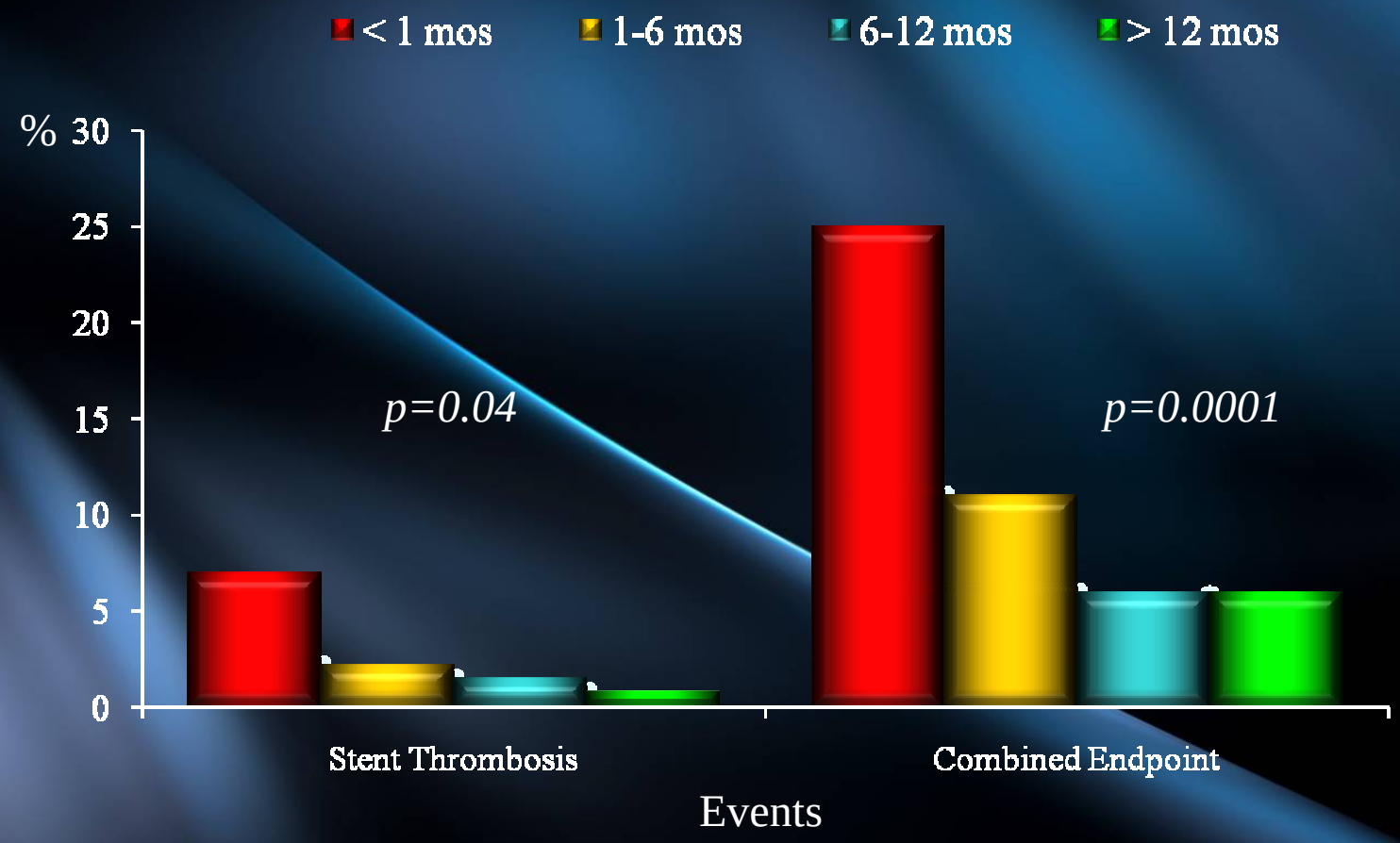




Ferreira-Gonzalez, I. et al. Circulation 2010;122:1017-1025

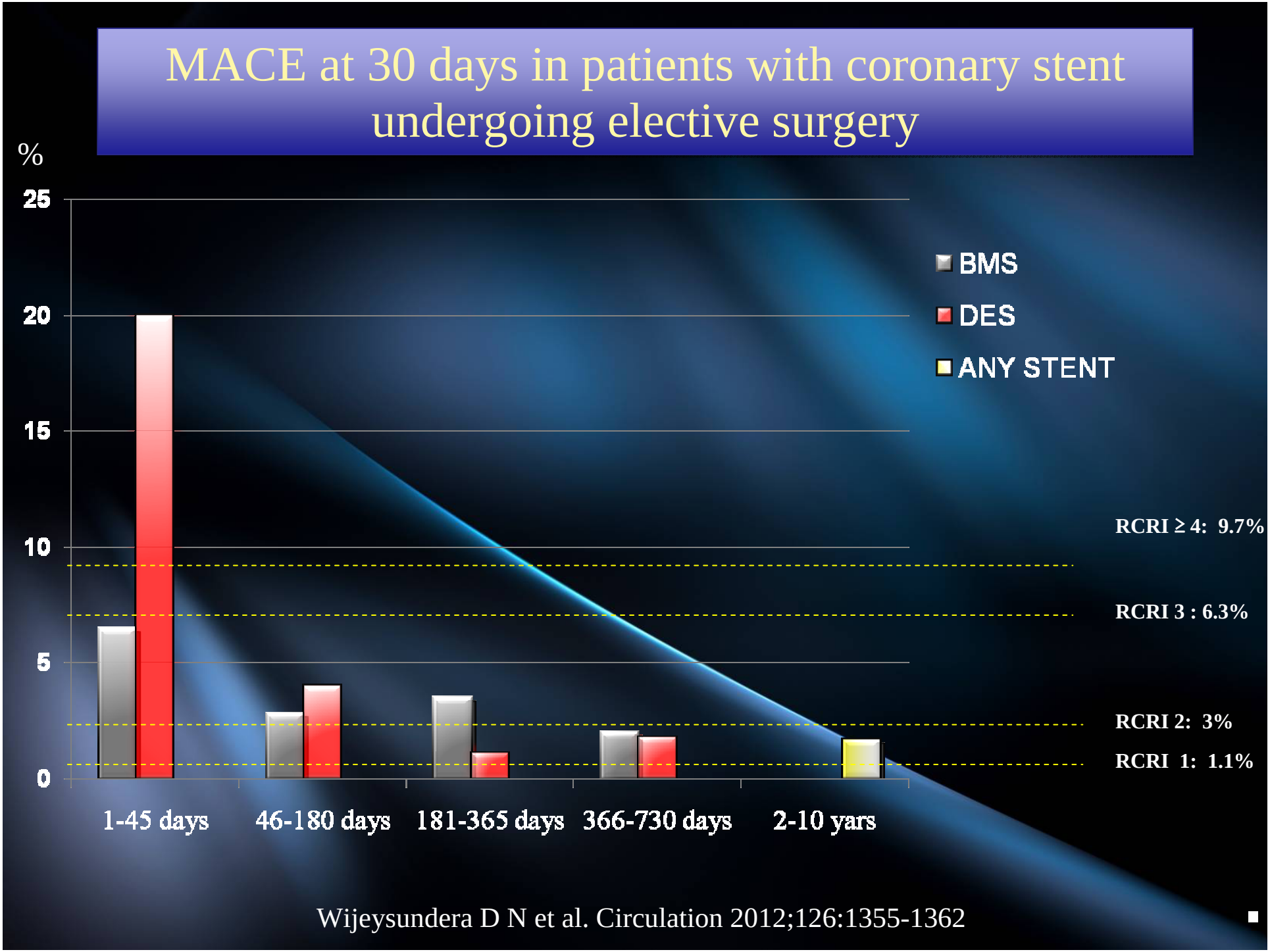
G. Parodi et al. Am J Cardiol 2012;109:214-218

Events as stratified by time from PCI to surgery



Anwaruddin S. et al. J Am Coll Cardiol Intv 2009;2:542–9

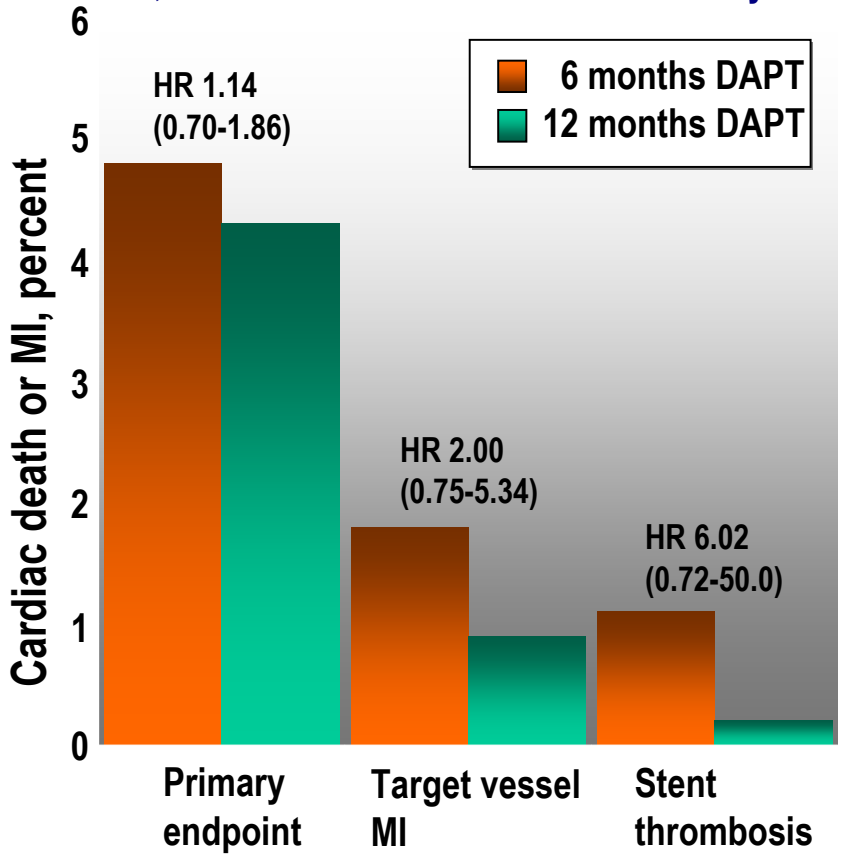
MACE at 30 days in patients with coronary stent undergoing elective surgery

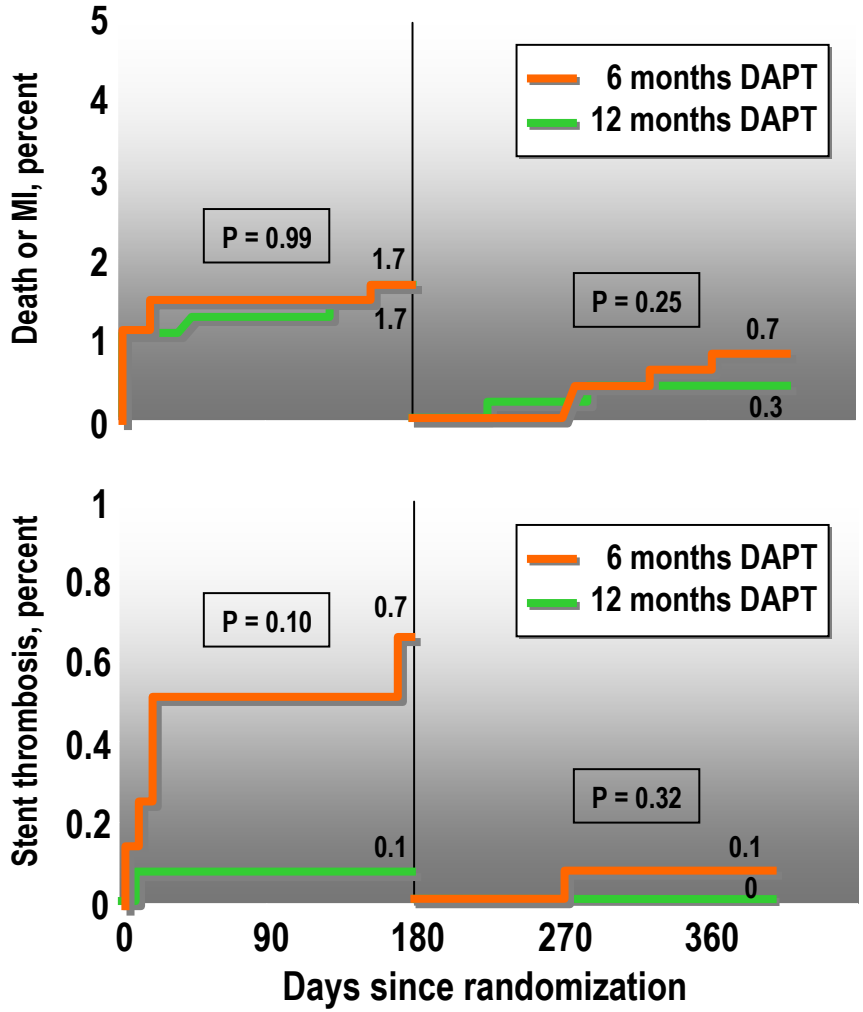


Wijeysundera D N et al. Circulation 2012;126:1355-1362

EXCELLENT TRIAL
6 vs 12 months DAPT after coronary stenting

1443 patients undergoing PCI (52% w/ACS); 75% EES
In 6-month arm, median duration of DAPT was 190 days



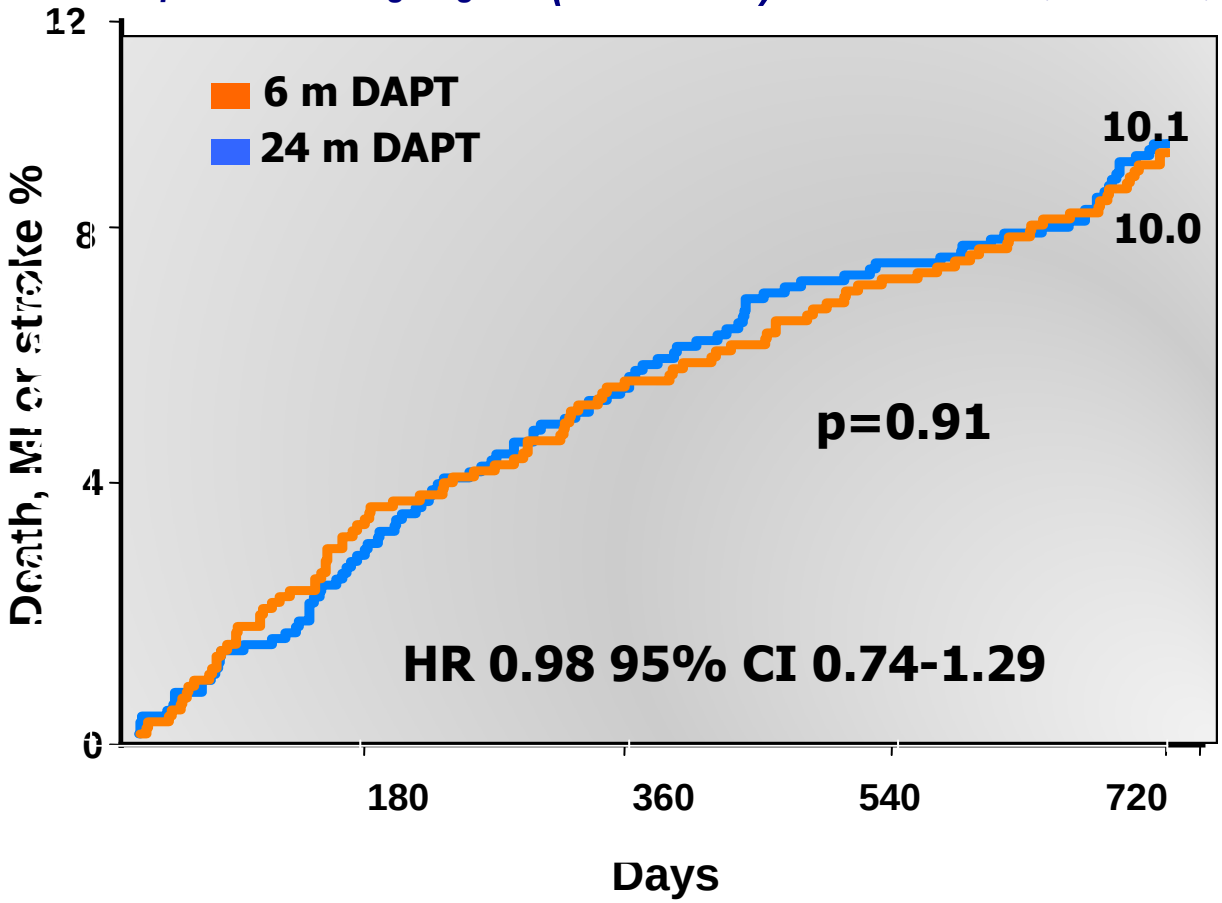


Cardiac death, MI, ischemia-driven target vessel revascularization

Gwon H, et al. Circulation 2012; 125: 505-513

PRODIGY
6 vs 24 months DAPT after coronary stent

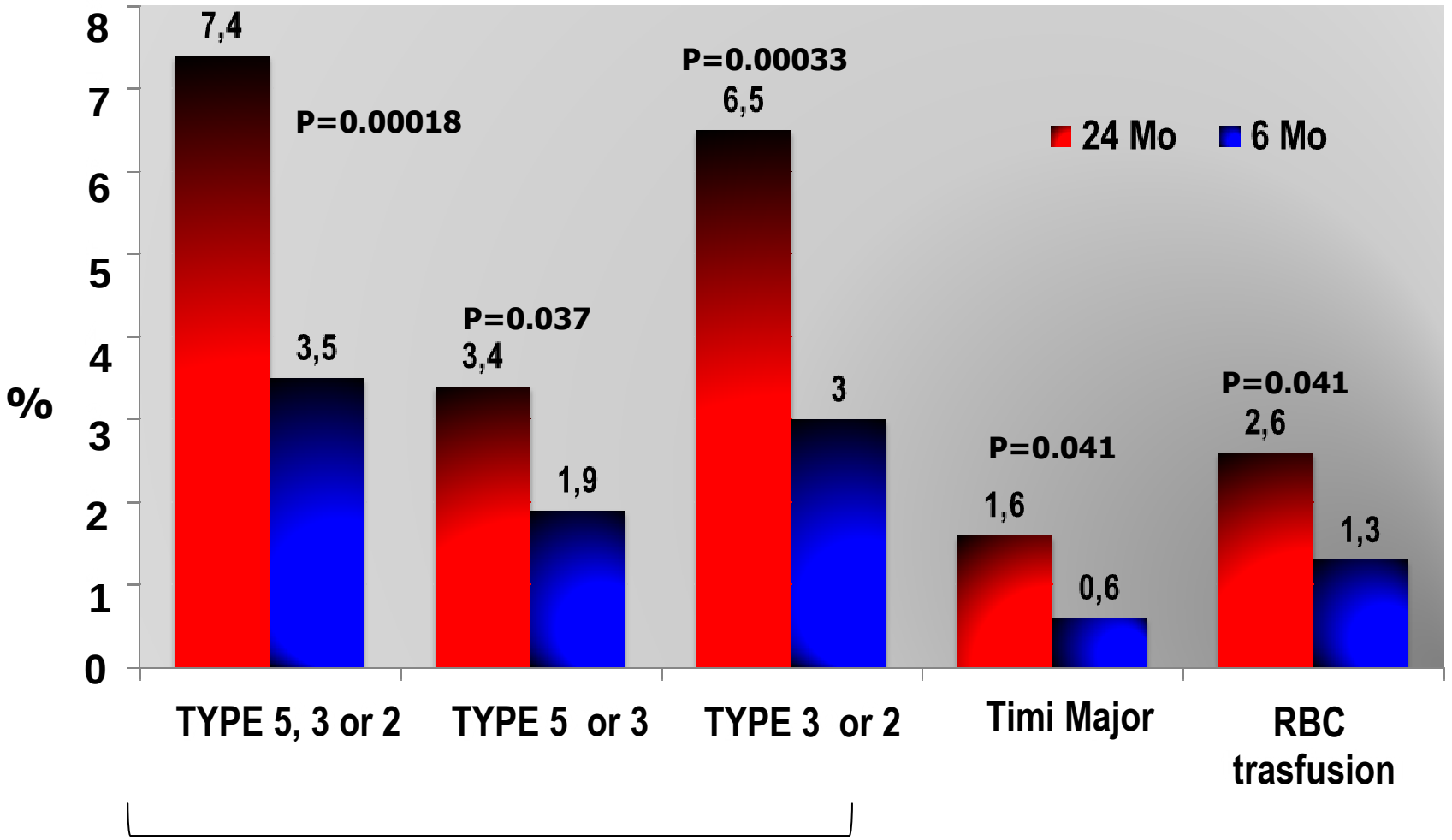
1970 all-comers patients undergoing PCI (75%ACS) 50% EES or ZES, 25% PES, 25% BMS



Valgimigli M, Campo G, Monti M et al. Circulation 2012, 125:2015-2026

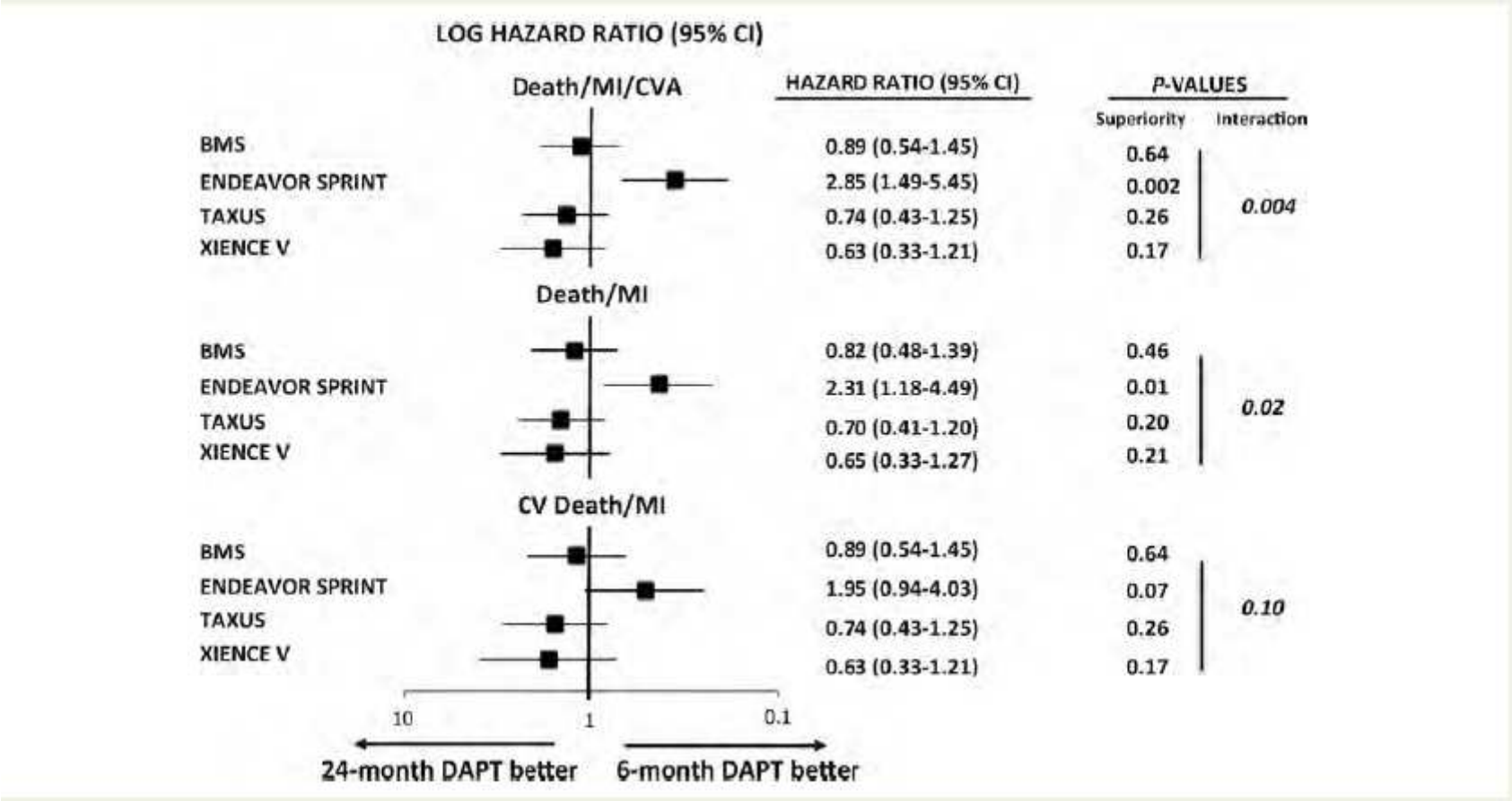
PRODIGY

Bleeding Events and RBC Transfusion



Valgimigli M, Campo G, Monti M et al. Circulation 2012, 125:2015-2026

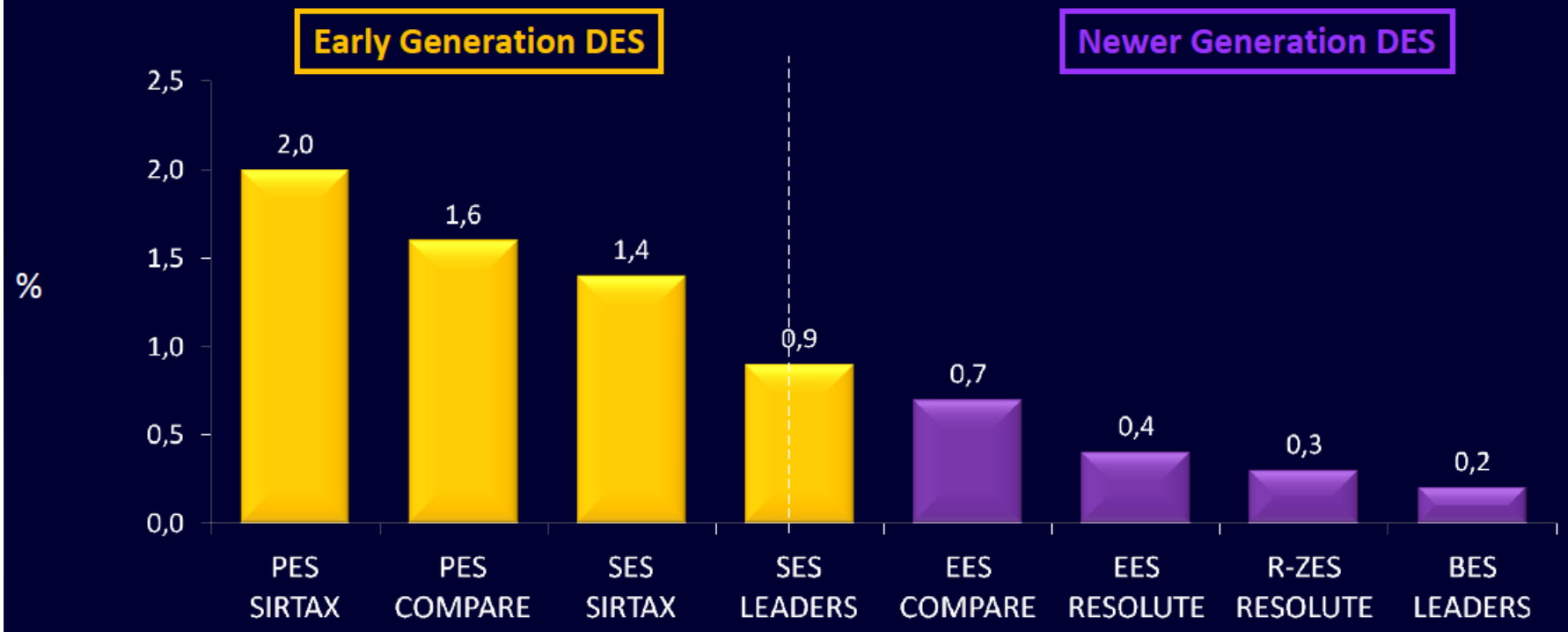
THE PRODIGY study
Should duration of DAPT depend on the type of implanted stent?



Valgimigli M, et al. Eur Heart J 2013

DES Thrombosis in Perspective

Very Late Definite ST in All-Comers Trials at 3 Years



Stefanini G, Windecker S. *Circulation Card Intv* 2012; 5:332-5

Incidence and Impact of Dual Antiplatelet Therapy (DAPT) Cessation on Adverse Events following Percutaneous Coronary Intervention (PCI):

Results from the Real-World PARIS Registry

Roxana Mehran, MD

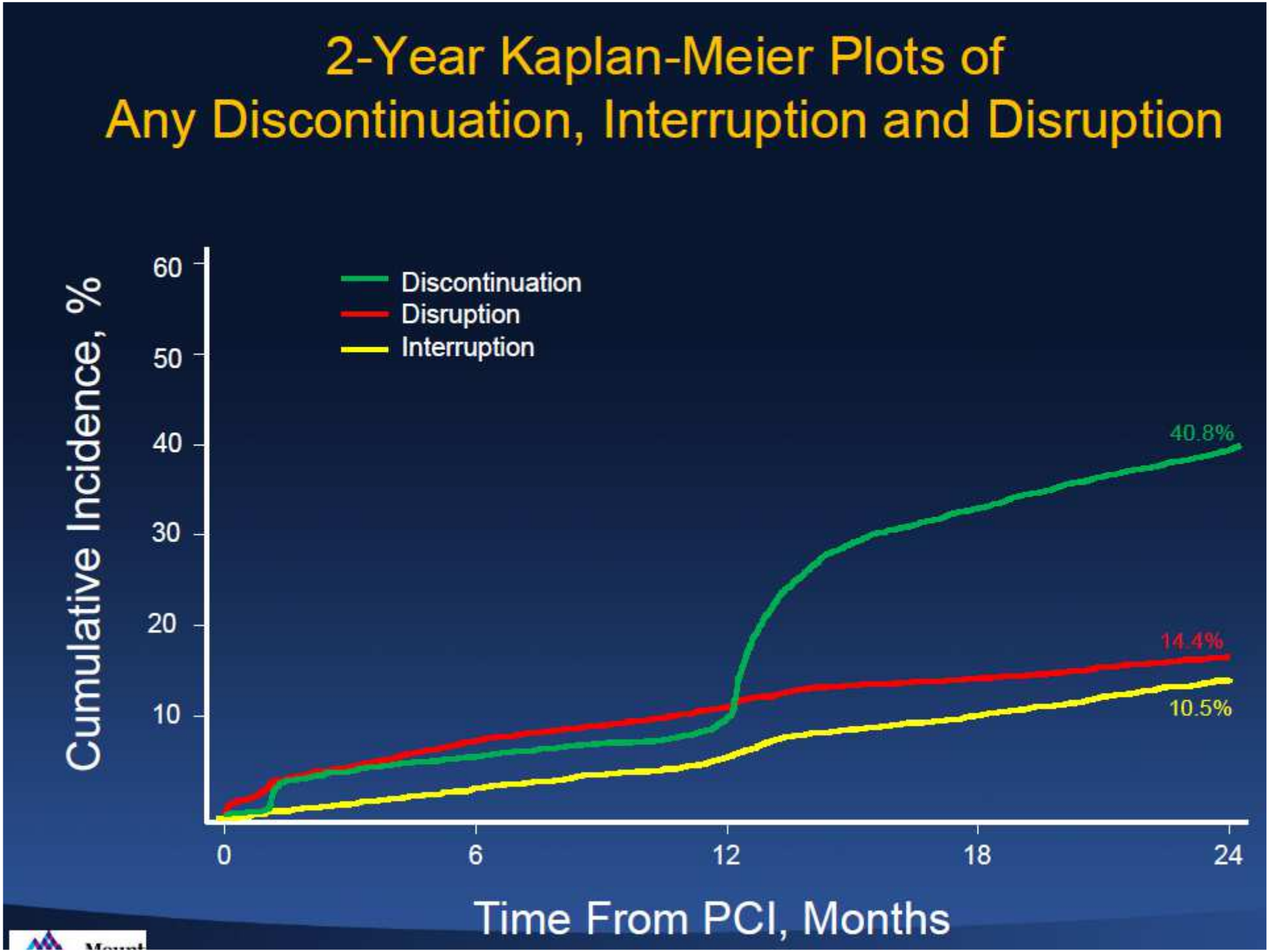
Professor of Medicine (Cardiology) and Health Evidence Policy
Director of Interventional Cardiovascular Research and Clinical Trials
The Icahn School of Medicine at Mount Sinai, New York, NY
on behalf of PARIS Investigators

Mount Sinai Heart

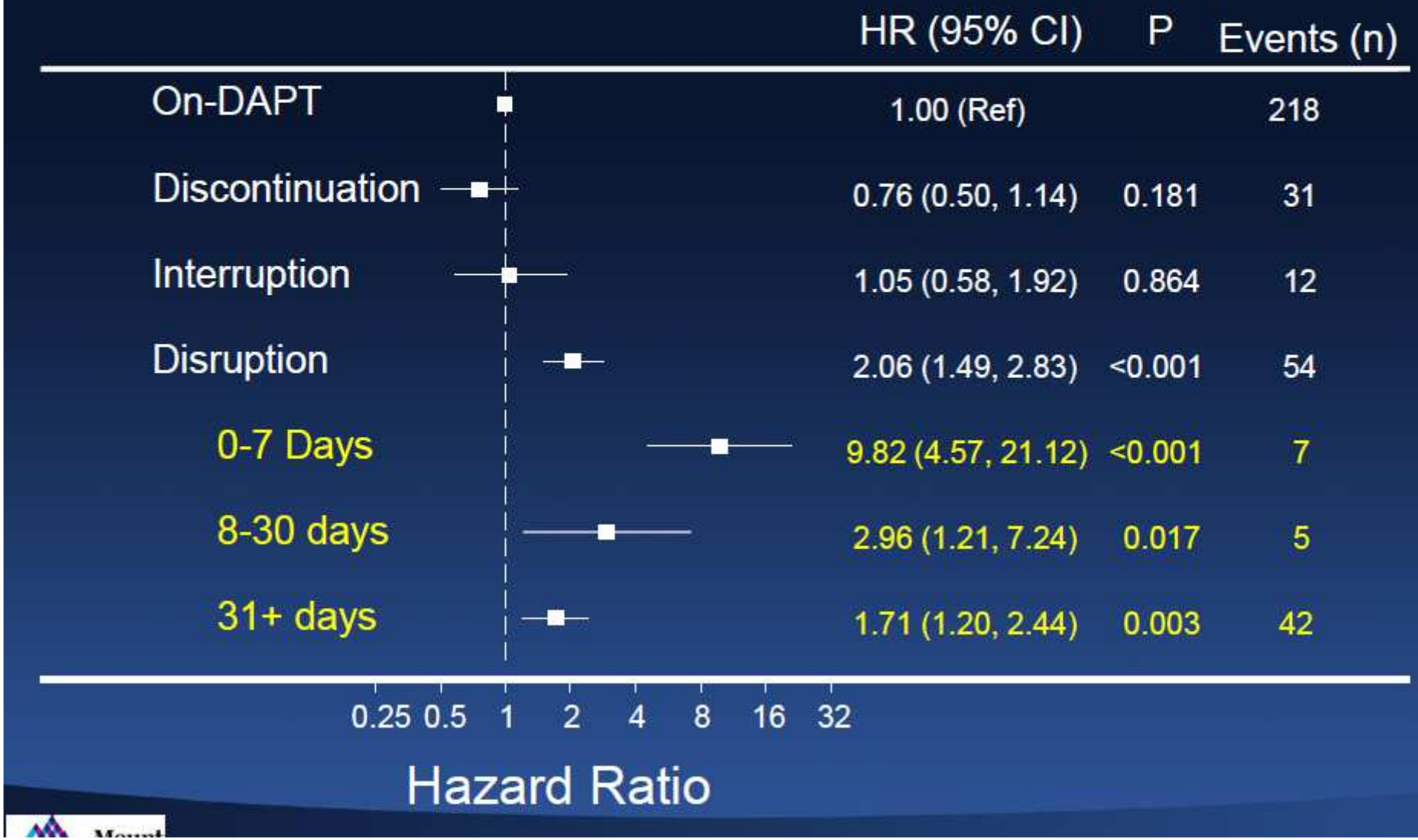
Modes of DAPT Cessation

- **Discontinuation**
  - patients had discontinued DAPT as per recommendation of their physician who felt the patient no longer needed therapy
- **Interruption**
  - patients had interrupted DAPT use on a voluntary basis and as guided by a physician due to (e.g. surgery)
  - DAPT was then reinstituted within 14 days
- **Disruption**
  - patients had disrupted DAPT use due to bleeding or non-compliance.

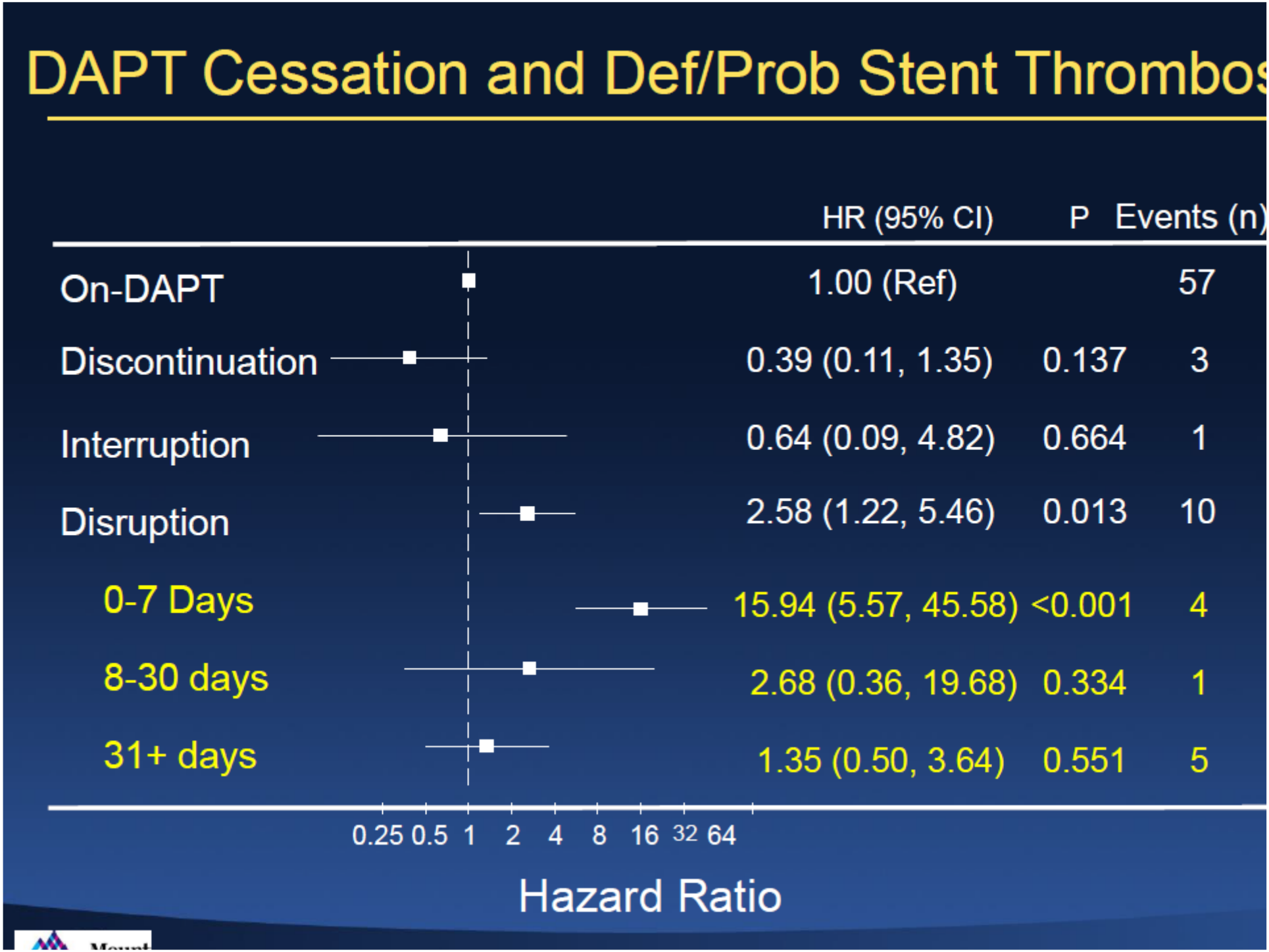
2-Year Kaplan-Meier Plots of Any Discontinuation, Interruption and Disruption



DAPT Cessation and Cardiac Death, Def/Prob ST, Spontaneous MI



DAPT Cessation and Def/Prob Stent Thrombos



Pazienti in terapia antiaggregante

Devono essere considerate condizioni ad elevato rischio trombotico:

- **Recente (< 30 giorni) impianto di qualsiasi stent coronarico**
- **Impianto di stent medicato negli ultimi 12 mesi**
- **Sindrome coronarica acuta nei ultimi 12 mesi**

In questi pazienti, qualora sia necessaria la sospensione della duplice terapia antiaggregante, essa andrà discussa con lo specialista cardiologo in relazione alla necessaria valutazione del bilanciamento tra il rischio emorragico e quello trombotico.

Pazienti ad alto rischio trombotico

Nei pazienti in cui è necessaria la sospensione del tienopiridinico, tale interruzione andrà programmata almeno 5 giorni prima della procedura nel caso del clopidogrel o ticlopidina o ticagrelor (7 giorni prima nel caso del prasugrel)

In questi pazienti dovrà essere obbligatoriamente mantenuta la terapia con aspirina

In quei pazienti con elevato rischio trombotico in cui è necessaria la sospensione della duplice terapia antiaggregante in vista di una procedura interventistica urgente, si potrà considerare la sospensione del clopidogrel 5 giorni prima e l'inizio di trattamento con un farmaco inibitore del recettore piastrinico GP2b/3a da sospendersi 4 ore prima dalla procedura

La sostituzione della duplice terapia antiaggregante con eparina non frazionata o eparina a basso peso molecolare è da considerarsi inefficace

Pazienti ad basso rischio trombotico

Devono essere considerate condizioni **a basso rischio trombotico**:

a) Cardiopatia ischemica cronica dopo 1 mese dopo stent metallico
b) Impianto di stent medicato più di 12 mesi prima
c) Sindrome coronarica acuta più di 12 mesi prima

In questi pazienti è possibile sospendere la duplice antiaggregazione con relativa sicurezza, proseguendo la sola terapia con ASA.

Stent coronarico e chirurgia: la gestione perioperatoria della terapia antiaggregante nel paziente portatore di stent coronarico candidato a intervento chirurgico

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Evento ANMCO - GISE LOMBARDIA

Terapia antiaggregante nei pazienti con stent candidati a chirurgia

Stresa
15 Settembre 2012

PRIMO ANNUNCIO

Stent coronarico e chirurgia: la gestione perioperatoria della terapia antiaggregante nel paziente portatore di stent coronarico candidato a intervento chirurgico

Tabella 1. Definizione del rischio trombotico.

Rischio basso	Rischio intermedio	Rischio alto
• >6 mesi dopo PCI con BMS	• >1 mese <6 mesi dopo PCI con BMS • >6 mesi <12 mesi dopo DES	• <1 mese dopo PCI con BMS • <6 mesi dopo DES
• >12 mesi dopo PCI con DES	• >12 mesi dopo DES a rischio elevato (stent lunghi, multipli, in *overlapping*, piccoli vasi, biforcazioni, tronco comune, *last remaining vessel*)	• <12 mesi dopo DES a rischio elevato (stent lunghi, multipli, in *overlapping*, piccoli vasi, biforcazioni, tronco comune, *last remaining vessel*)

La presenza di sindrome coronarica acuta in occasione della PCI, pregressa trombosi di stent, frazione di eiezione <35%, insufficienza renale cronica, diabete mellito aumentano il rischio di trombosi intrastent. I pazienti sottoposti a bypass aortocoronarico ed i pazienti con sindrome coronarica acuta non sottoposti a PCI vengono considerati ad alto rischio entro il primo mese, rischio intermedio tra 1 e 6 mesi, basso rischio oltre i 6 mesi. I pazienti sottoposti a PCI con il solo palloncino sono ritenuti ad alto rischio entro 2 settimane, a rischio intermedio tra 2 e 4 settimane, a basso rischio oltre le 4 settimane.
ASA, aspirina; BMS, stent metallico; DES, stent medicato; PCI, angioplastica coronarica.

Tabella 8. Endoscopia digestiva[113-128].

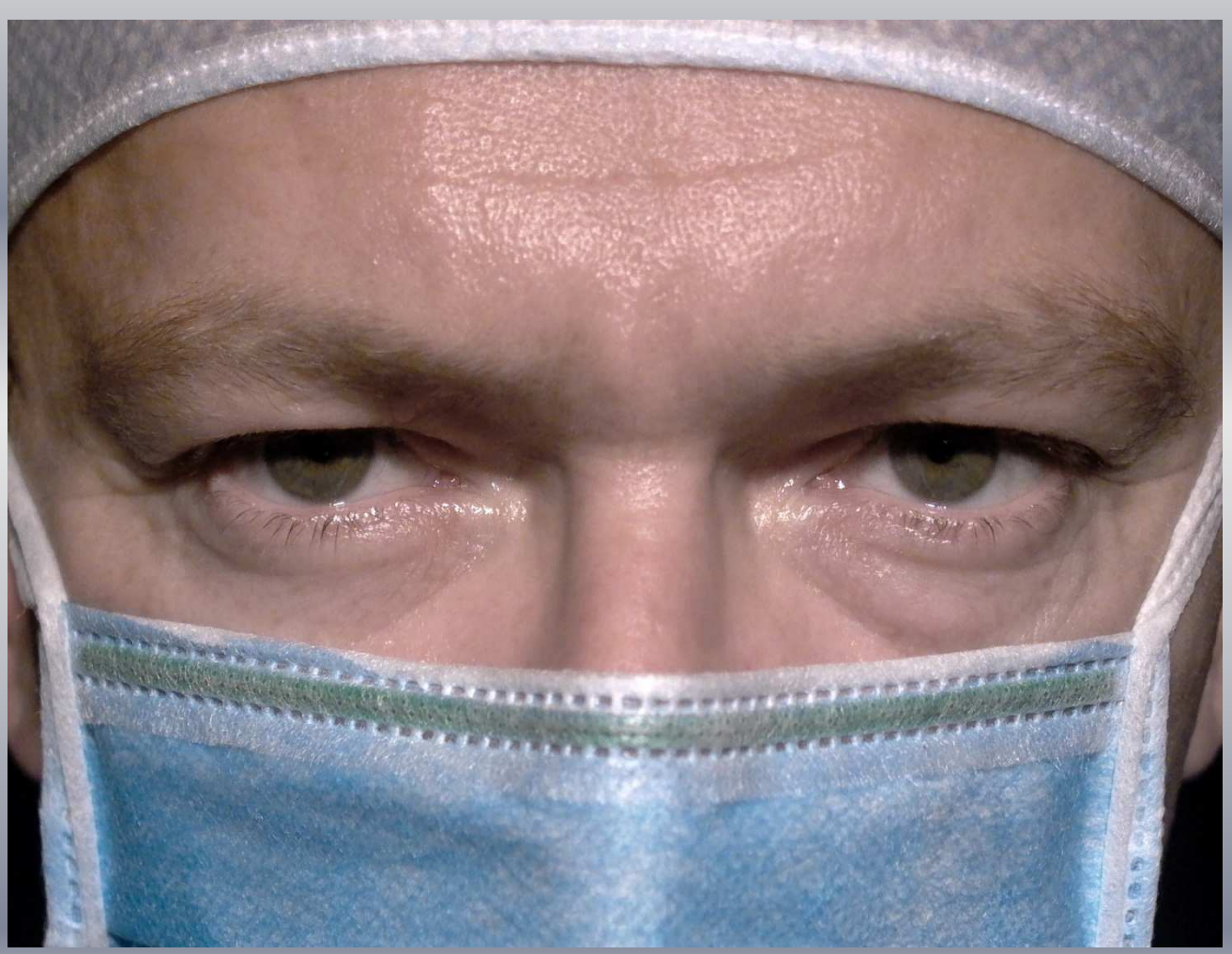
Rischio emorragico	Rischio trombotico		
	Basso	**Intermedio**	**Alto**
Basso EGDS, colonscopia ± biopsia Ecoendoscopia senza biopsia Polipectomia polipi <1 cm ERCP, stent, dilatazione Papilla senza sfinterotomia	*ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* proseguire	*Chirurgia elettiva:* non controindicata *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* proseguire	*Chirurgia elettiva:* non controindicata *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* proseguire
Intermedio Endoscopia + biopsia con ago sottile (FNA) di lesioni solide Dilatazione di stenosi (esofagocardiali, colorettali) Stent apparato gastroenterico Coagulazione con argon plasma Sfinterotomia endoscopica (ERCP) Polipectomia polipo >1 cm Gastrostomia percutanea Legatura/sclerosi varici esofagee Legatura/sclerosi emorroidi	*ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico[b]	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico *Bridge con piccole molecole[b]*
Alto Dilatazione per acalasia Mucosectomia/resezione sottomucosa Ecografia con biopsia FNA di lesioni cistiche pancreatiche Ampullectomia papilla di Vater	*ASA:* sospendere *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* sospendere *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico *Bridge con piccole molecole[b]*	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico *Bridge con piccole molecole[b]*

Tabella 11. Pneumologia[134-138].

Rischio emorragico	Rischio trombotico		
	Basso	**Intermedio**	**Alto**
Basso Broncoscopia ispettiva, broncoaspirato, lavaggio bronchiolo-alveolare	*ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* proseguire	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* proseguire
Intermedio Biopsie bronchiali	*ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico[b]	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico *Bridge con piccole molecole*[b]
Alto Biopsie polmonari e transbronchiali Broncoscopia operativa (con broncoscopio rigido)	*ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico[b]	*Chirurgia elettiva:* differire *Chirurgia non differibile:* *ASA:* proseguire *Inibitori recettore $P2Y_{12}$:* - sospendere 5 giorni prima[a] - riprendere entro 24-72h, con dose di carico *Bridge con piccole molecole*[b]

ASA, aspirina.
[a]7 giorni prima per prasugrel; [b]discussione collegiale del rischio anche con familiari/paziente.

“The strongest risk factor for bleeding is the surgeon.
A good surgeon is a dry surgeon”



Dr. Freek Verheugt (Cardiologist)


GRAZIE PER LA VOSTRA ATTENZIONE