The Freshly Stented Patient Who Is Bleeding, Has DAPT Allergy, or Needs Non-Cardiac Surgery

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INTERVENTIONAL CARDIOLOGIST

GENESIS 14/11/2012

Hellenic Institute of Cardiovascular Diseases

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What could possibly be thematically common among "Freshly Stented Patients" with:

Bleeding
DAPT Allergy
Needing Non-Cardiac Surgery

TO AVOID Thrombosis: DON'T STOP DAPT!

TUESDAY

ESC Congress News

WORLD HEART FEDERATION

World Congress of Cardiology 2006

The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

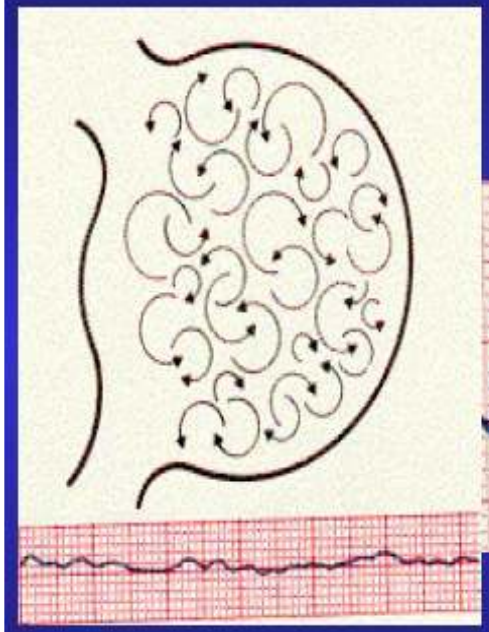
"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the

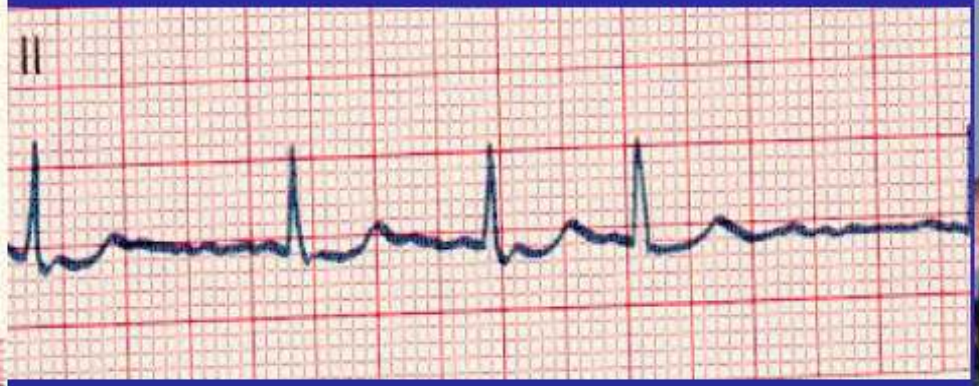
Thrombosis Trials

- ASA ORAL or IV
- Lytics IV
- Unfractionated Heparin IV
- Factor Xa inhibitors IV
- GP IIb / IIIa inhibitors IV
- Direct Thrombin inhibitors IV
- Direct Thrombin inhibitors ORAL
- ADP receptor antagonist ORAL
- ADP receptor antagonist IV
- Warfarin

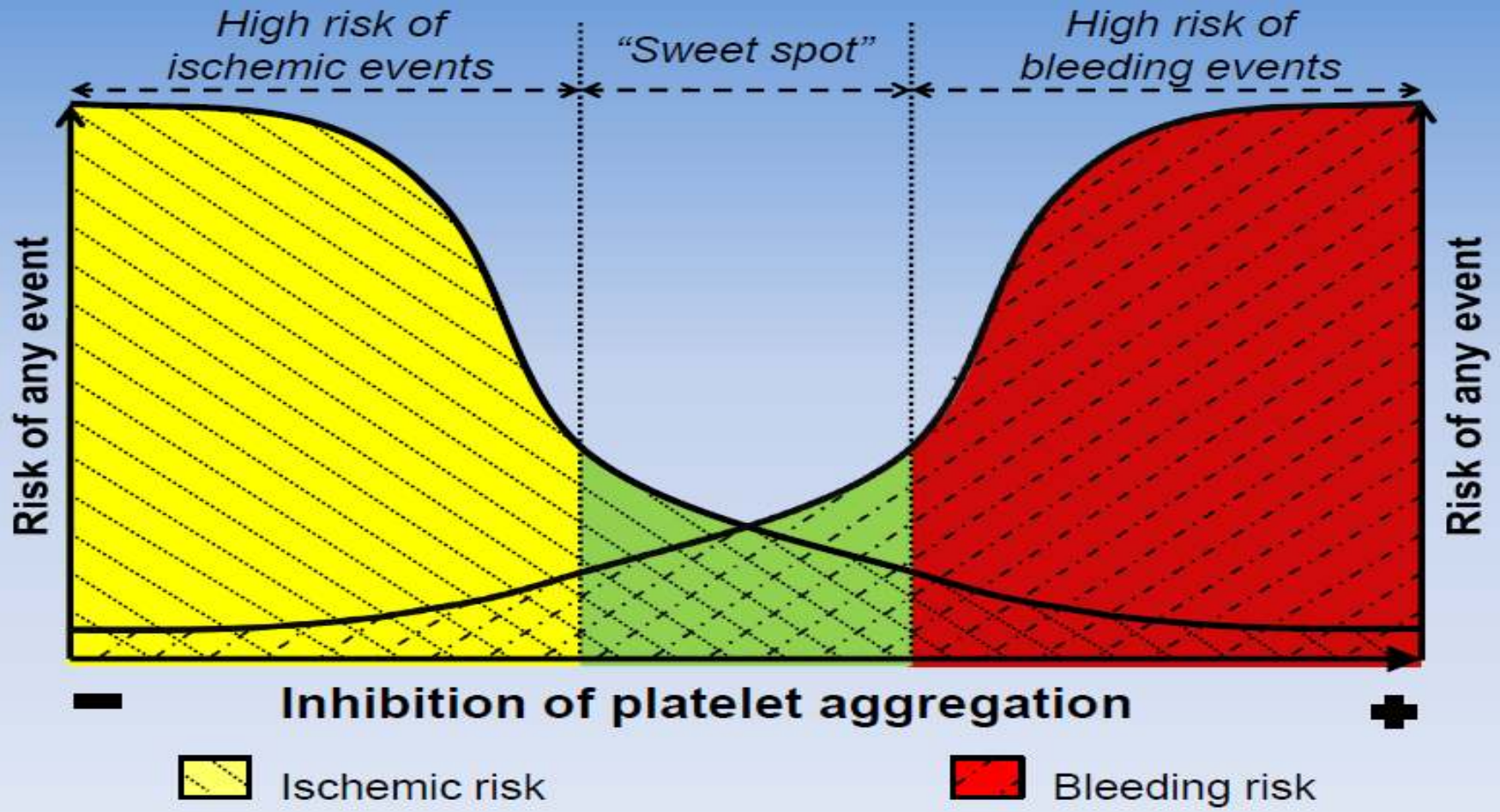

ASA
Clopidogrel
Ticlopidine
Warfarin
GPIIb/IIIa
Heparin
Hirudin
GPIIb/IIIa
SK
tPA
rPA
LMWH
Hirudin

Aging population



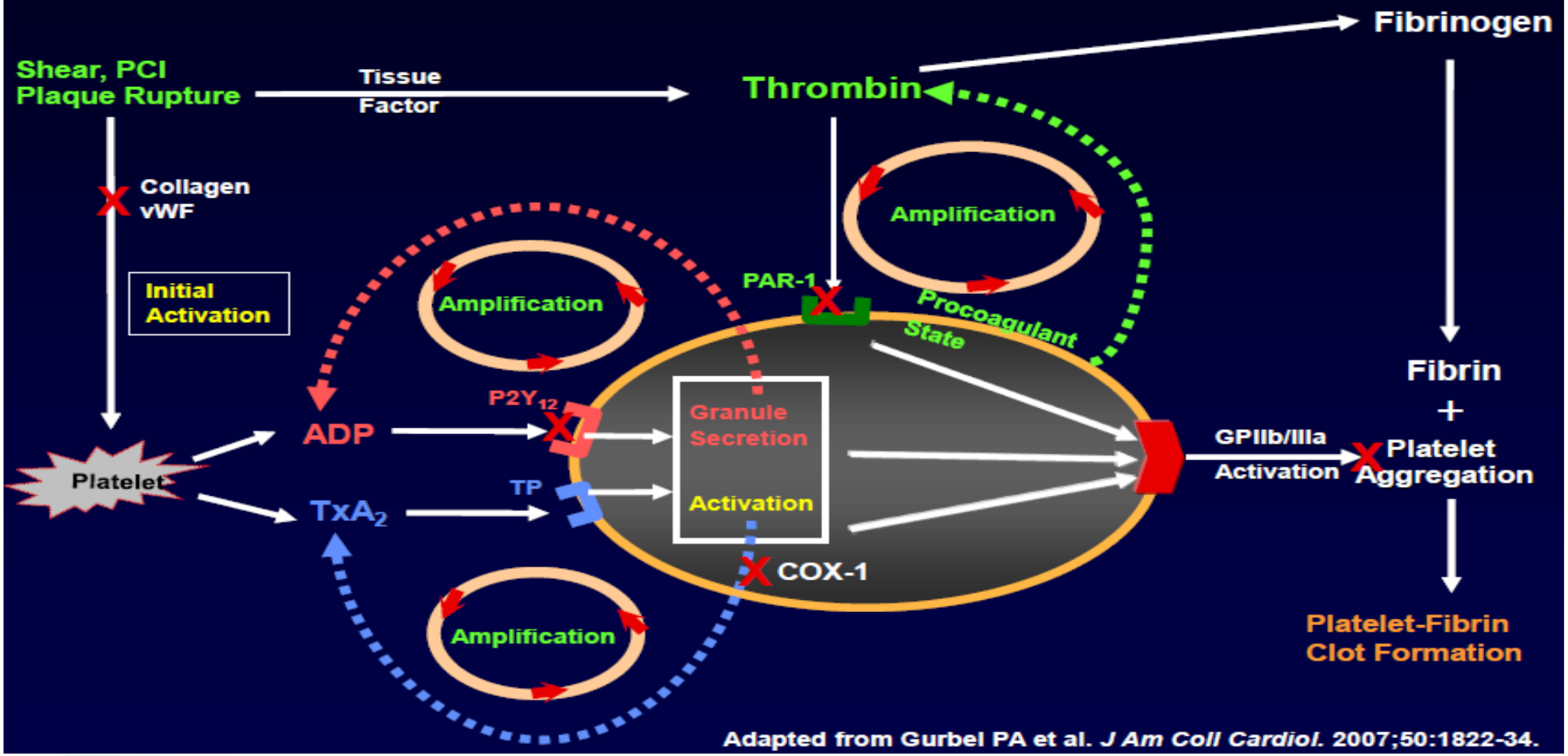


Balancing Safety and Efficacy



Ferreiro & Angiolillo. Thromb Haemost 2010 (in press)

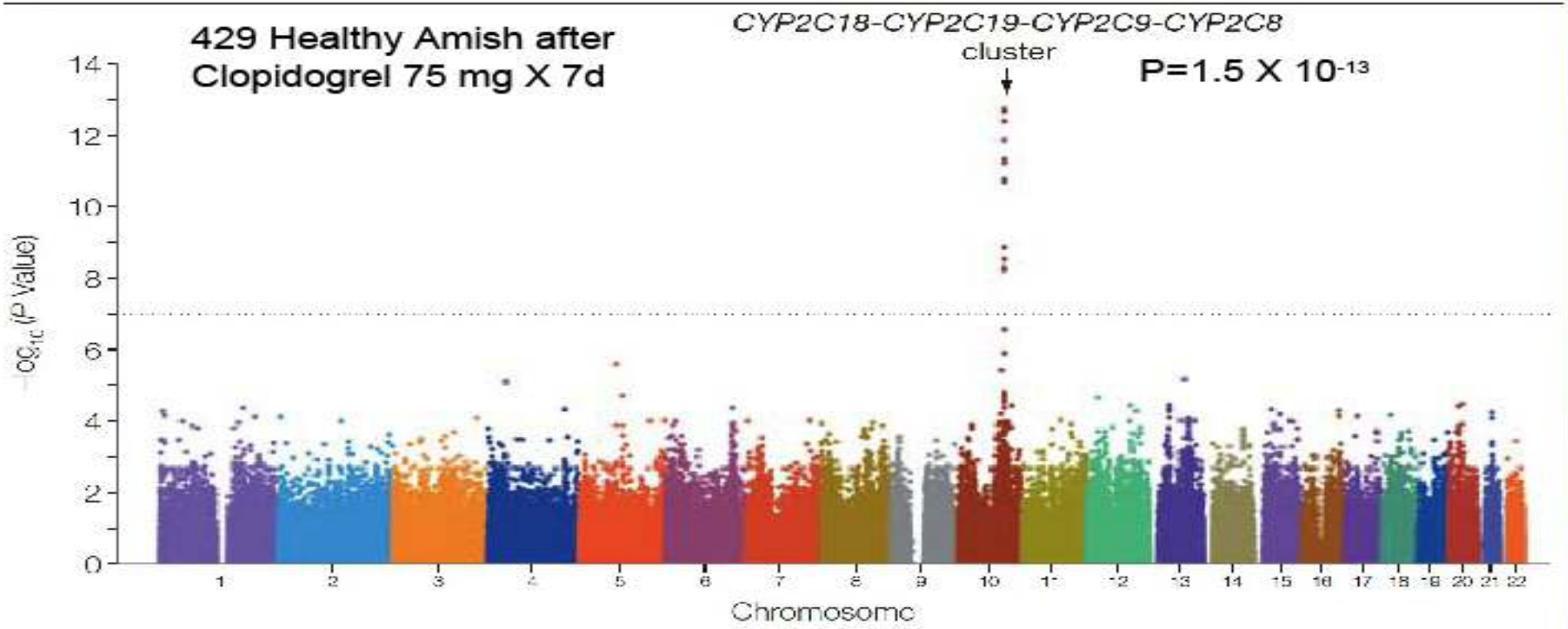
Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis



Adapted from Gurbel PA et al. *J Am Coll Cardiol.* 2007;50:1822-34.

JAMA

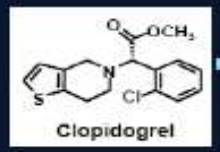
Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy



Shuldiner AR et al JAMA. Aug 26 2009;302(8):849-857.

SCRIPPS CLINIC

Mechanism of Clopidogrel Response Variability

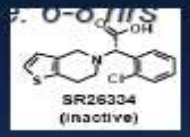


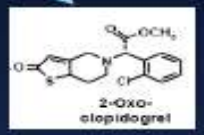
Intestinal Absorption

- 50% bioavailability
- P-glycoprotein down-regulation
- ABCB1 gene polymorphism

Carboxylesterases? 85%

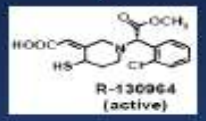
Hepatic CYP P450 metabolism 15%





OXIDATION

- CYP2C19 — polymorphisms, PPIs
- CYP1A2 — smoking
- CYP2B6



- CYP2C19 — polymorphisms, PPIs
- CYP2C9 — polymorphism
- CYP1A2 — smoking
- CYP2B6
- CYP3A — statins, polymorphism, calcium antagonists

BMI, diabetes, caffeine

$P2Y_{12}$ Receptor

Wide and Unpredictable Pharmacodynamic Response

FDA Safety Warning with Clopidogrel

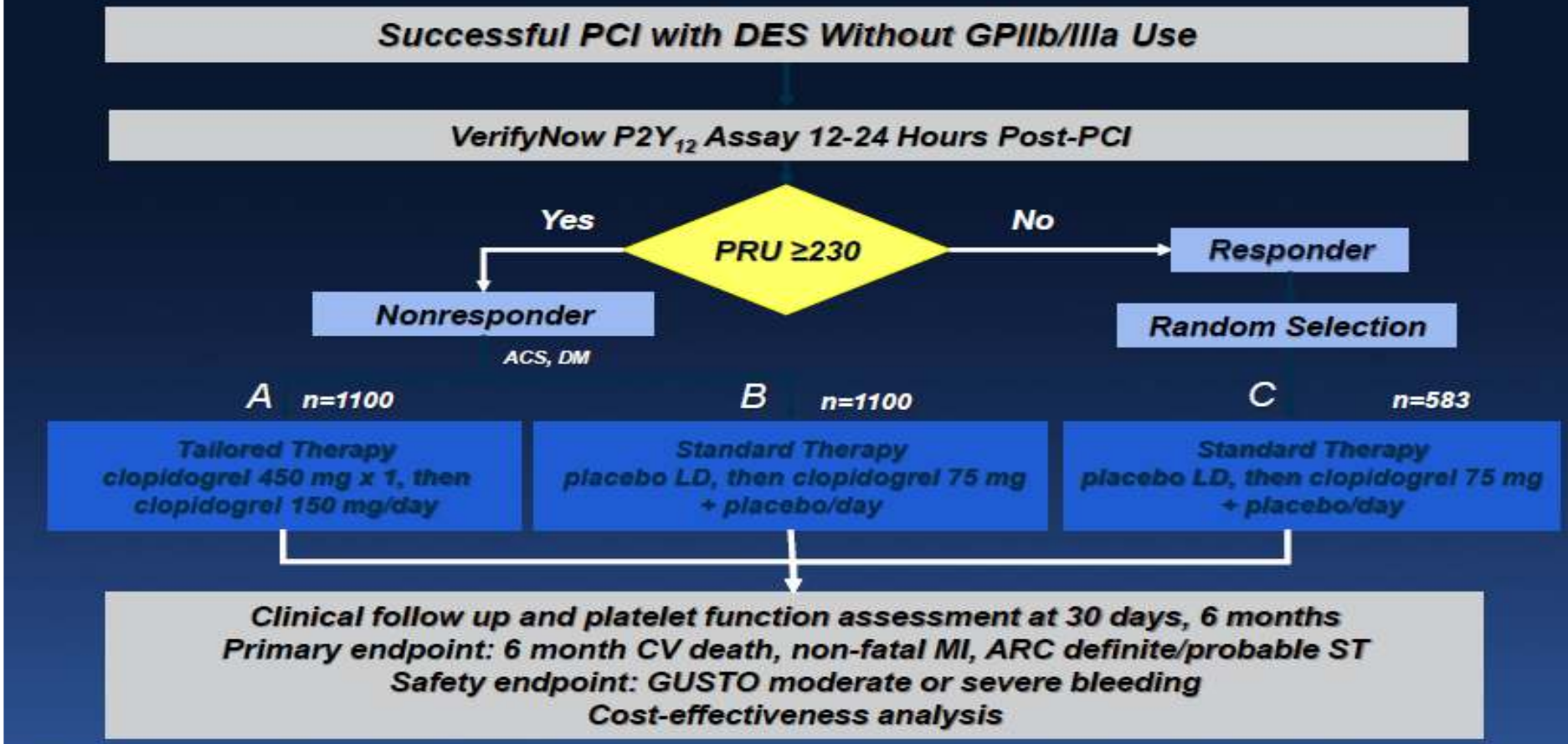
FDA recommends that healthcare professionals should:

- Be aware that some patients may be poor metabolizers of clopidogrel. They do not effectively convert clopidogrel to its active form because of low
  CYP2C19 activity. The effectiveness of clopidogrel as a preventive therapy is reduced in these patients
- Be aware that tests are available to determine a patient's CYP2C19 status
- Consider use of other antiplatelet medications or alternative dosing strategies for clopidogrel in patients who have been identified as poor metabolizers
- Be aware that although a higher-dose regimen (600 mg LD followed by 150 mg QD) in poor metabolizers increases antiplatelet response, an appropriate-dose regimen for poor metabolizers has not been established in a clinical outcome trial
- Review the newly approved clopidogrel drug label for complete information on the use of clopidogrel

Mount Sinai HEART

FDA = United States Food and Drug Administration.

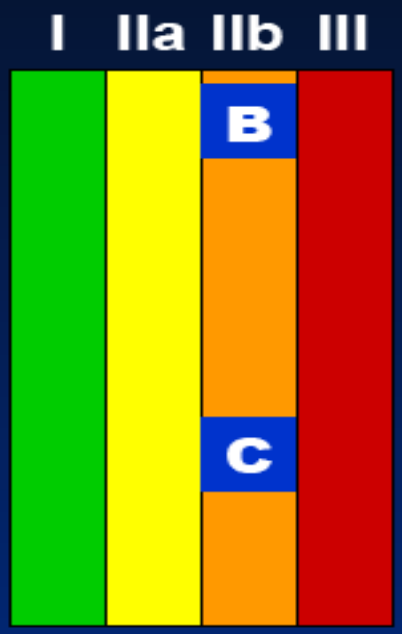
GRAVITAS


Successful PCI with DES Without GPIIb/IIIa Use
VerifyNow P2Y12 Assay 12-24 Hours Post-PCI
PRU ≥230
Yes
No
Responder
Nonresponder
ACS, DM
Random Selection
A n=1100
B n=1100
C n=583
Tailored Therapy
clopidogrel 450 mg x 1, then
clopidogrel 150 mg/day
Standard Therapy
placebo LD, then clopidogrel 75 mg
+ placebo/day
Standard Therapy
placebo LD, then clopidogrel 75 mg
+ placebo/day
Clinical follow up and platelet function assessment at 30 days, 6 months
Primary endpoint: 6 month CV death, non-fatal MI, ARC definite/probable ST
Safety endpoint: GUSTO moderate or severe bleeding
Cost-effectiveness analysis

2011 ACC/AHA UA/NSTEMI Guidelines Focused Update

Recommendations for Additional Management of Antiplatelet and Anticoagulant Therapy

New Recommendation



Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management

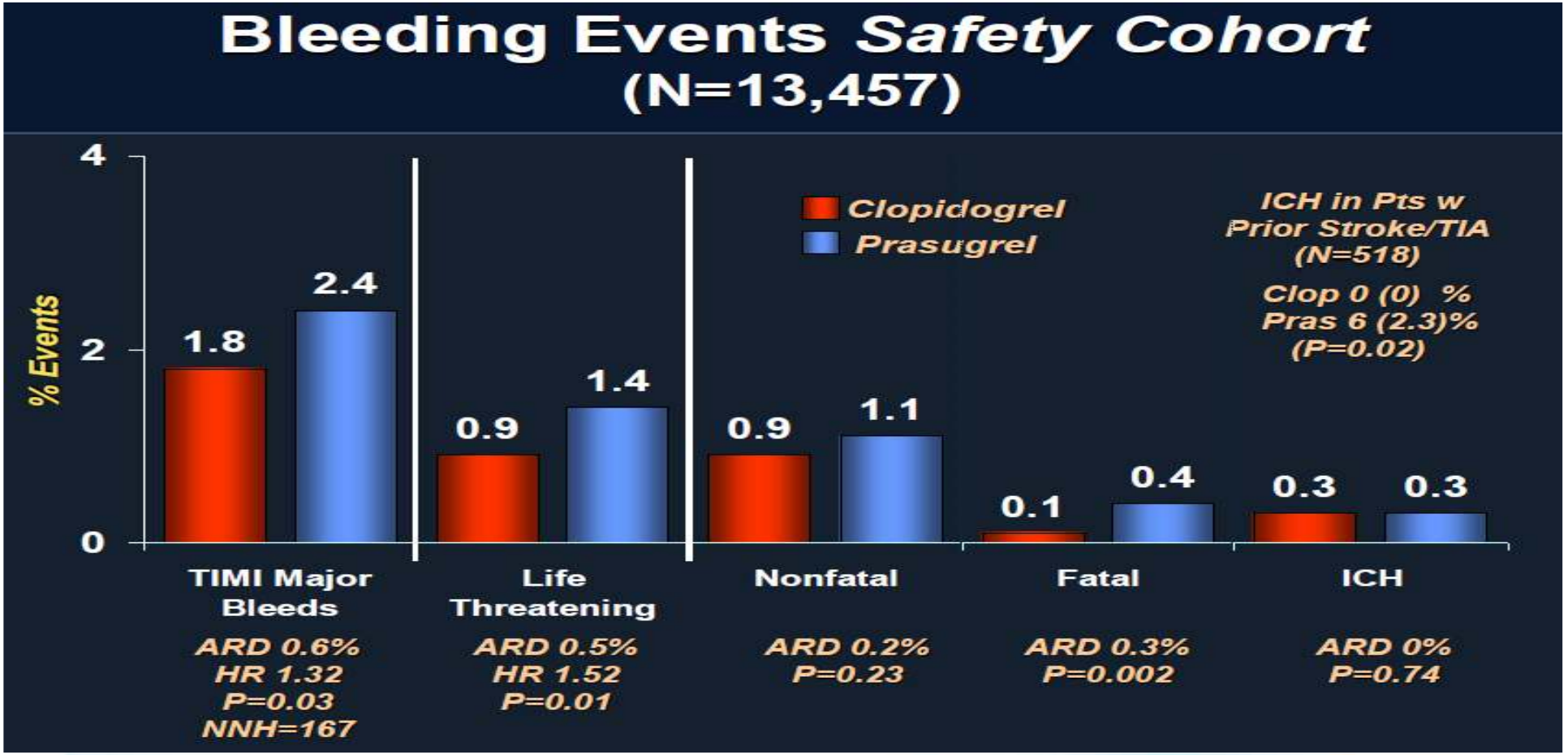
Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management

Class IIb: Benefit ≥ Risk; ***Treatment may be considered***
Additional studies w/broad objectives needed; additional registry data would be helpful.

Comparison of $P2Y_{12}$ Receptor Antagonists: Ticagrelor vs Thienopyridines

Name	Type of Molecule	Route of Administration	Mode of Action
Ticagrelor	Cyclo-pentyl-triazolo-pyrimidine	Oral	Direct, Reversible
Clopidogrel	Thienopyridine	Oral	Prodrug, Irreversible
Prasugrel	Thienopyridine	Oral	Prodrug, Irreversible

TRITON

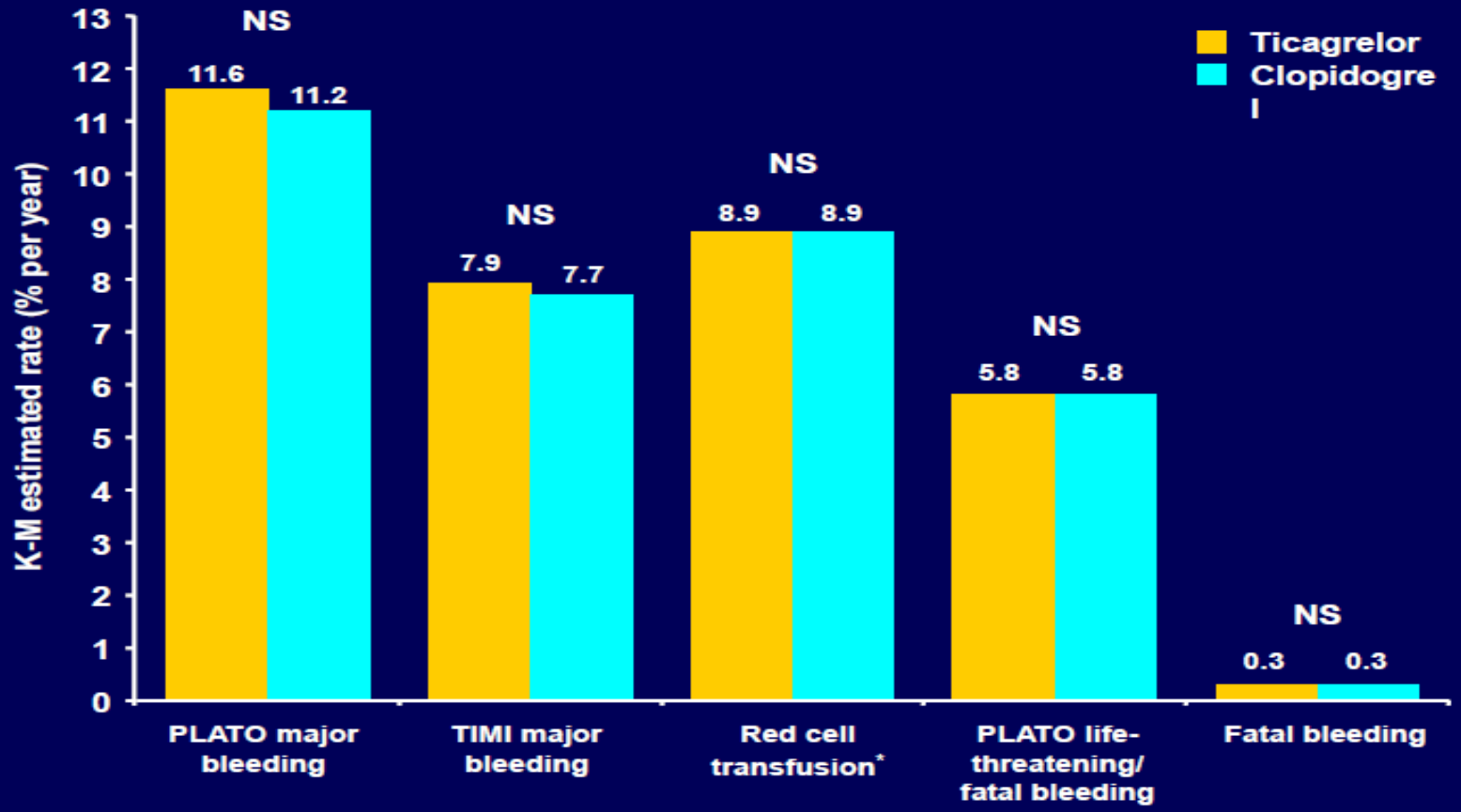

Bleeding Events Safety Cohort
(N=13,457)
% Events
4
2
0
Clopidogrel
Prasugrel
1.8
2.4
0.9
1.4
0.9
1.1
0.1
0.4
0.3
0.3
TIMI Major Bleeds
ARD 0.6%
HR 1.32
P=0.03
NNH=167
Life Threatening
ARD 0.5%
HR 1.52
P=0.01
Nonfatal
ARD 0.2%
P=0.23
Fatal
ARD 0.3%
P=0.002
ICH
ARD 0%
P=0.74
ICH in Pts w Prior Stroke/TIA (N=518)
Clop 0 (0) %
Pras 6 (2.3)%
(P=0.02)

Black Box Warning with Prasugrel

1. Contraindicated in patients with pathologic bleeding (such as peptic ulcer or ICH) and in those with a history of TIA or stroke.
2. In patients age 75 and older, prasugrel is generally not recommended because of the increased risk of intracranial and fatal bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI). In these situations, the drug's effect appears to be greater, and its use may be considered.
3. Use cautiously in patients who weigh less than 60 kg because of the increased risk of bleeding.
4. Use cautiously in patients at risk for increased bleeding from trauma, surgery, or other pathologic conditions and in those with severe hepatic impairment.

Total major bleeding

PLATO



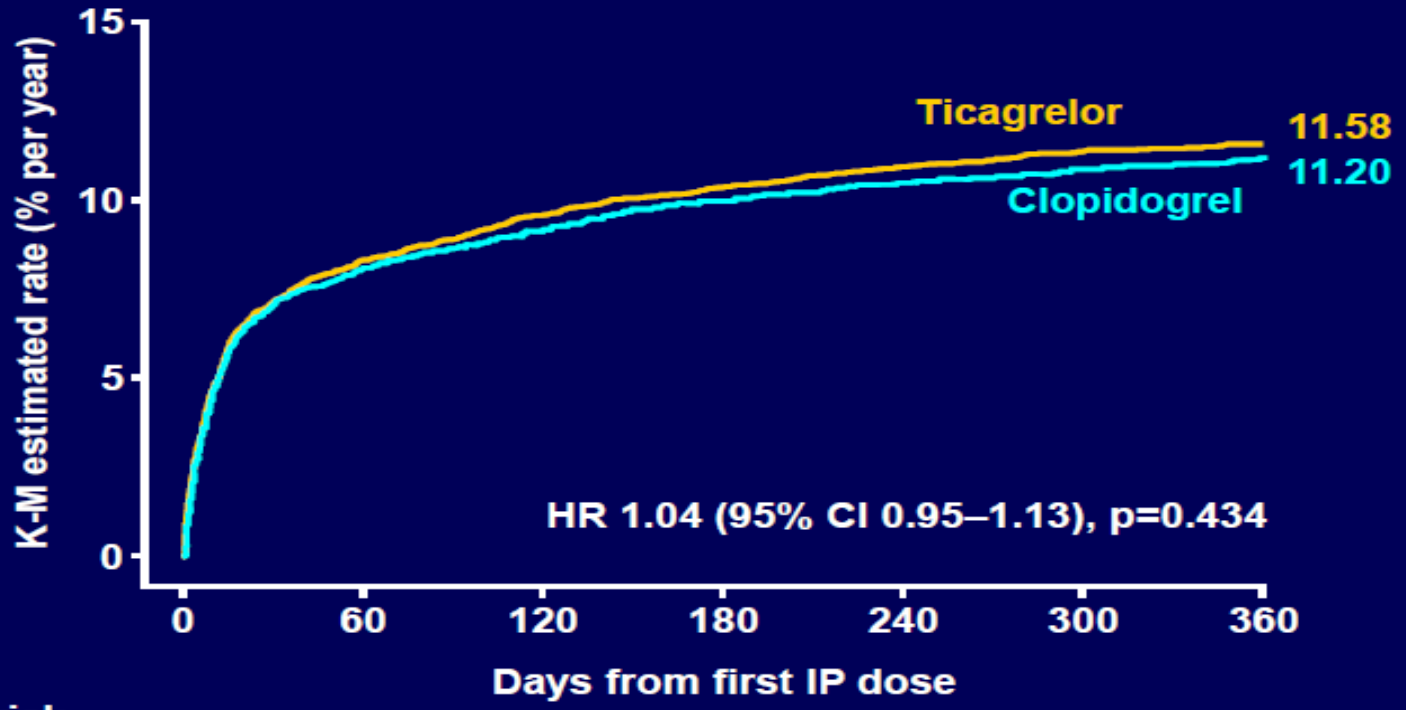
Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15;
*Proportion of patients (%); NS = not significant

Duke Clinical Research Institute

UCR
UPPSALA CLINICAL RESEARCH CENTER

Time to major bleeding – primary safety event

PLATO



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

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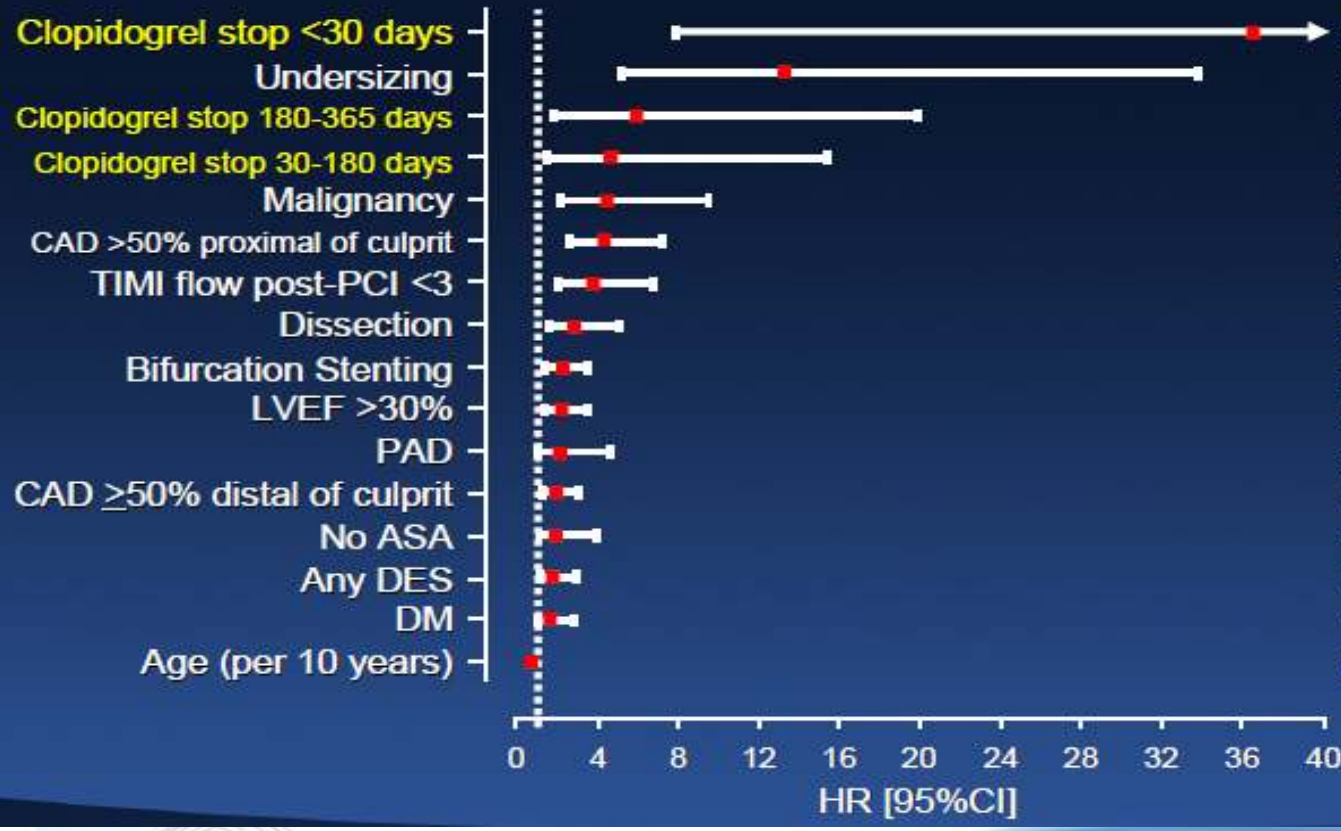
The PLATO trial demonstrated that, for the first time, the oral antiplatelet drug ticagrelor reduces CV mortality on top of the standard of care

PLEOTROPIC ACTION !!!

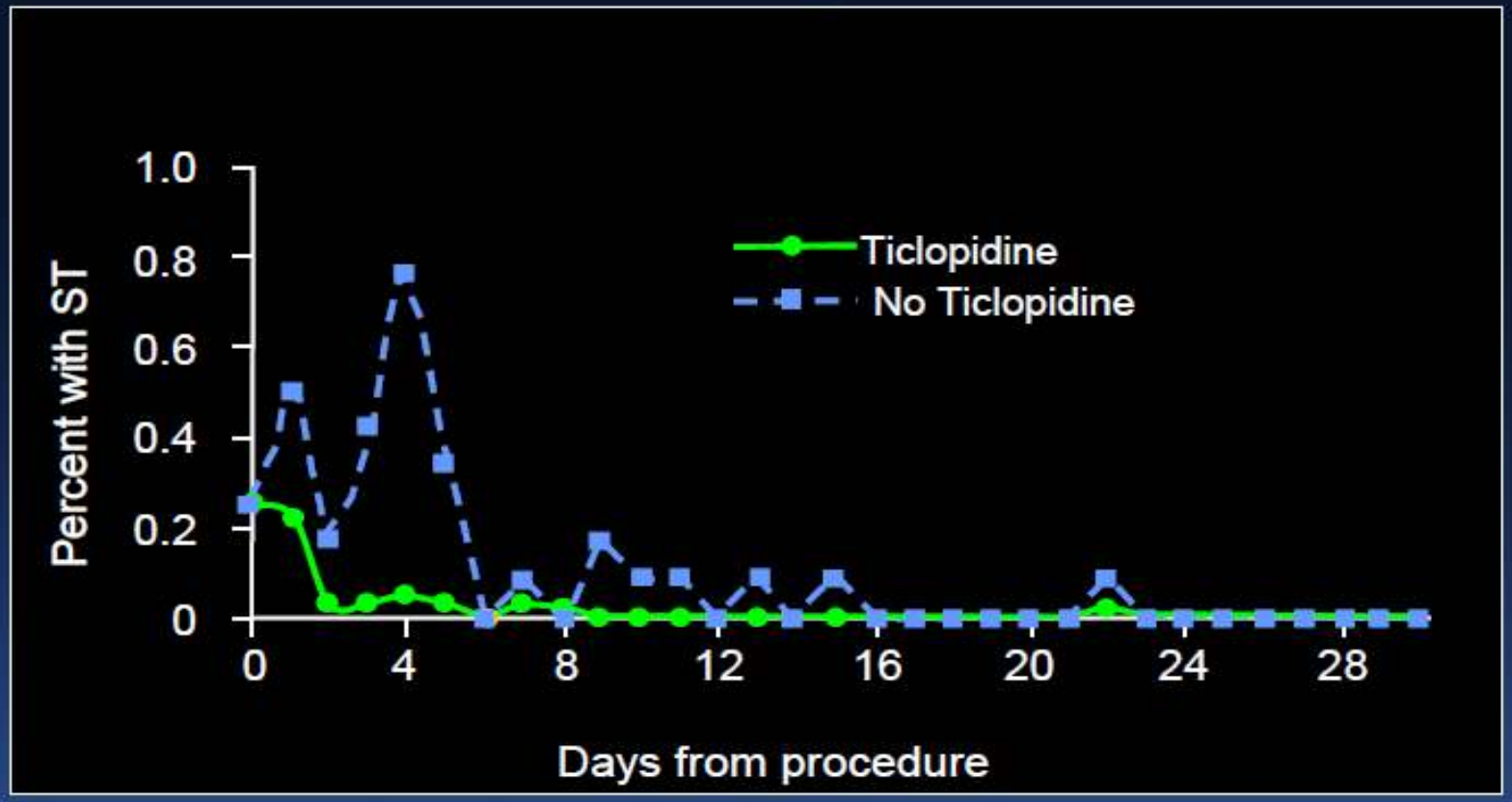
Independent Predictors of Stent Thrombosis: Dutch Registry (n=21,009 with DES or BMS)

Definite stent thrombosis occurred in 437 (2.1%) pts



	HR	95% CI	*P* Value
Clopidogrel stop <30 days	36.53	[7.96-167.77]	*P*<0.0001
Undersizing	13.39	[5.27-34.04]	*P*<0.0001
Clopidogrel stop 180-365 days	5.87	[1.74-19.80]	*P*=0.004
Clopidogrel stop 30-180 days	4.63	[1.40-15.35]	*P*=0.01
Malignancy	4.50	[2.14-9.49]	*P*<0.0001
CAD >50% proximal of culprit	4.40	[2.71-7.16]	*P*<0.0001
TIMI flow post-PCI <3	3.77	[2.09-6.80]	*P*<0.0001
Dissection	2.88	[1.67-5.00]	*P*=0.0002
Bifurcation Stenting	2.27	[1.48-3.47]	*P*=0.0002
LVEF >30%	2.27	[1.43-3.60]	*P*=0.0005
PAD	2.13	[1.01-4.51]	*P*=0.048
CAD ≥50% distal of culprit	1.98	[1.32-2.95]	*P*=0.0009
No ASA	1.91	[1.01-3.88]	*P*=0.049
Any DES	1.88	[1.21-2.94]	*P*=0.005
DM	1.66	[1.02-2.70]	*P*=0.04
Age (per 10 years)	0.80	[0.68-0.94]	*P*=0.007

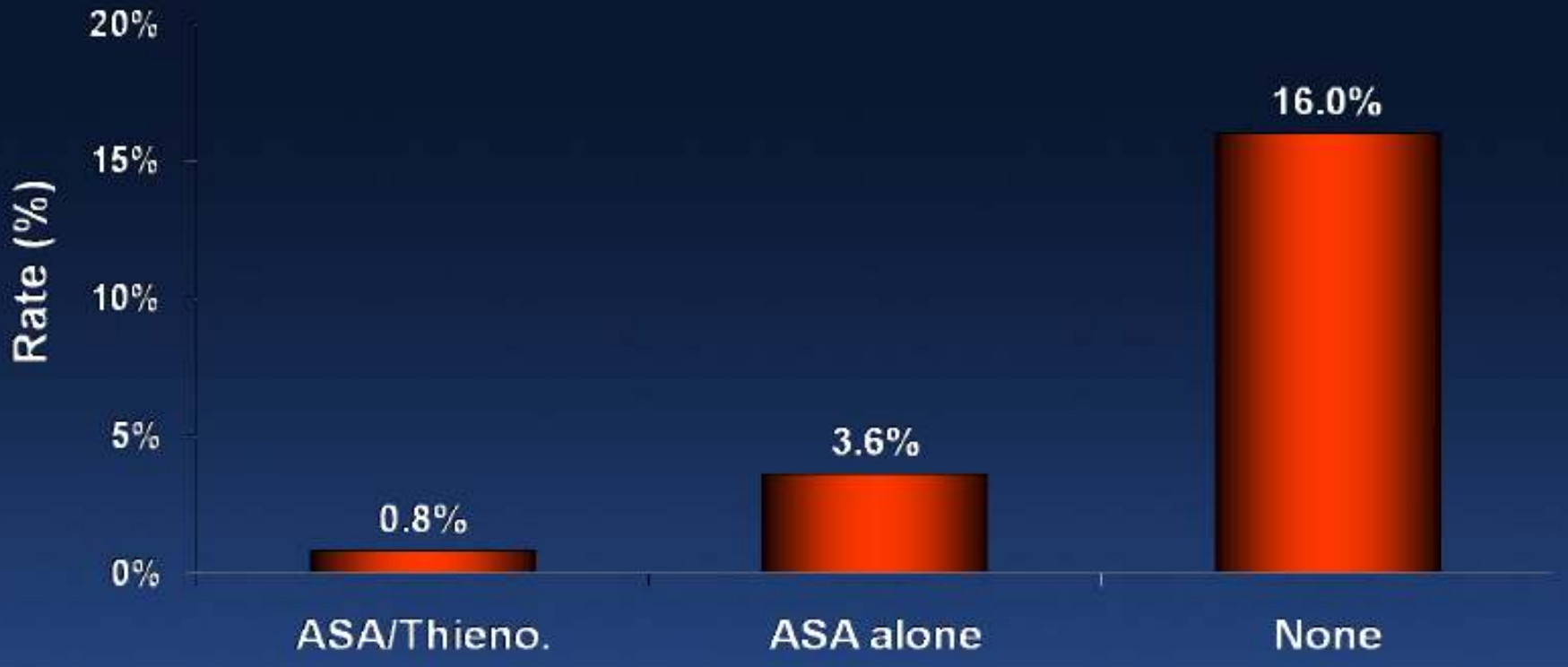
Timing of Stent Thrombosis after BMS Implantation



Major benefit of ticlopidine with BMS was prevention of SAT in first 2 weeks after stenting

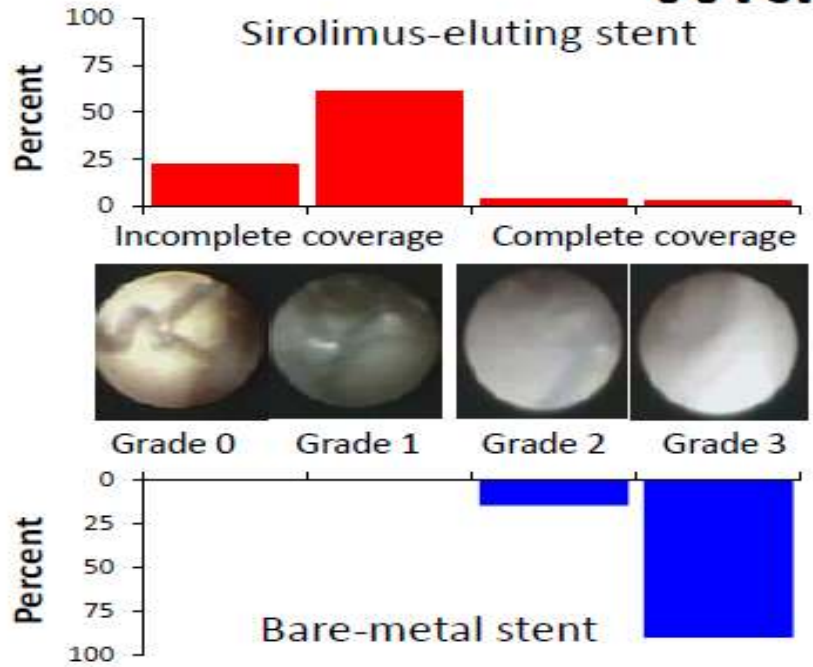
Estimated Risks of Subacute ST

Based upon historical data with BMS

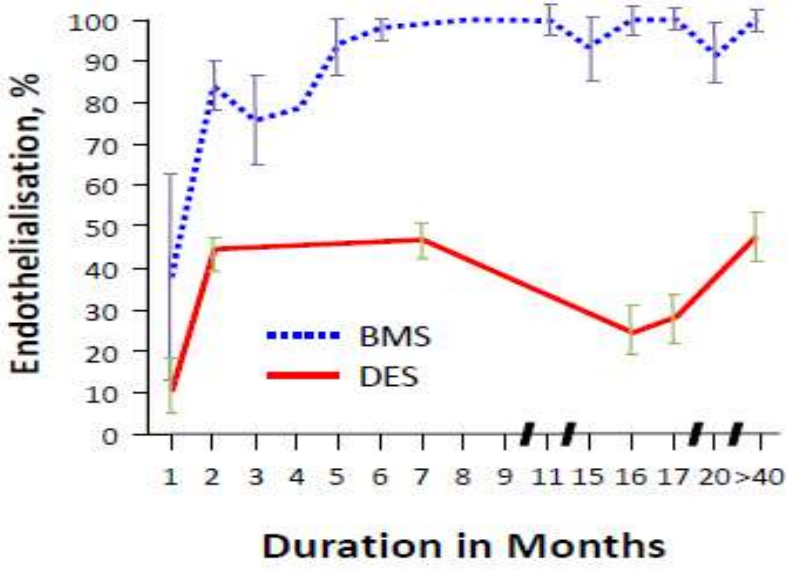


Lack of DAPT can be catastrophic!

Incomplete Strut Endothelialisation With DES?



Angioscopy at 8 months post SES implantation[1]



Virmani autopsy data[2]

Longer period of antiplatelet therapy is needed after DES

SES, sirolimus-eluting stent.
1. Kotani J, et al. *J Am Coll Cardiol.* 2006;47:2108–11. 2. Joner M, et al. *J Am Coll Cardiol.* 2006;48:193–202.

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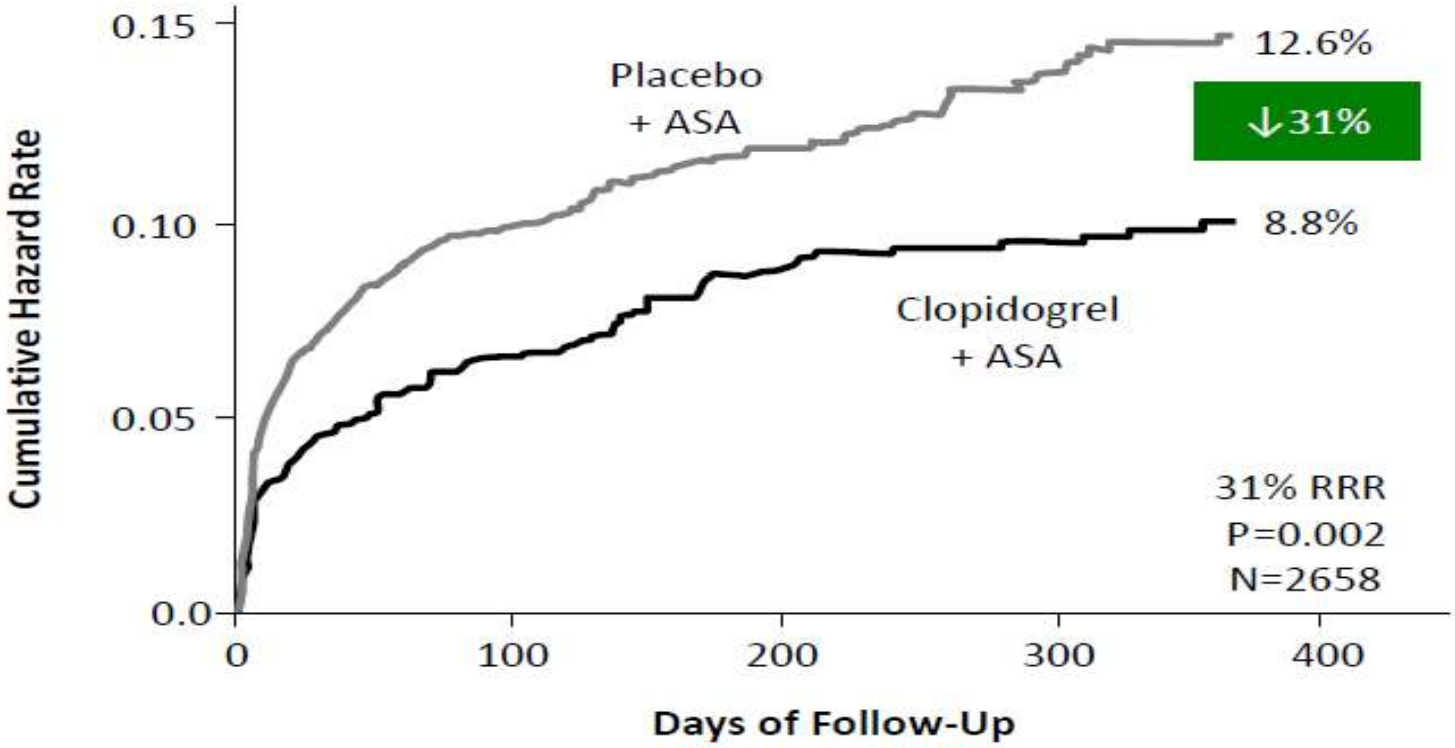
PCI-CURE: Widening Benefit Over Time?



ASA, aspirin; PCI-CURE, Study of PCI patients in the Clopidogrel in Unstable Angina to Prevent Recurrent Event trial.
Mehta SR, et al. *Lancet.* 2001;385:527–33.

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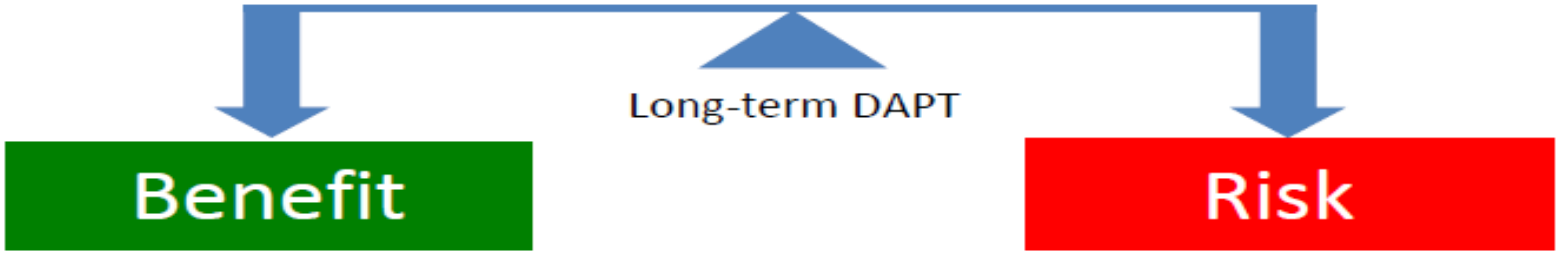
Benefit-Risk Balance of Long-Term vs. Short-Term DAPT Post-PCI



- Prevention of late stent thrombosis
- Secondary preventive effect

- Increased bleeding risk
- Excess cost
- Delayed procedures impacting QOL

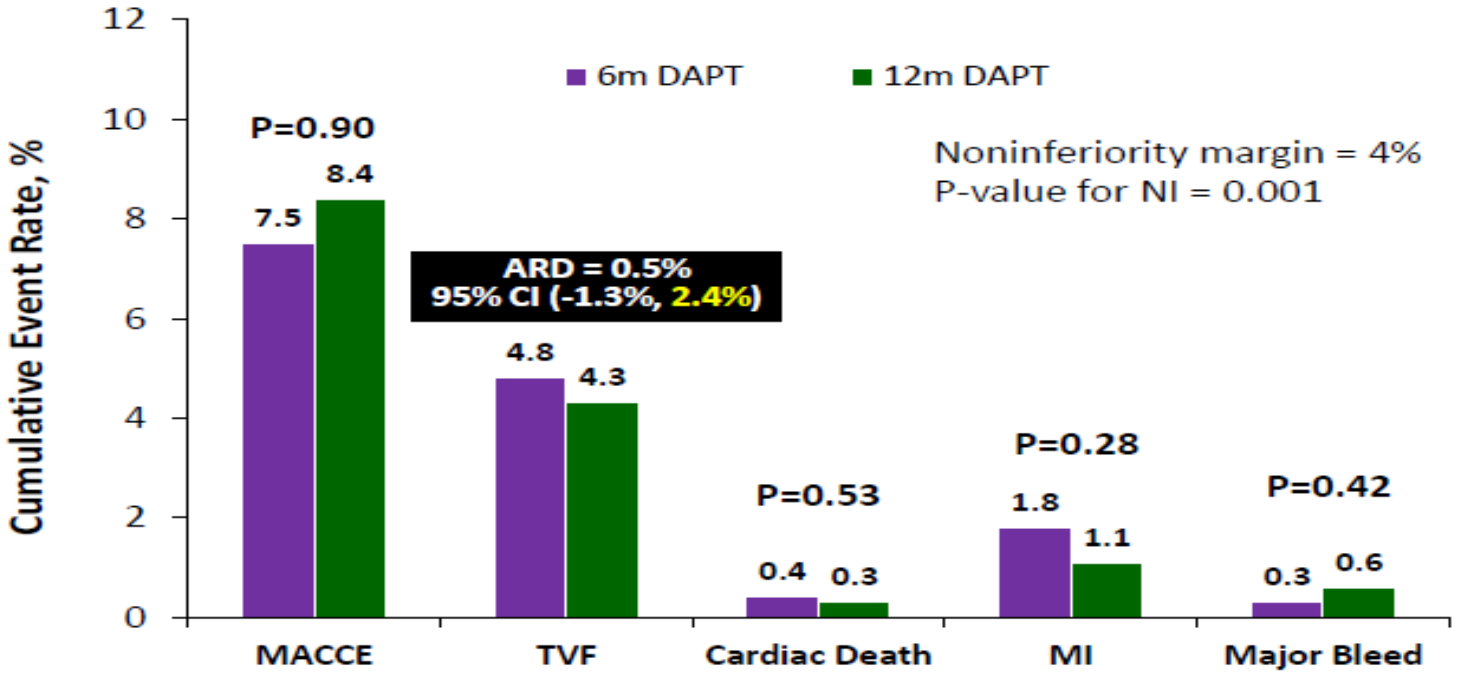
Does the benefit-risk-cost tradeoff justify long-term over short-term DAPT, especially given the improved risk profile of newer generation stents?

DAPT, dual antiplatelet therapy; QOL, quality of life.

The EXCELLENT Trial

PEP = TVF (Cardiac Death, MI, TVR)

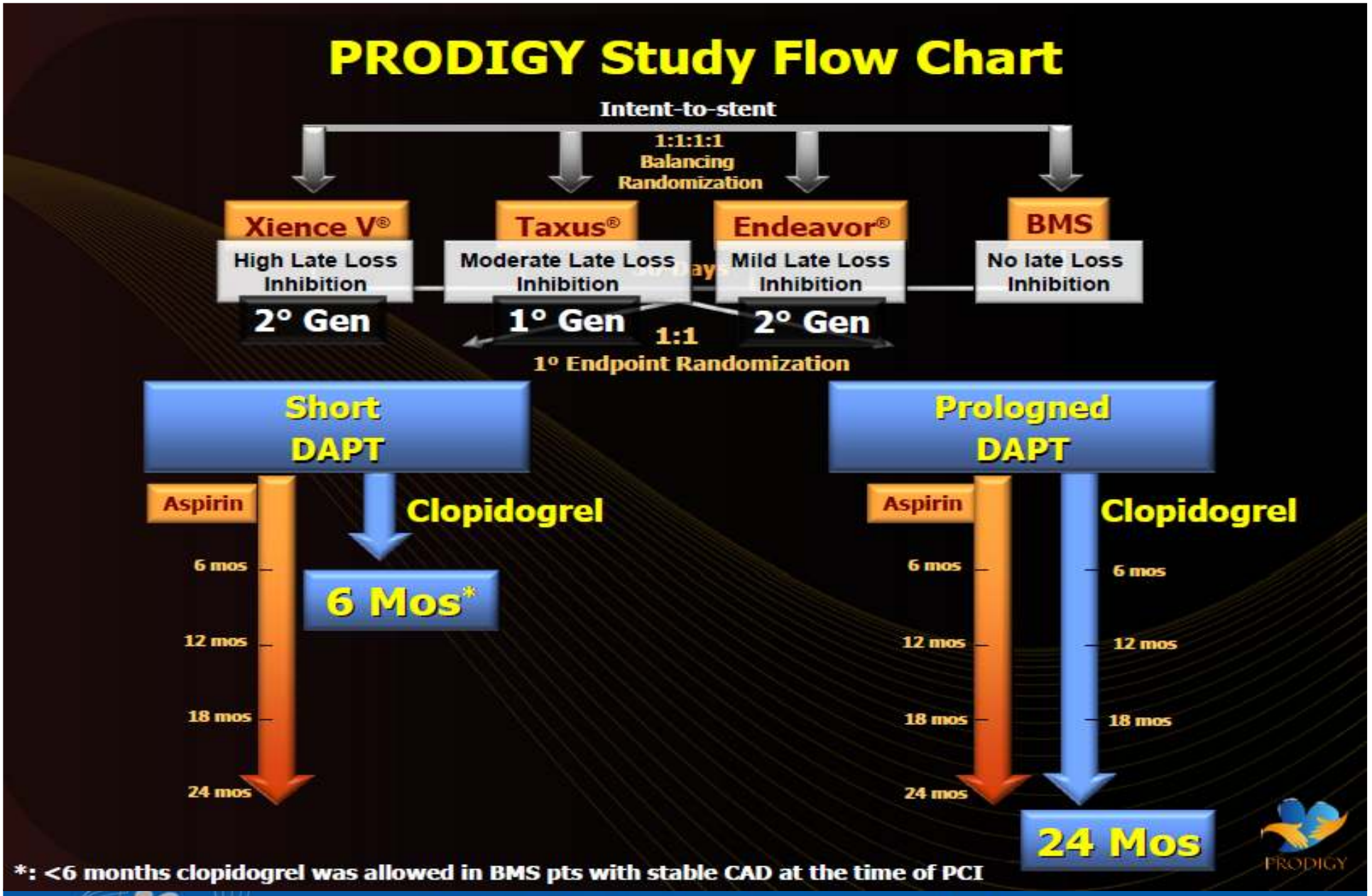
- N=1443 randomised at the time of PCI to 6- vs. 12-month DAPT after EES or SES
- 60–68% of patients adhered to study treatment



EES, everolimus-eluting stent; EXCELLENT, Efficacy of Xience/Promus Cypher to Reduce Late Loss After Stenting; NI, noninferiority; TVF, target vessel failure.

Gwon HC, et al. *Circulation.* 2010;125:505–13.

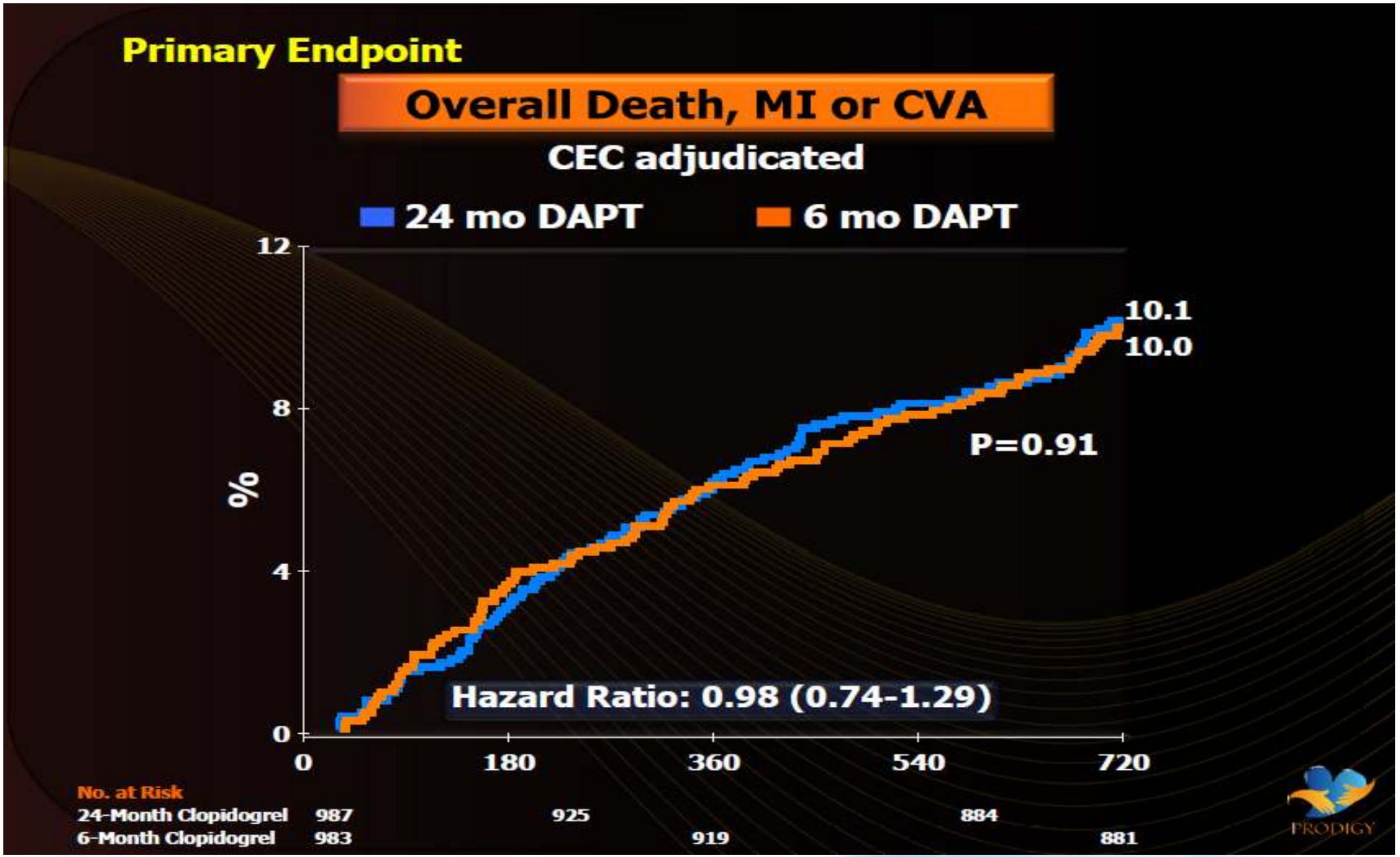
PRODIGY Study Flow Chart



Primary Endpoint

Overall Death, MI or CVA

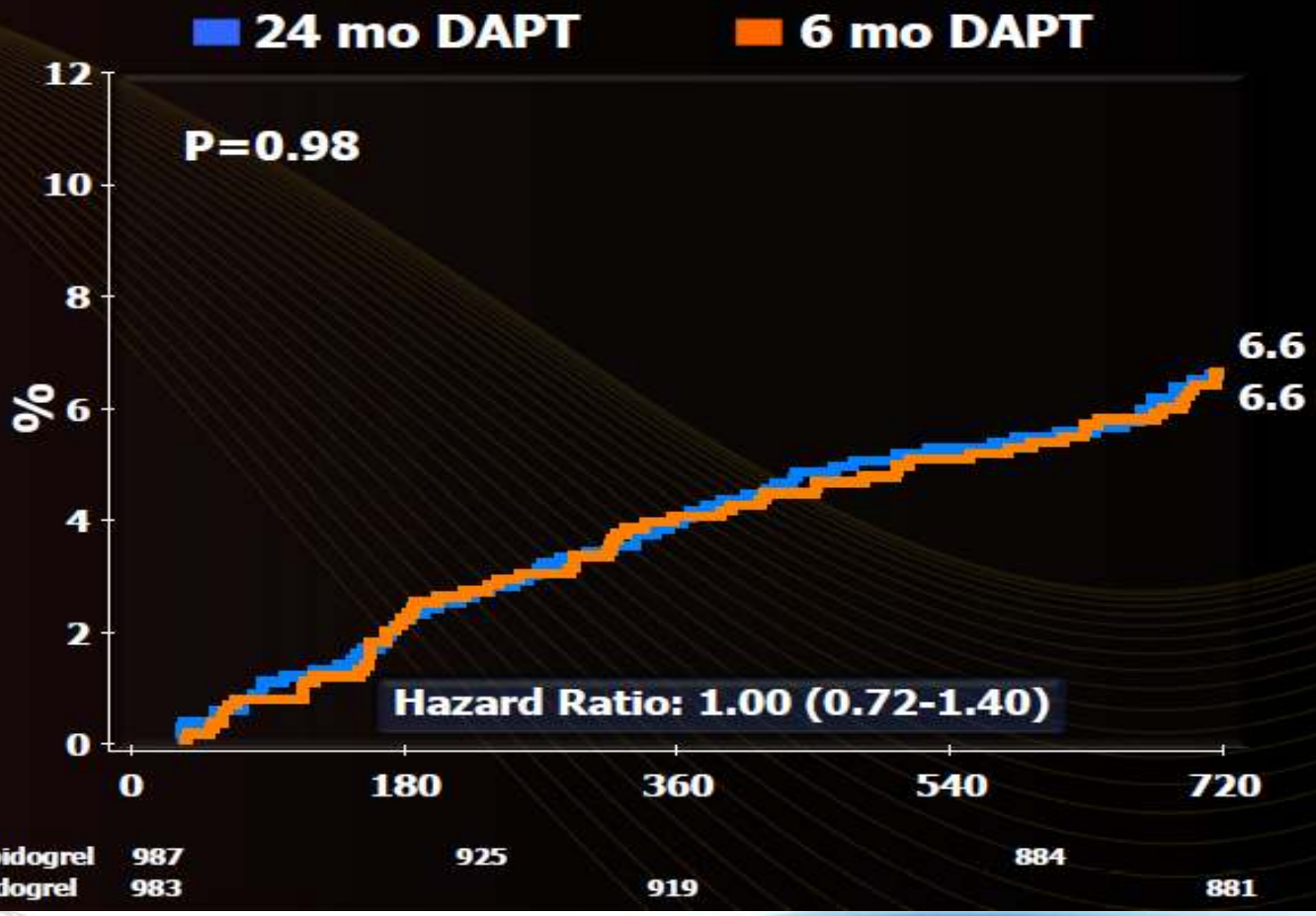
CEC adjudicated



PRODIGY

Secondary Endpoint

Death from any cause

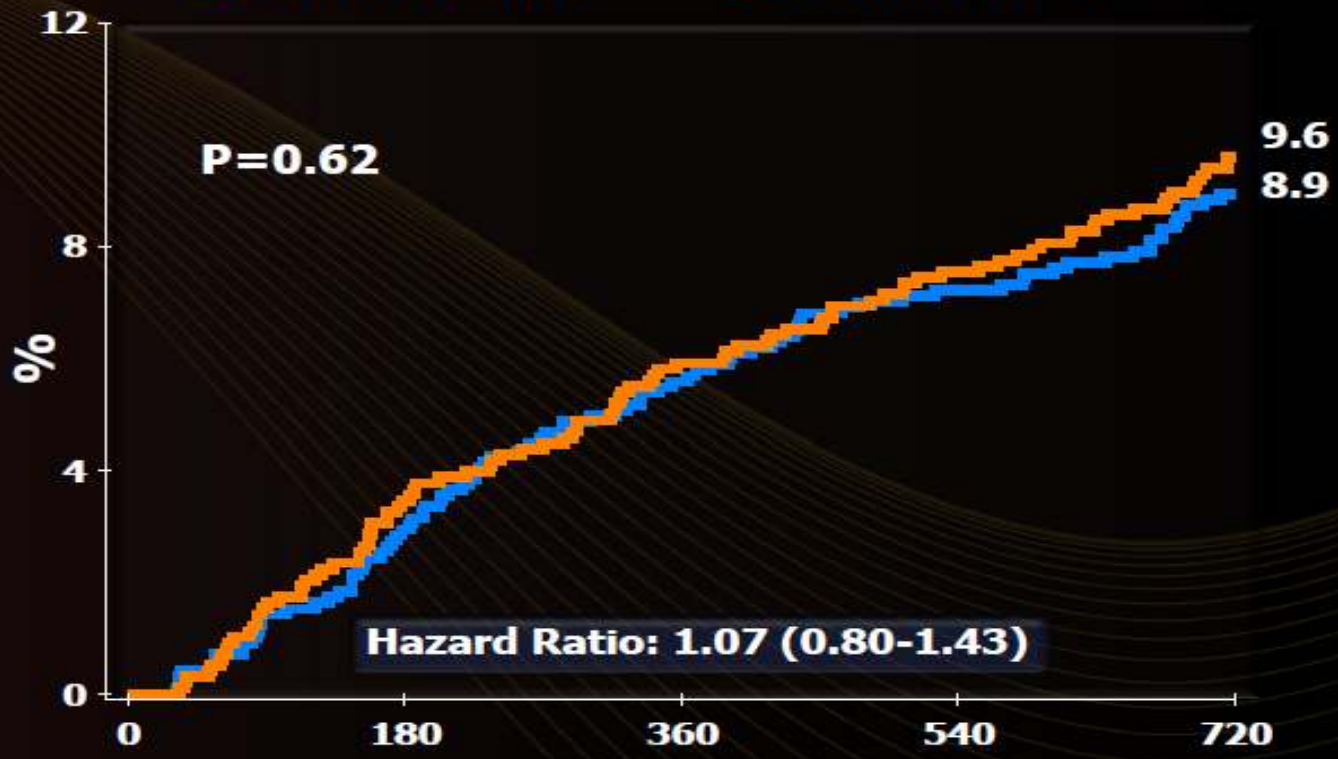


PRODIGY

Secondary Endpoint

Death from any cause or MI

CEC adjudicated



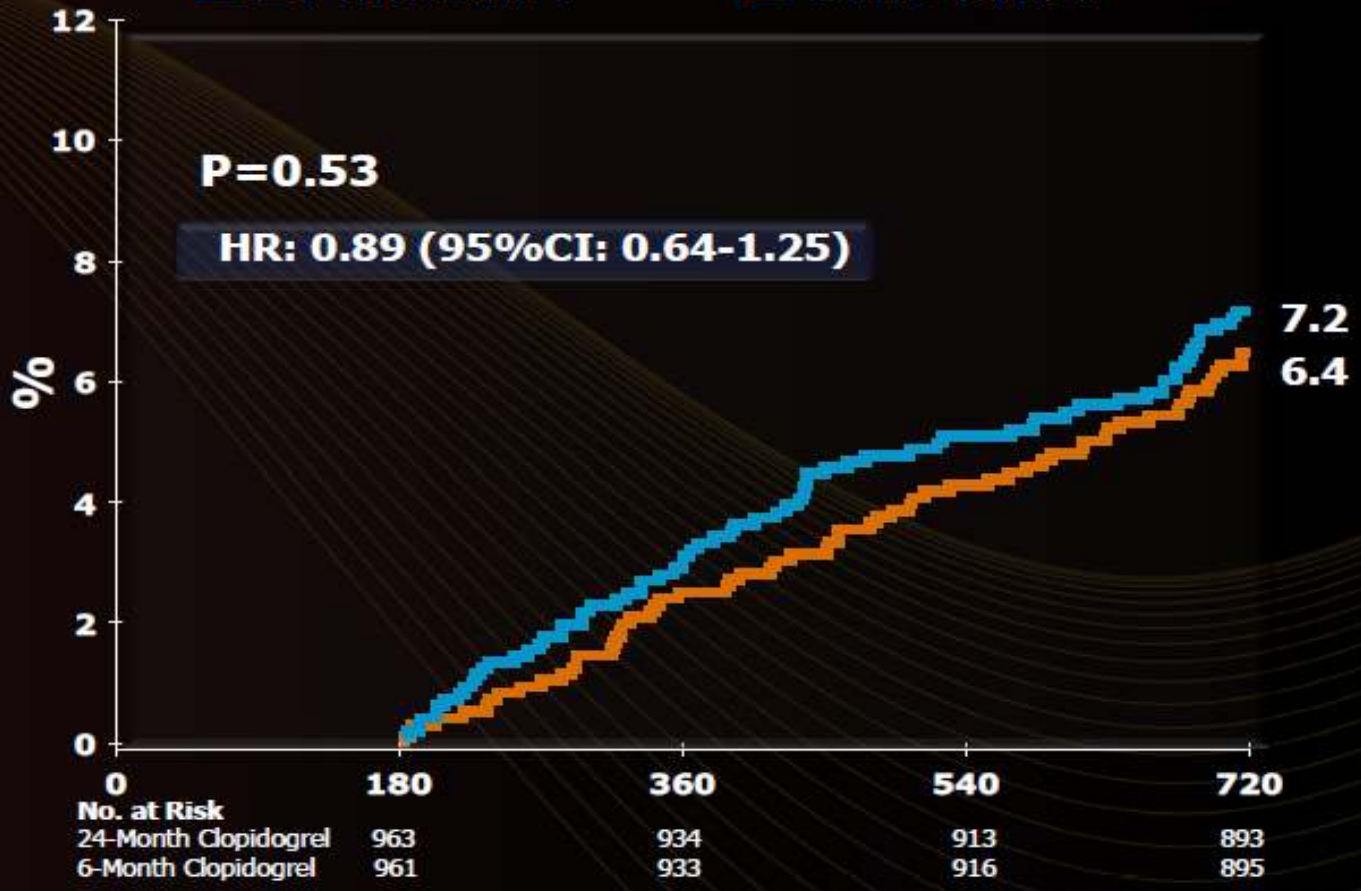
No. at Risk					
24-Month Clopidogrel	987	925	884		
6-Month Clopidogrel	983	919		881	

PRODIGY

Landmark Analysis

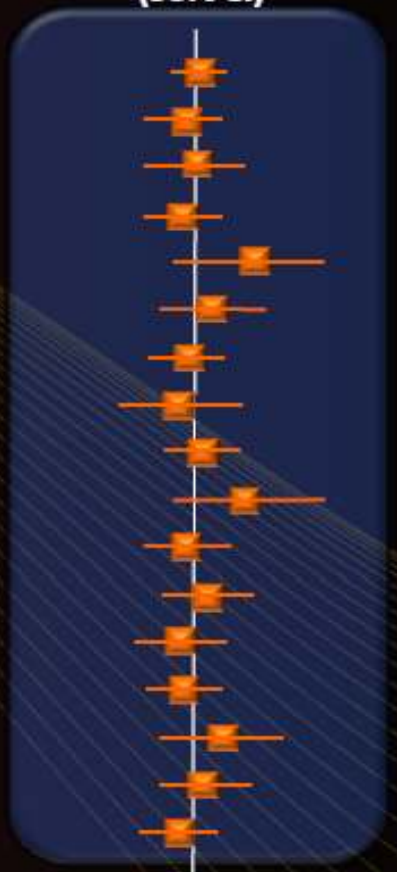
CEC adjudicated

Death from any cause, MI or CVA from 6 months onwards



PRODIGY

Subgroup analysis of the Primary Endpoint



	HAZARD RATIO (95% CI)	P-VALUES	
		Superiority	Interaction
Overall	0.98 (0.74-1.29)	0.91	
Male	1.09 (0.77-1.55)	0.85	0.91
Female	1.00 (0.60-1.68)	0.66	
≥ 65 yr	1.12 (0.82-1.51)	0.48	0.09
< 65 yr	0.57 (0.28-1.16)	0.12	
Diabetes	0.85 (0.53-1.38)	0.72	0.47
No Diabetes	1.06 (0.76-1.50)	0.52	
Bare metal stents	1.13 (0.68-1.86)	0.64	0.53
Drug-eluting Stents	0.93 (0.67-1.30)	0.66	
Stable Coronary Disease	0.60 (0.29-1.23)	0.16	0.14
Unstable Coronary Disease	1.07 (0.79-1.45)	0.63	
Single Lesion Treatment	0.88 (0.62-1.28)	0.51	0.38
Multiple Lesions Treatment	1.14 (0.74-1.76)	0.55	
Complex Lesion(s) Treated	1.07 (0.77-1.49)	0.68	0.31
Simple Lesion(s) Treated	0.78 (0.46-1.32)	0.35	
Creatinine Clearance > 60 ml/min	0.90 (0.58-1.38)	0.62	0.38
Creatinine Clearance ≤ 60 ml/min	1.14 (0.78-1.65)	0.50	

LOG HAZARD RATIO (95% CI)

10 1 0.1

24-month DAPT better

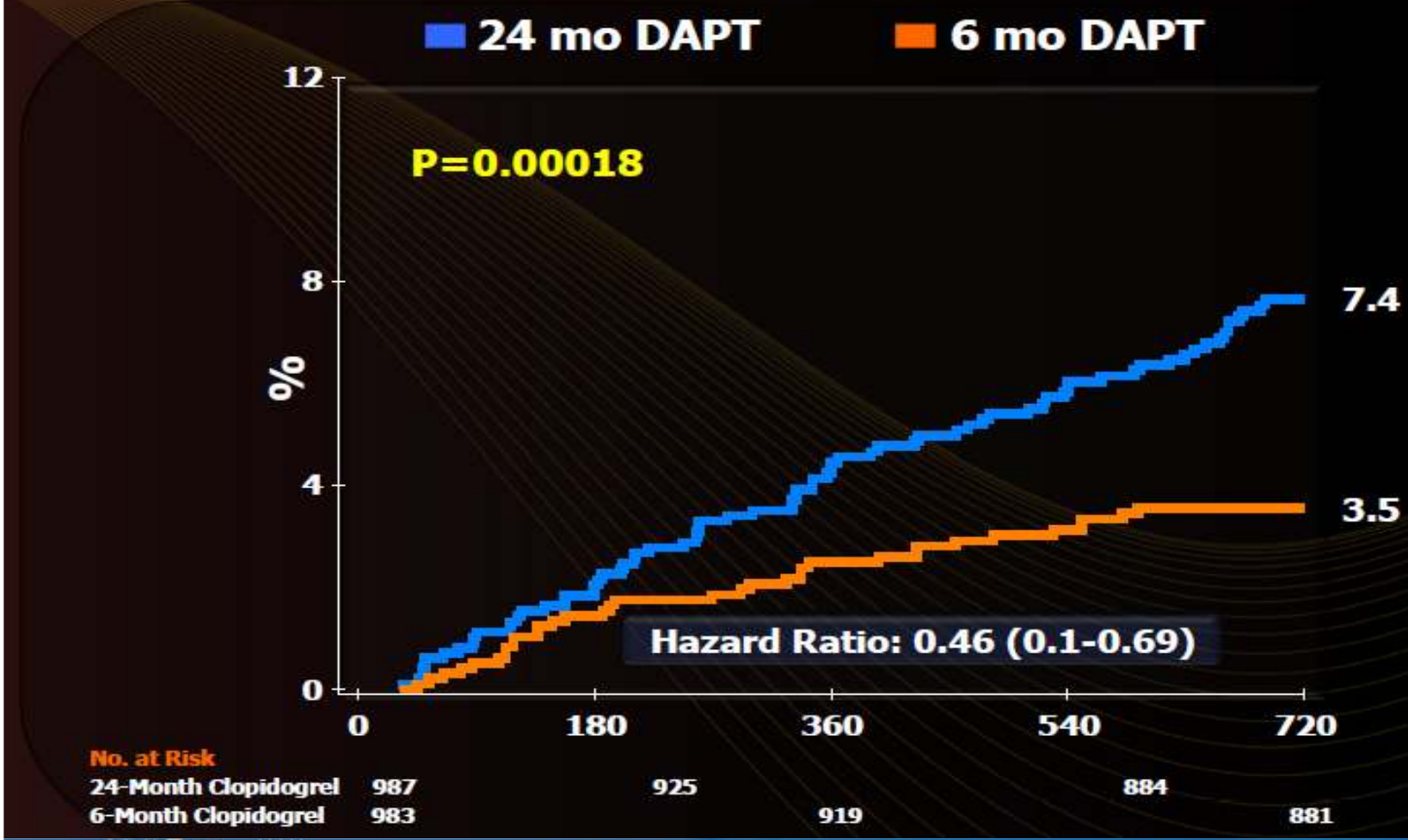
6-month DAPT better

PRODIGY

Key Safety Endpoint

Type II, III or V BARC bleeding

CEC adjudicated



PRODIGY

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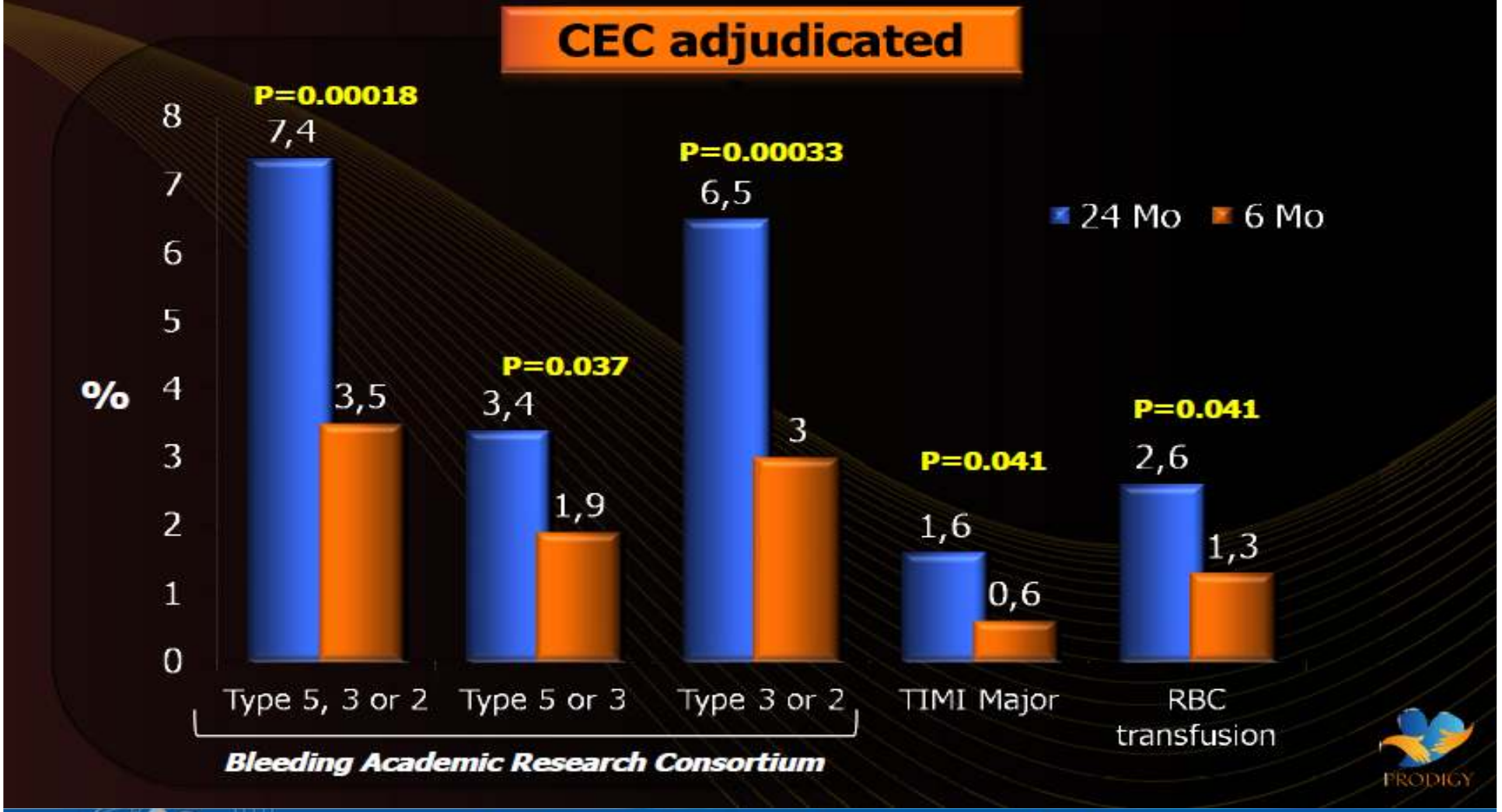
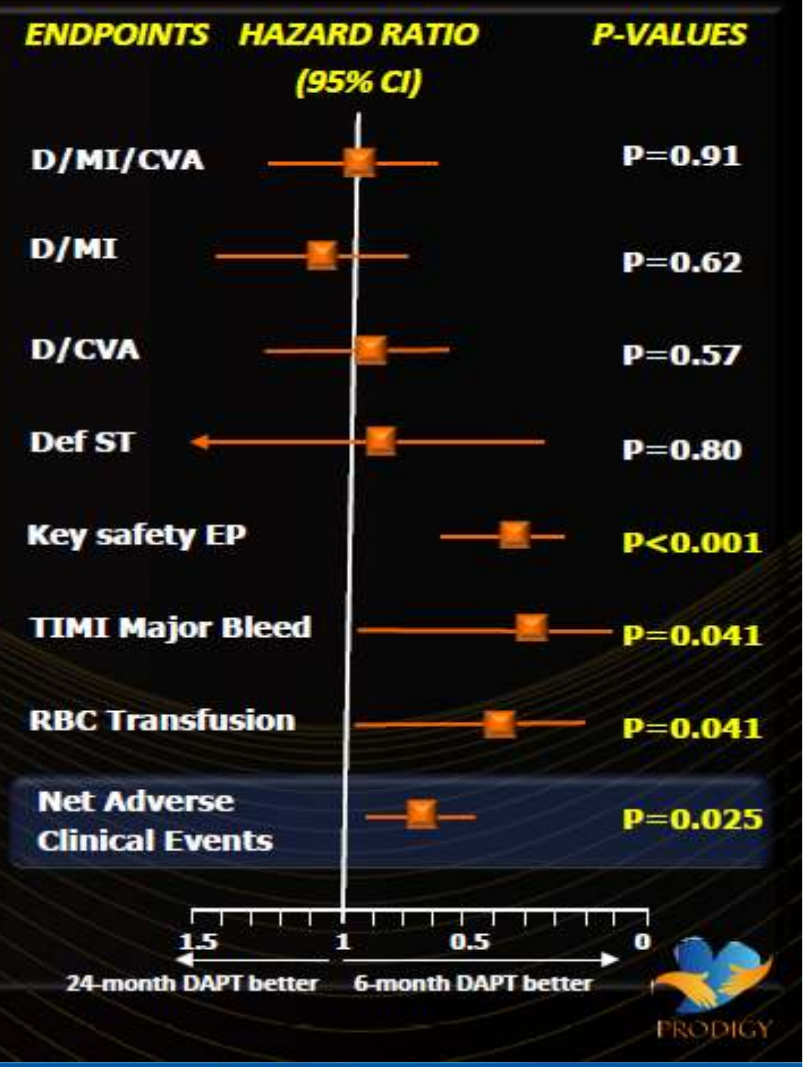
Bleeding Events and RBC Transfusion



Summary

Our study failed to show that prolonging DAPT for 24 months is superior to 6 month duration of Tx in pts receiving 1 or 2 gen DES or at least 1 month after BMS

While we cannot rule out the possibility that a smaller than previously anticipated benefit may exist, the clear increase in bleeding, transfusion and net adverse clinical events, suggests that current recommendations may have overemphasized the benefit over the risk of combined long-term aspirin and clopidogrel



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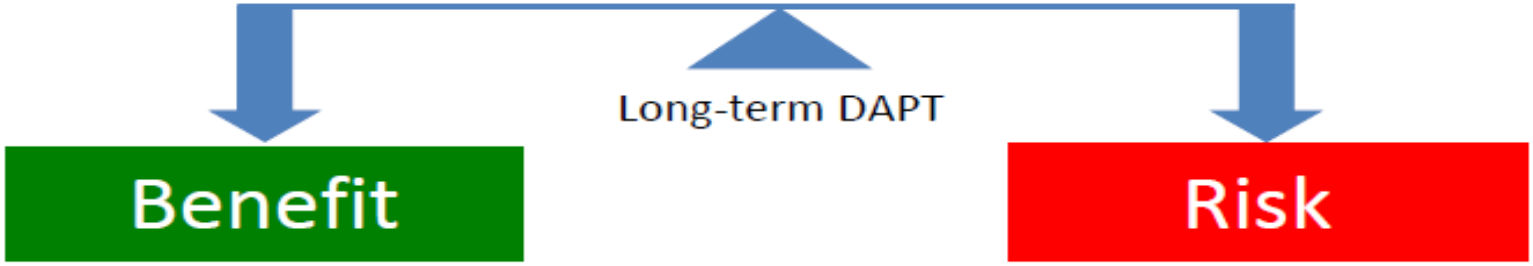
Optimal Duration of DAPT

The Science of Medicine



Benefit

- Prevention of late stent thrombosis
- Secondary preventive effect

Risk

- Increased bleeding risk
- Excess cost
- Delayed procedures impacting QOL

Insufficient evidence to adjudicate optimal duration of dual antiplatelet therapy

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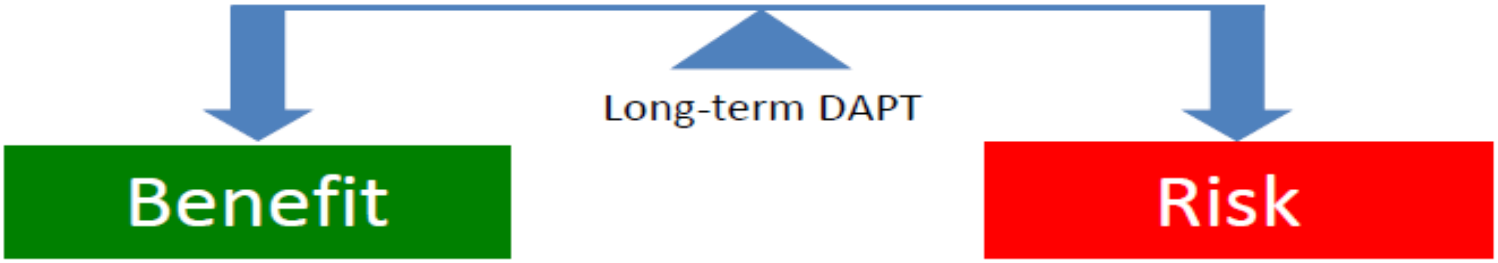
Optimal Duration of DAPT

The Art of Medicine

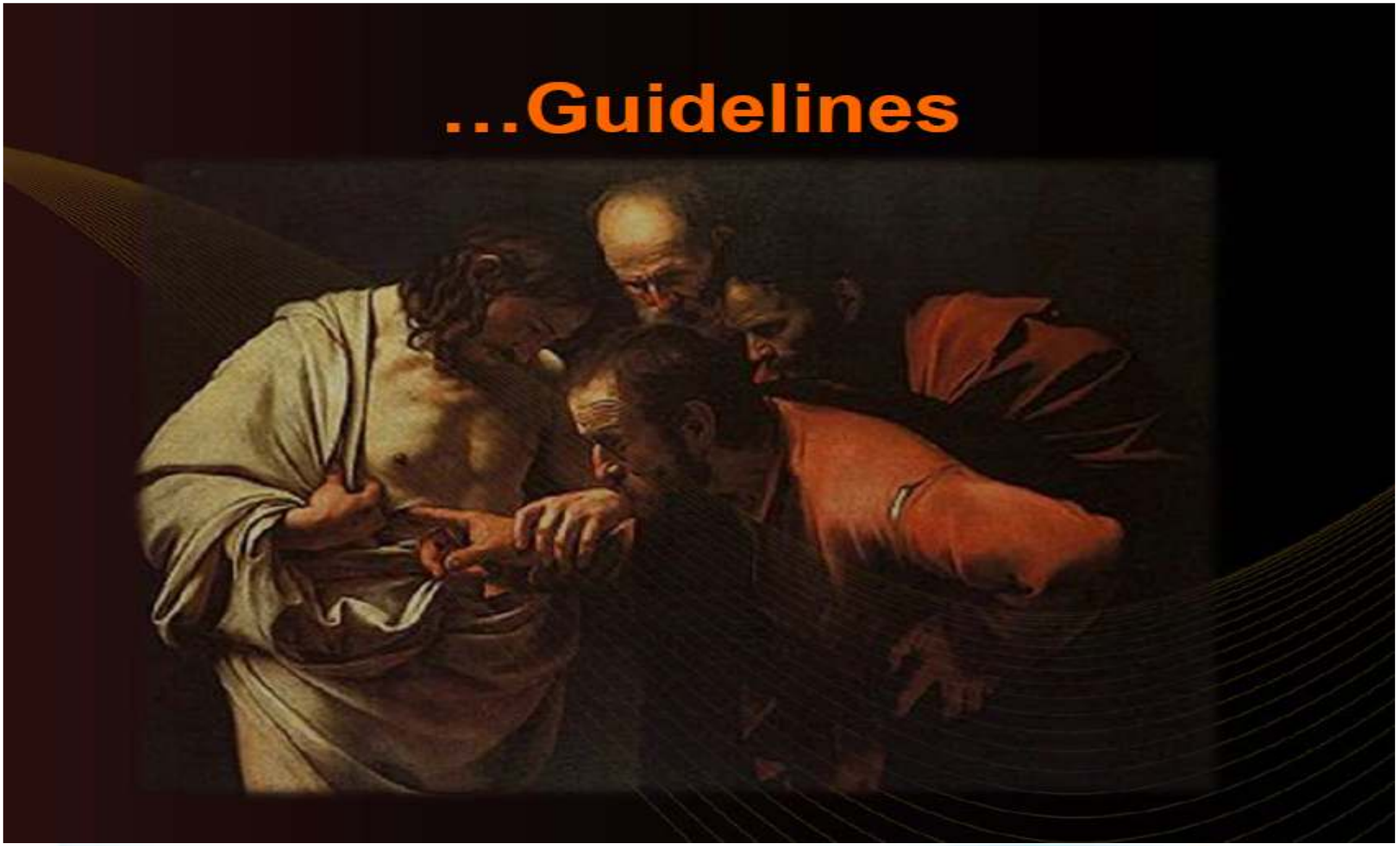


- Prevention of late stent thrombosis
- Secondary preventive effect

- Increased bleeding risk
- Excess cost
- Delayed procedures impacting QOL

- **May consider in high-risk patients with previous stent thrombosis and ACS who are compliant and at low risk for bleeding**
- **May consider in high-risk intervention (complex lesion, diabetics, etc.)**

…Guidelines



2010 ESC/EACTS Revascularisation Guidelines

Duration of $P2Y_{12}$ Inhibitor Treatment Post-PCI

Dual Antiplatelet Therapy Post-PCI

- 1 month after BMS implantation in stable angina
- 6–12 months after DES in all patients
- 12 months in all patients after ACS, irrespective of revascularisation

Recent data suggest that DAPT for 6 months may be sufficient because late and very late stent thrombosis correlate poorly with discontinuation of DAPT

ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery.
Wijns W, et al. *Eur Heart J.* 2010;31:2501–55.

2011 ACC/AHA/SCAI PCI Recommendations

Duration of $P2Y_{12}$ Inhibitor Treatment Post-PCI

	Class I (Benefit >>> risk) (*Highly recommended*)	Class II		Class III (Risk ? Benefit) (*Not recommended*)
		IIa (Benefit >>risk) (*Reasonably recommended*)	IIb (Benefit ? risk) (*May be considered*)	
Level B (Single randomised trial or nonrandomised studies)	DES (ACS or non-ACS) BMS (ACS) - Clopidogrel: 75 mg x12m - Prasugrel: 10 mg x12m - Ticagrelor: 90 mg x12m BMS (non-ACS) Ideally x 1m, and up to 12m if bleeding risk not high (x2 wks)			Prasugrel in pts with h/o TIA or stroke
Level C (Consensus opinion, case studies, or standard of care)		Bleeding risk > benefit DAPT: <12m	DES (ACS or non-ACS) DAPT x >12m	

Paucity of high-quality (LOE A) evidence!

ACC, American College of Cardiology; ACS, acute coronary syndromes; AHA, American Heart Association; h/o, history of LOE, level of evidence; SCAI, Society for Cardiovascular Angiography and Interventions; TIA, transient ischaemic attack.
Levine GN, et al. *J Am Coll Cardiol.* 2011;58:e44–122. Levine GN, et al. *Circulation*. 2011;124:e574–651.

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Ongoing Trials on DAPT Post-PCI

Trial name	Subjects	DES type	DAPT duration	Primary end point
DAPT*	20,645 12-m event free	All DES and BMS	12m vs. 30m	D/MI/CVA at 33m
ISAR-SAFE*	6000 6-m event free	All DES	6m vs. 12m	D/MI/CVA/ST/Bleed at 15m
OPTIMIZE	3120 Non-STEMI	ZES	3m vs. 12m	D/MI/CVA/Bleed at 12m
SECURITY	4000 Non-ACS CAD	EES, PES, ZES, BMS	6m vs. 12m	Definite/probable ST at 24m
ITALIC	3200 Non-ACS CAD	Xience DES	6m vs. >6m in ASA responders	D/MI/uTVR/CVA/Bleed at 12m
ARCTIC	2500 All comer	All DES	12m vs. 18-30m	D/MI/uTVR/ST at 18-30m
OPTIDUAL	1966 All comer	All DES	12m vs. 36m	D/MI/CVA/Bleed at 36m
SCORE	280 MI	All DES	12m vs. 24m	D/MI at 24m
Global LEADERS	16,000 All comers PCI	All DES	1m vs. 12m**	Death/Q-wave MI at 24m

*Double-blind.
**Subsequent monotherapy.

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Optimal Duration of DAPT

Conclusions

- No large methodologically rigorous study has assessed prospectively whether long-term DAPT would be clinically better than short-term DAPT
- Several large ongoing studies may resolve the uncertainties regarding optimal duration of DAPT
- Until we have more evidence, it is too early to say that 6–12m of DAPT is enough for all patients post-PCI
- Customised approach would be ideal
- Long-term DAPT might be preferable in targeting
  - High-risk patient with previous ST, MI, DM
  - Complex intervention (LM disease, bifurcation, MVD, etc.)

DM, diabetes mellitus; LM, left main; MVD, multivessel disease.


16 11 2001

The Bleeding Patient

- Most bleeding can be managed while on dual-antiplatelet therapy
  - All bleeding eventually stops!
- If cessation is required, the risk of subacute ST depends upon:
  - Time since PCI / Duration of cessation
  - Risk of initial PCI (ACS vs. non-ACS, etc)
  - NOT on BMS vs. DES in the first 2 wks

Replace 2 - blødnings definition

Lincoff AM et al. JAMA 2003; 289: 853-863.

PCI-related bleeding is associated with increased rate of clinical events

Bleeding Complication	Major (n=588)	Minor (n=1,394)	None (n=8,992)
Death	7.5%* †	1.8%*	0.6%
Q-Wave myocardial infarction	1.2%*	0.7% ‡	0.2%
Non-Q-Wave myocardial infarction	30.7%* †	16.8%*	11.8%
Repeat lesion angioplasty	1.9%* §	0.8% ‡	0.3%
Major adverse cardiac event	6.6%*†	2.2%*	0.6%

*p <0.001 vs none; †p<0.001 vs minor; ‡p<0.01 vs none; §p <0.05 vs minor

Kinnaird et al Am J Cardio 2003

The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet, Jurriën ten Berg

The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing (clinicaltrials.gov NCT00769938)

Background

1/ Long term oral anticoagulant therapy (OAC) is obligatory (class I) in:
- most patients with atrial fibrillation
- patients with mechanical heart valves

2/ Over 30% of these patients have concomitant ischemic heart disease
When these patients need to undergo percutaneous coronary stenting, there is also an indication for aspirin and clopidogrel

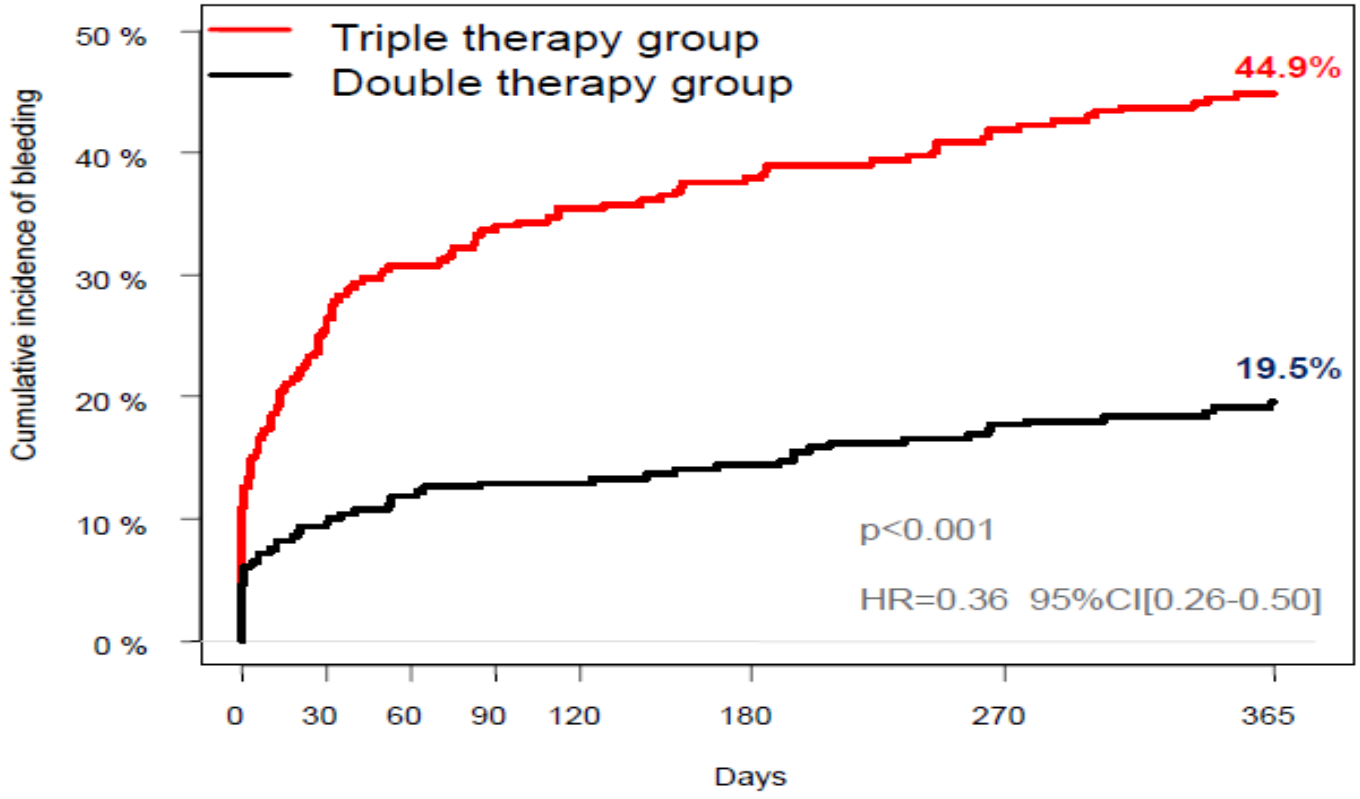
3/ Triple therapy (OAC, aspirin and clopidogrel) is recommended according to the guidelines but is also known to increase the risk of major bleeding
Major bleeding increases mortality

4/ No prospective randomized data available

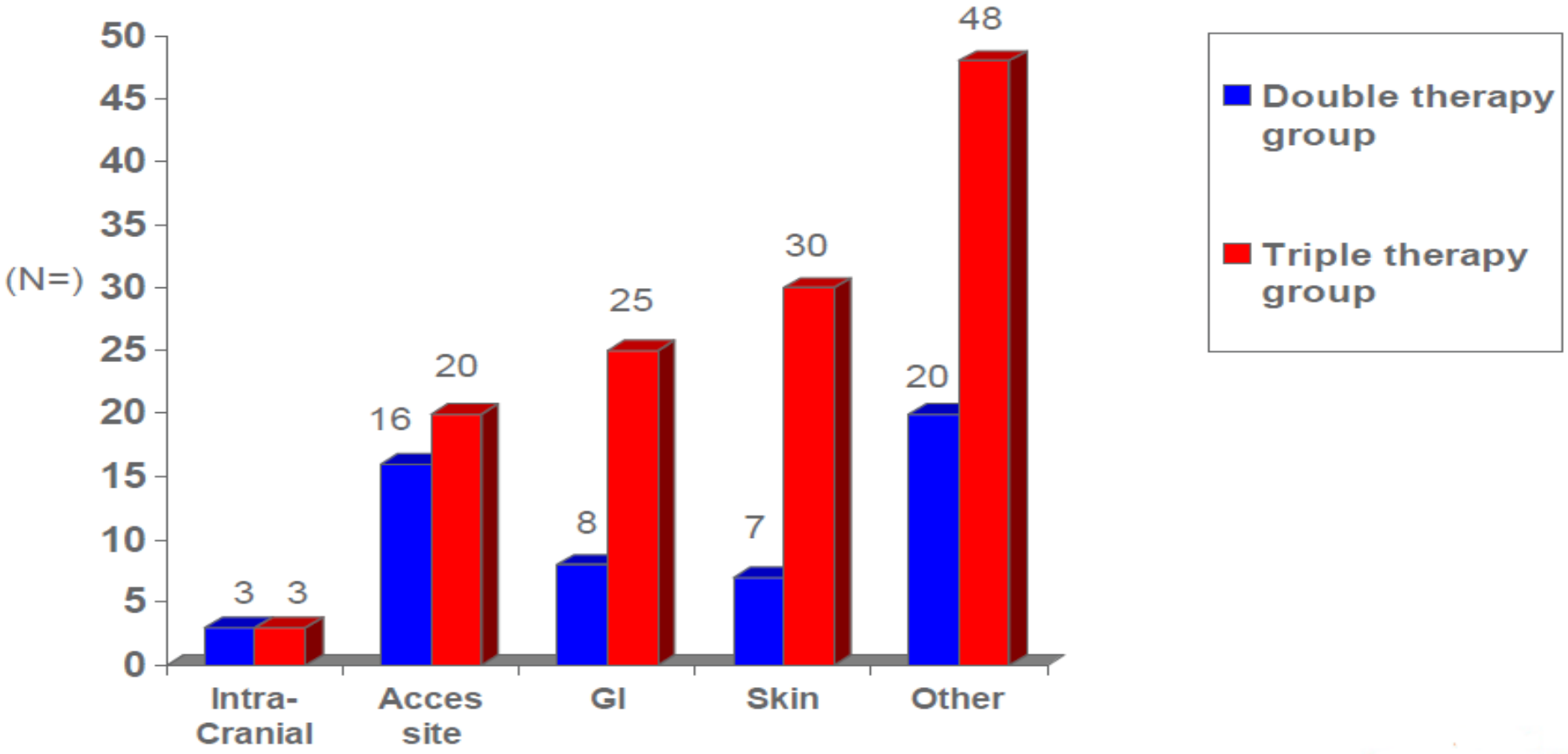
Aim of the study

To test the hypothesis that in patients on OAC undergoing PCI, *clopidogrel alone* is superior to the combination *aspirin and clopidogrel* with respect to bleeding but is not increasing thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)

Primary Endpoint: Total number of bleeding events

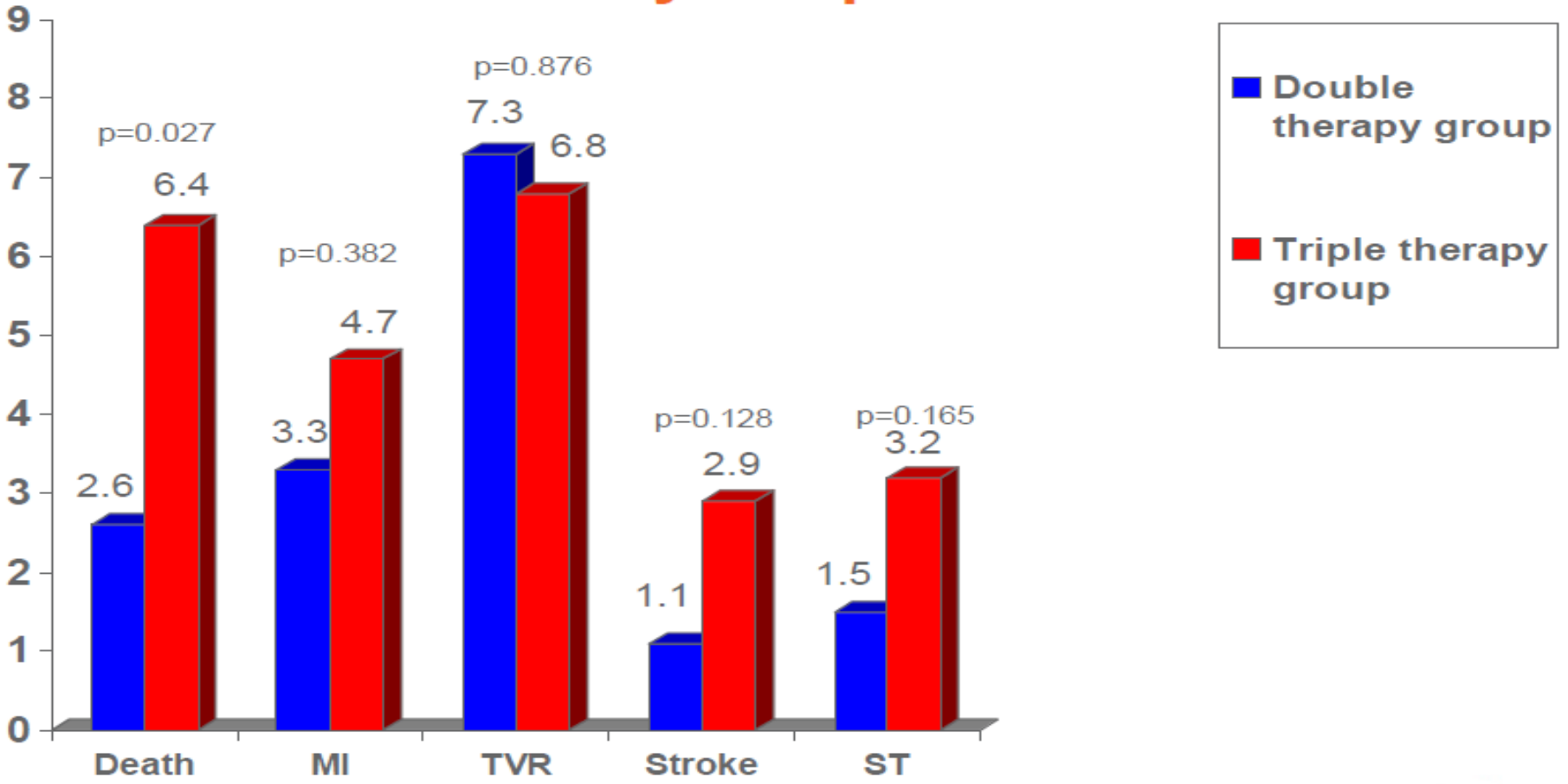


Locations of TIMI bleeding: Worst bleeding per patient



GI=gastro intestinal; Other bleeding consists of eye, urogenital, respiratory tract, retroperitoneal, mouth, PMpocket bleeding

Secondary Endpoint



MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

Conclusions

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting

2. Primary endpoint was met: as expected, OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way

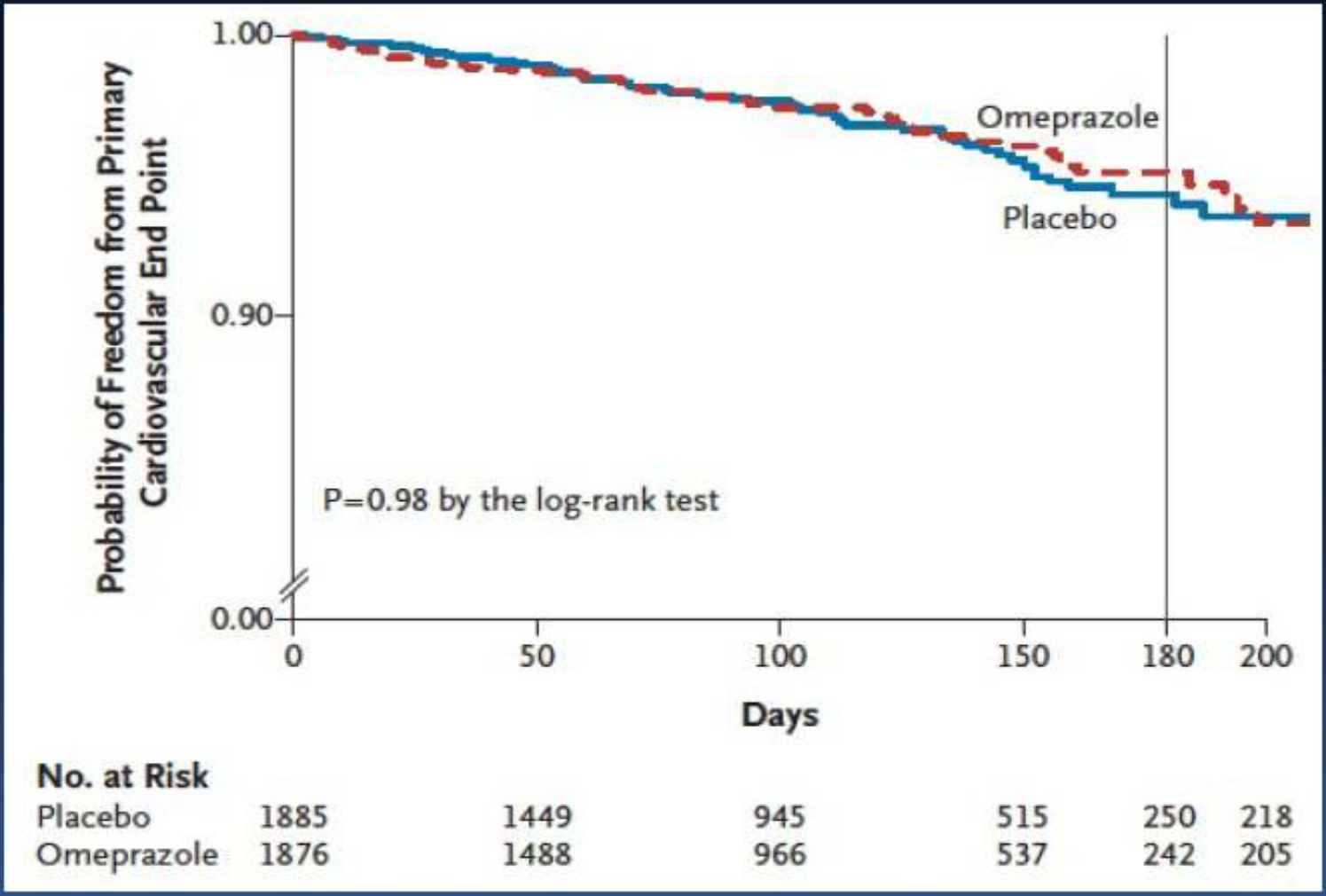
3. Secondary endpoint was met: with dual therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death

4. Less all-cause mortality with dual therapy

Implications

We propose that a strategy of oral anticoagulants plus clopidogrel, but without aspirin could be applied in this group of high-risk patients on OAC when undergoing PCI

COGENT: CV Events



No. at Risk

Placebo	1885	1449	945	515	250	218
Omeprazole	1876	1488	966	537	242	205

COGENT: Major results

Outcome	Omeprazole (%)	Placebo (%)	HR (95% CI)	p
Composite of GI events*	1.1	3.4	0.34 (0.18-0.63)	<0.001
Overt GI bleeding	0.2	1.2	0.13 (0.03-0.56)	0.001
Composite of cardiac events	4.9	5.7	0.99 (0.68-1.44)	0.96
MI	1.2	1.5	0.92 (0.44-1.90)	0.81
Revascularization	4.0	4.6	0.91(0.59-1.38)	0.64

*Primary end point: GI bleeding, symptomatic GI ulcer, gastric pain with ≥5 gastroduodenal erosions, obstruction, or perforation

Multivariate Model for Major Bleeding in Patients with NSTEMI

Variable	Adjusted OR	P-value
Age (per 10y increase)	1.22	0.0002
Female sex	1.36	0.0116
History of renal insufficiency	1.53	0.0062
History of bleeding	2.18	0.014
GPIIb/IIIa blockers	1.86	<0.001
Percutaneous interventions	2.24	<0.0001

Moscucci. Eur Heart J 2003;24:1815

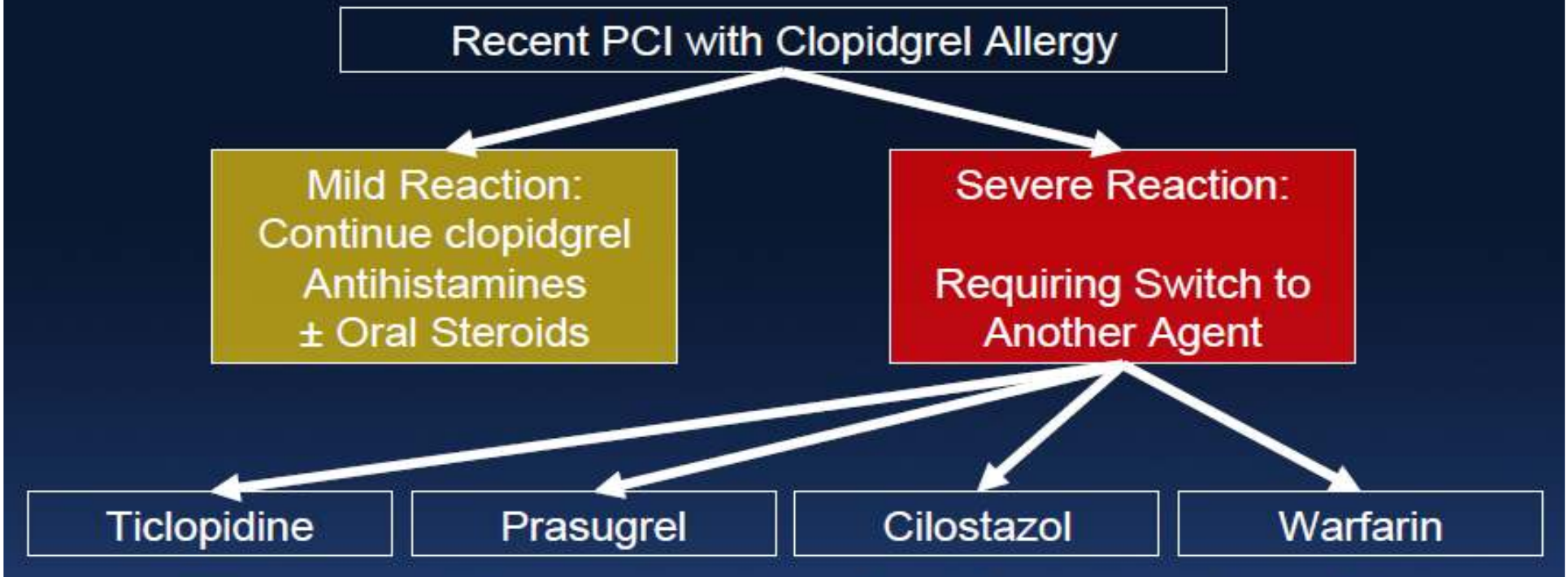
Strategies to Deal With Bleeding

- **Hemodynamic resuscitation is critical**
- Continue DAPT if at all possible
- Continue ASA alone while P2Y12 inhibitor is off
  - Minimize time off P2Y12 inhibitor
  - Most IV bridging strategies are not applicable here

Clopidogrel Allergy

- Majority of cases occur <2 wks
- Incidence ranges from 1-6%
- Most frequent reaction is cutaneous, maculopapular rash
  - Reaction may/may not be due to clopidogrel
  - Antihistamines and/or short course of steroids can be effective in >85% of patients

Algorithm for Clopidgrel Allergy



- Up to 27% cross-reactivity
- Consider desensitization to clopidogrel

- *Also thienopyridine
- No data on x-allergy

- Study in elective PCI
- Less relevant now with other agents?

- Less effective than asa + thienopyridine

(Recent) Stents and Surgery: Not a good Combination!!!

- Perioperative thrombotic risk increases
  - ↑platelet aggregation, ↓fibrinoloysis
  - Catecholamine release
  - Hypotension
- Cessation of antiplatelet Rx often occurs
  - Surgeons are just used to it!

Outcomes According to Time Delay Between Stent Implantation and Non-Cardiac Surgery

	<42 Days	42 Days to 1 Year	>1 Year	*P*
	n=40	n=477	n=866	
BMS				
Death/any IHD event	18 (45)	65 (13.6)	101 (11.7)	<0.001
Death	2 (5)	5 (1)	1 (0.1)	<0.0001
MI	3 (7.5)	3 (0.6)	4 (0.5)	<0.0001
	n=19	n=255	n=282	
DES				
Death/any IHD event	7 (36.8)	41(16.1)	35 (12.4)	0.017
Death	1 (5.3)	2 (0.8)	1 (0.4)	0.049
MI	2 (10.5)	2 (0.8)	3 (1.1)	0.001

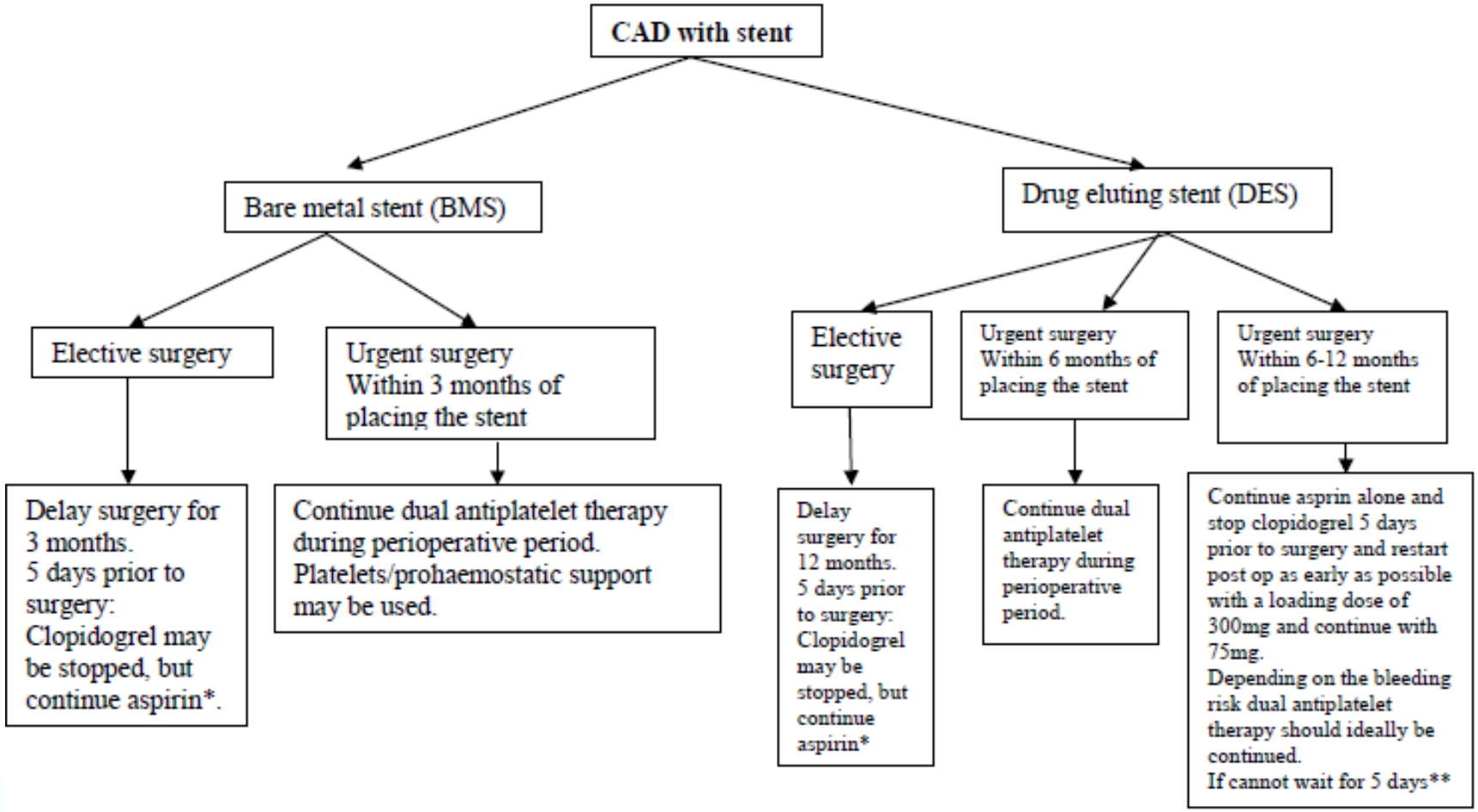
Strategies for Upcoming Surgery

- ***If at all possible, delay surgery!***
  - Ideally 6 weeks for BMS*
  - Ideally 6+ months for DES*
- If surgery is needed and bleeding risk acceptable, continue DAPT
  - But timing issues are less certain
- If bleeding risk is high, continue ASA and restart P2Y12 inhibitor ASAP
  - Could consider IIbIIIa bridging
- If no AP therapy, consider IIbIIIa bridge

Decision making algorithm in patients undergoing non-cardiac surgery

Initial check list

- a) Reason for antiplatelet therapy (CVA/CAD/others)
- b) Type of antiplatelet therapy used
- c) Time of the event
- d) If CAD – Stent/CABG and time of the same
- e) If stent- Bare metal Vs Drug eluting stent
- f) History of prior stent thrombosis
- g) Type of surgery- Risk of bleeding/thrombosis
- h) Elective/urgent surgery
- i) Co-morbidities in the patient (DM/Renal failure/EF)



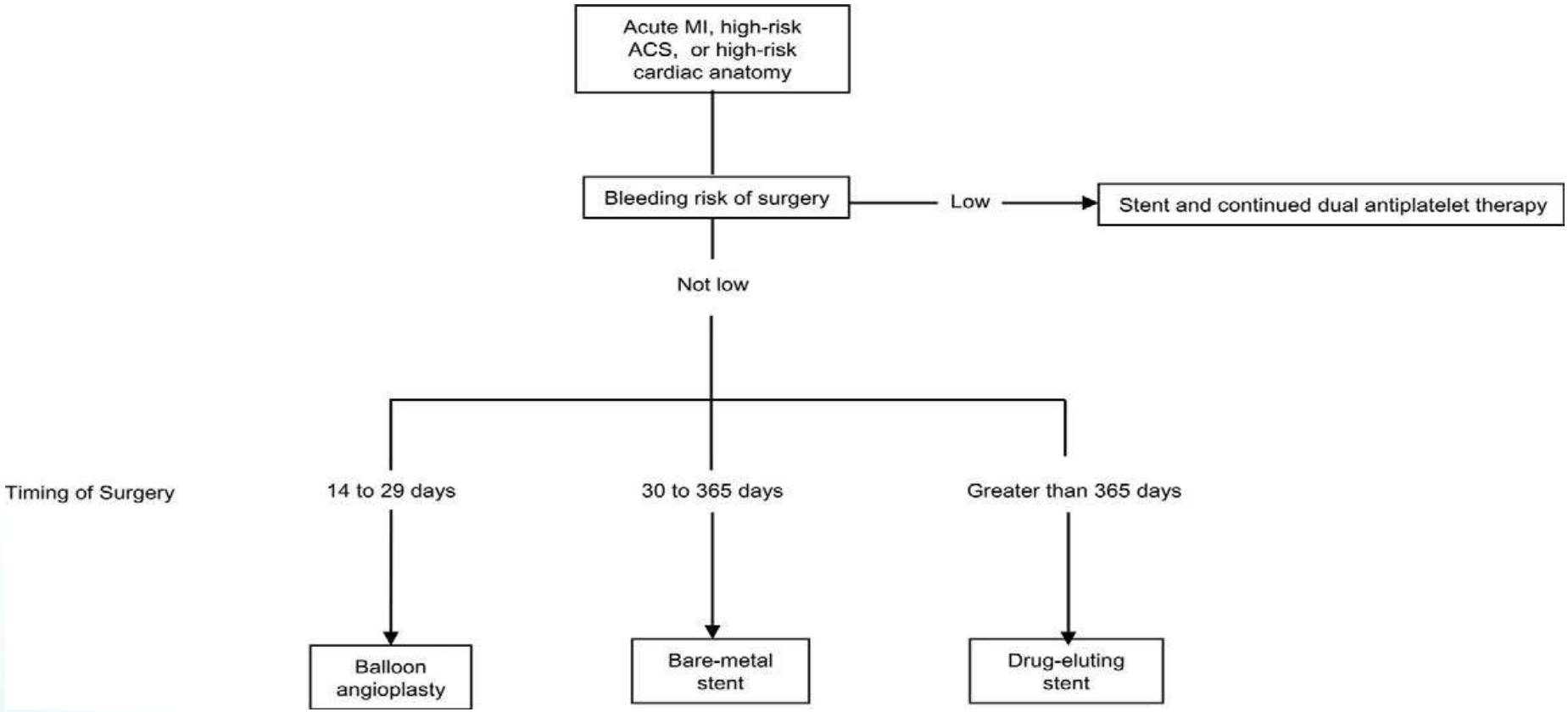
*Discontinuation of aspirin should be considered in those in whom hemostasis is difficult to control during the operative procedure (for e.g. Neurosurgery/posterior chamber of eye surgery/TURP).

** Continue the procedure with platelet support.

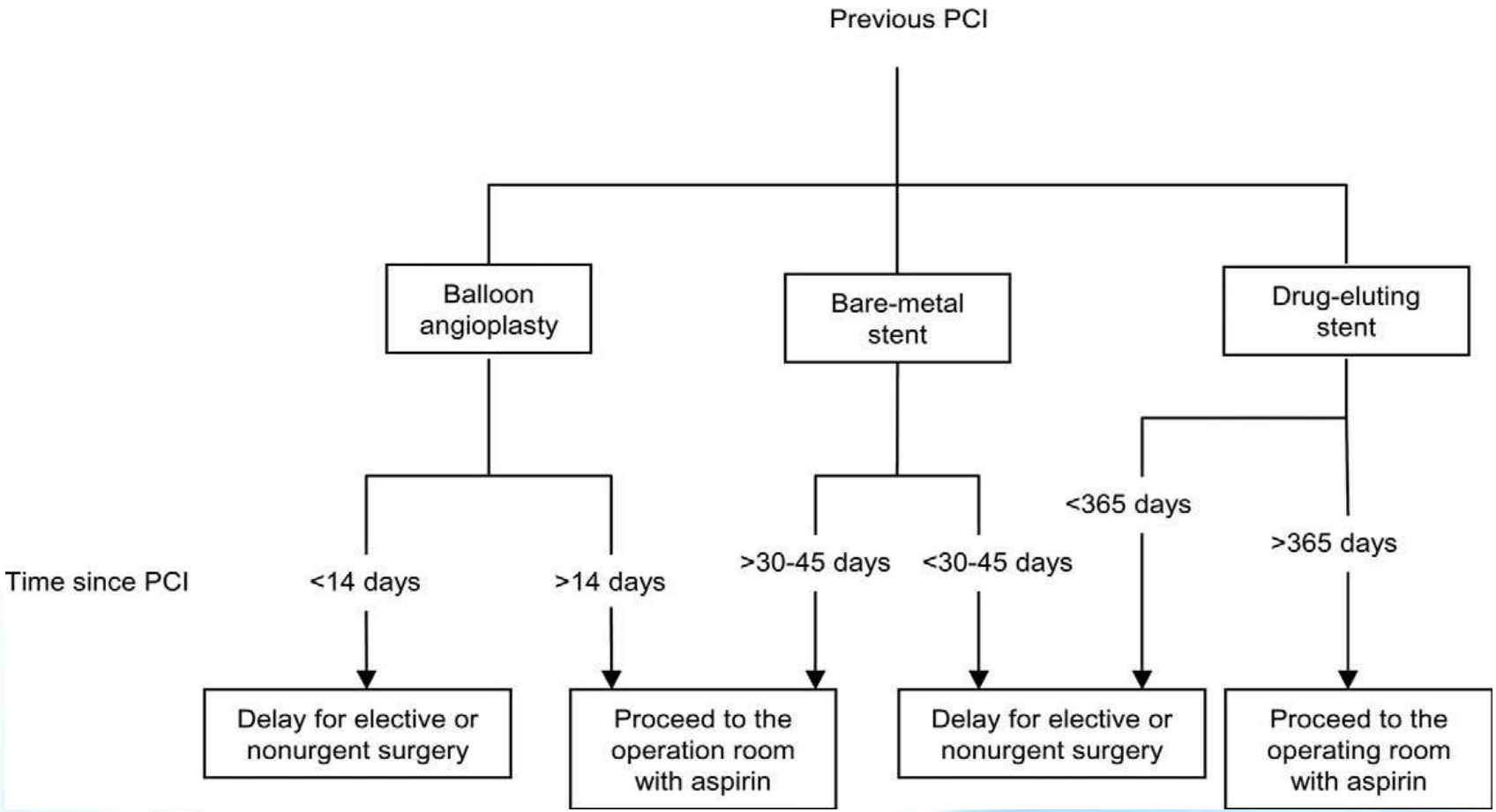
Bleeding Risk in Various Surgeries

Bleeding Risk	Clinical Severity	Type of Surgery
Low	• Transfusions rare	• Peripheral: plastic/general, biopsies • Minor orthopedic, ENT general • Endoscopy • Eye: anterior chamber • Dental
Intermediate	• Transfusions may be frequent • More re-op, LOS	• Visceral • Cardiovascular surgery • Major orthopedic, ENT • Urologic reconstructive
High	• Bleeding into a closed space	• Intracranial • Spinal • Eye: posterior chamber

2009 ACCF/AHA Perioperative Guidelines



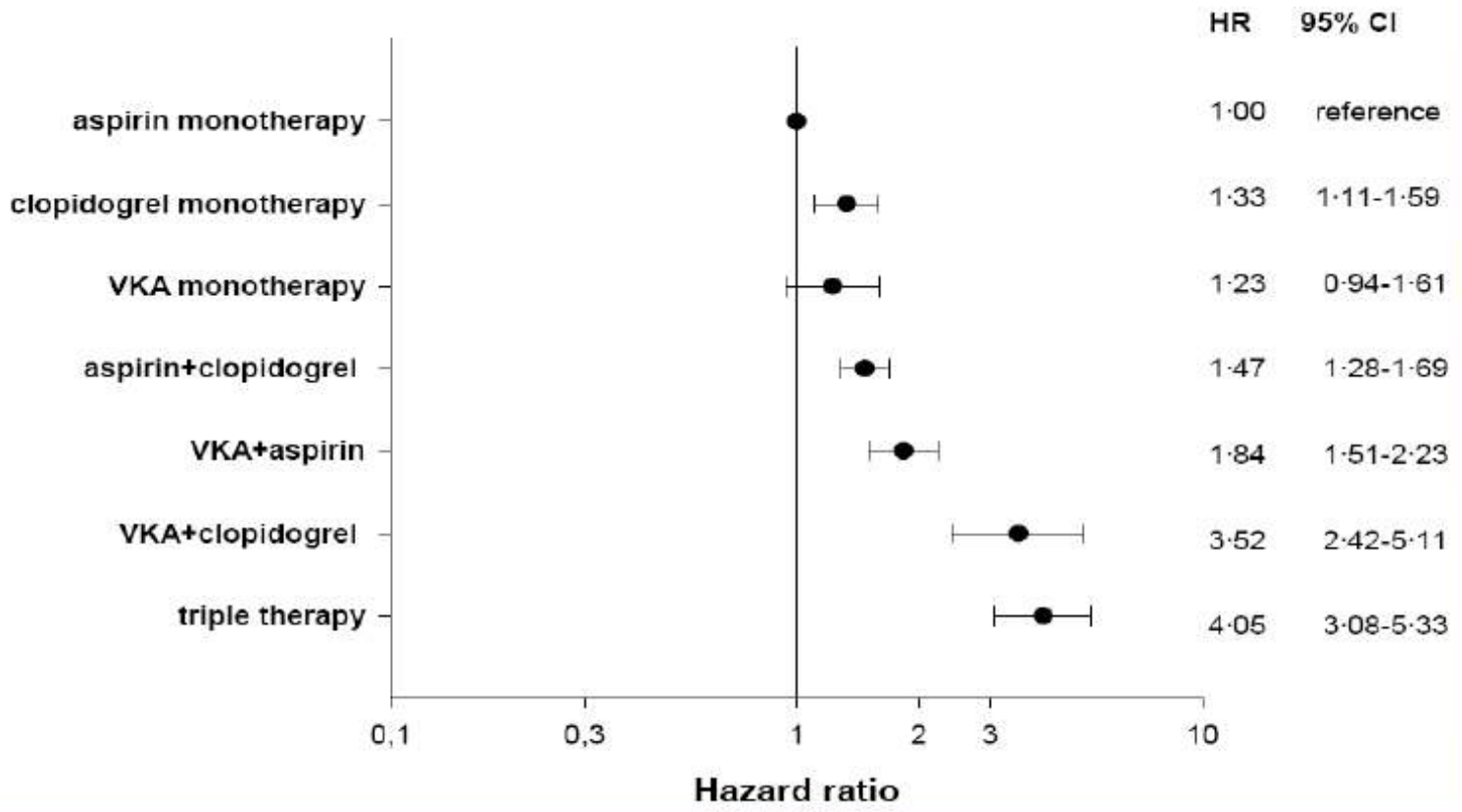
2009 ACCF/AHA Perioperative Guidelines




IF YOU HIT THIS SIGN,
YOU WILL HIT THAT BRIDGE

Results

Figure 2A: Adjusted risk of non-fatal and fatal bleedings



Conclusions

- Increased number of antithrombotics = increased bleeding
- At admittance

→Stent-type

- High risk combinations should be limited to the shortest possible duration

Conclusions

- Much of clinical decision-making in this area can be empiric, with limited prospective data
- To avoid thrombosis, don't stop DAPT
- Communication between patients and (several) providers is critical!

VERY LATE (67 MONTHS) DRUG-ELUTING STENT THROMBOSIS SOON AFTER DISCONTINUATION OF ANTIPLATELET THERAPY

C. Graidis, D. Dimitriadis, A. Ntatsios, A. D. Mavrogianni, F. Economou, V. Psifos, I. Vogiatzis, G. Spiromitros, K. Voloudakis, N. Chamouratidis.

Euromedica – Kyanous Stavros, Cardiology Department, Thessaloniki

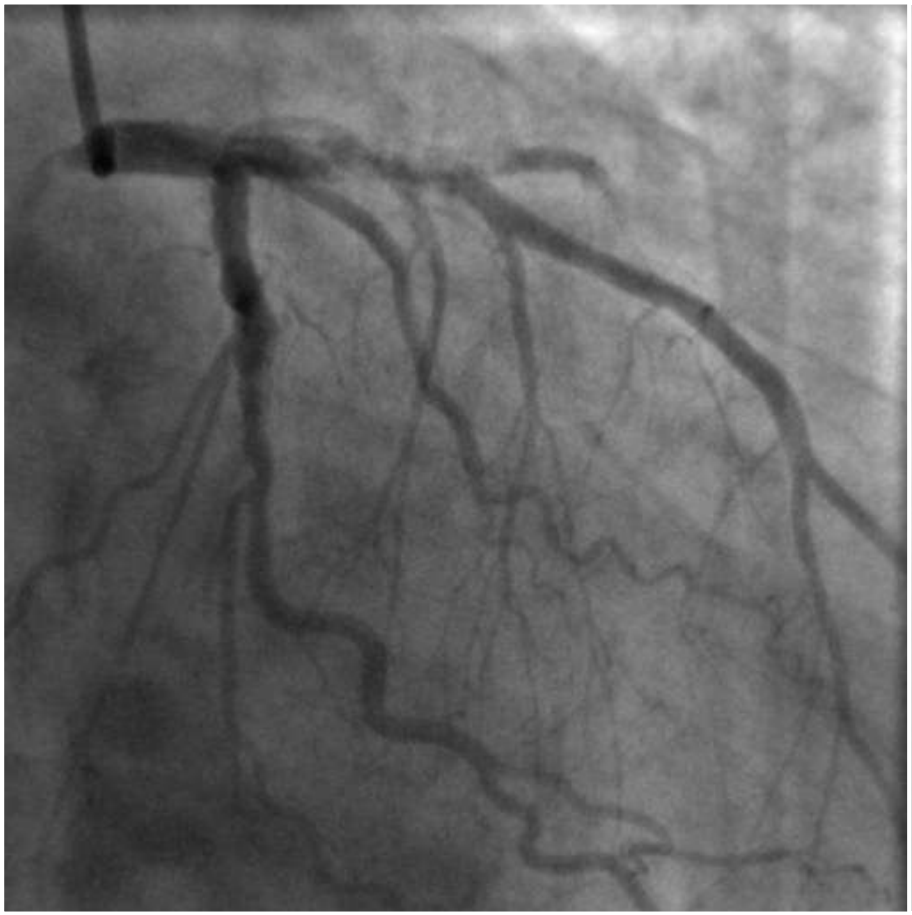
Interventional Cardiovascular Education 2009
Congress Hall 'Du Lac'
Ioannina, 3 – 5 December, 2009

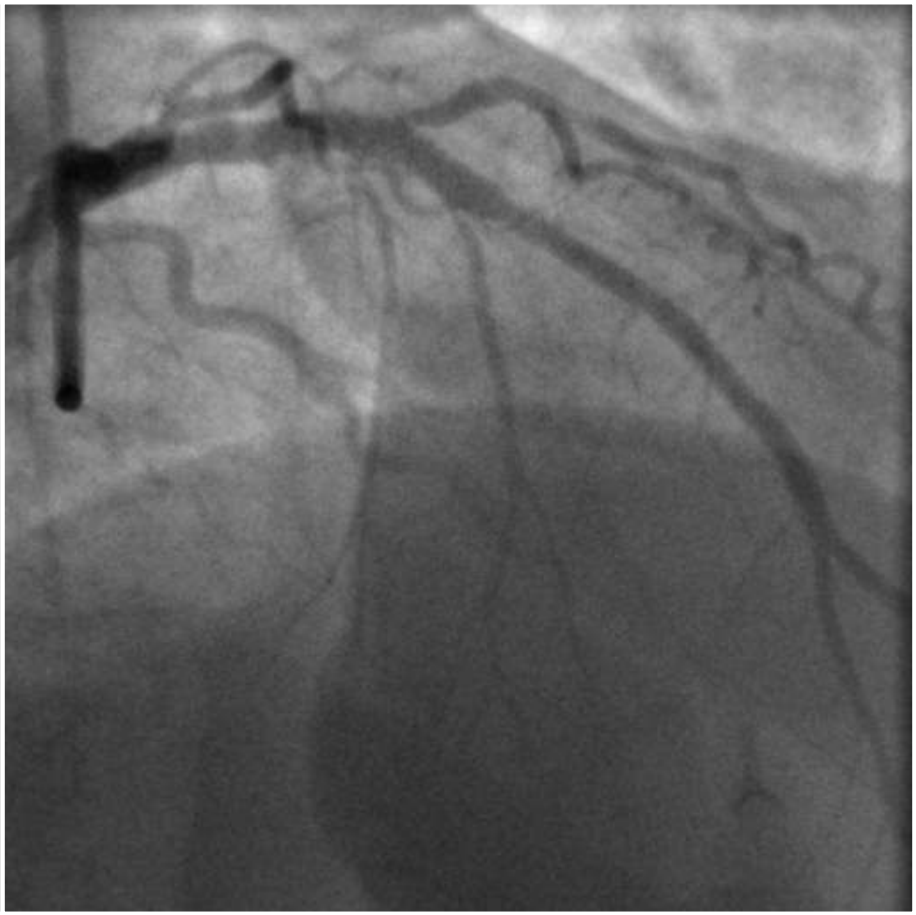
CASE 1

- 74 y.o. male.
- Risk factors for IHD: Hypertension, Dyslipidaemia, Ex-smoker.
- 13 Feb 2004: PCI for a bifurcation lesion LAD / D1 (Recent Anterior STEMI thrombolysed).
  - Crushing technique LAD: Cypher 3.5 x 18mm D1: Cypher 3 x 13mm
- No final kissing balloon performed. 67 months later (10 Sep 2009) and whilst being asymptomatic from the cardiac point of view, he was scheduled for endoscopic resection of colon polyps (History of lower GI bleeding).

- Advised to discontinue the thienopyridine monotherapy 7 days before the procedure and start LMWH.

- 3 hours after the endoscopic procedure he developed retrosternal chest pain, ECG showed ST elevation in the anterior leads and was transferred immediately to our cath lab.



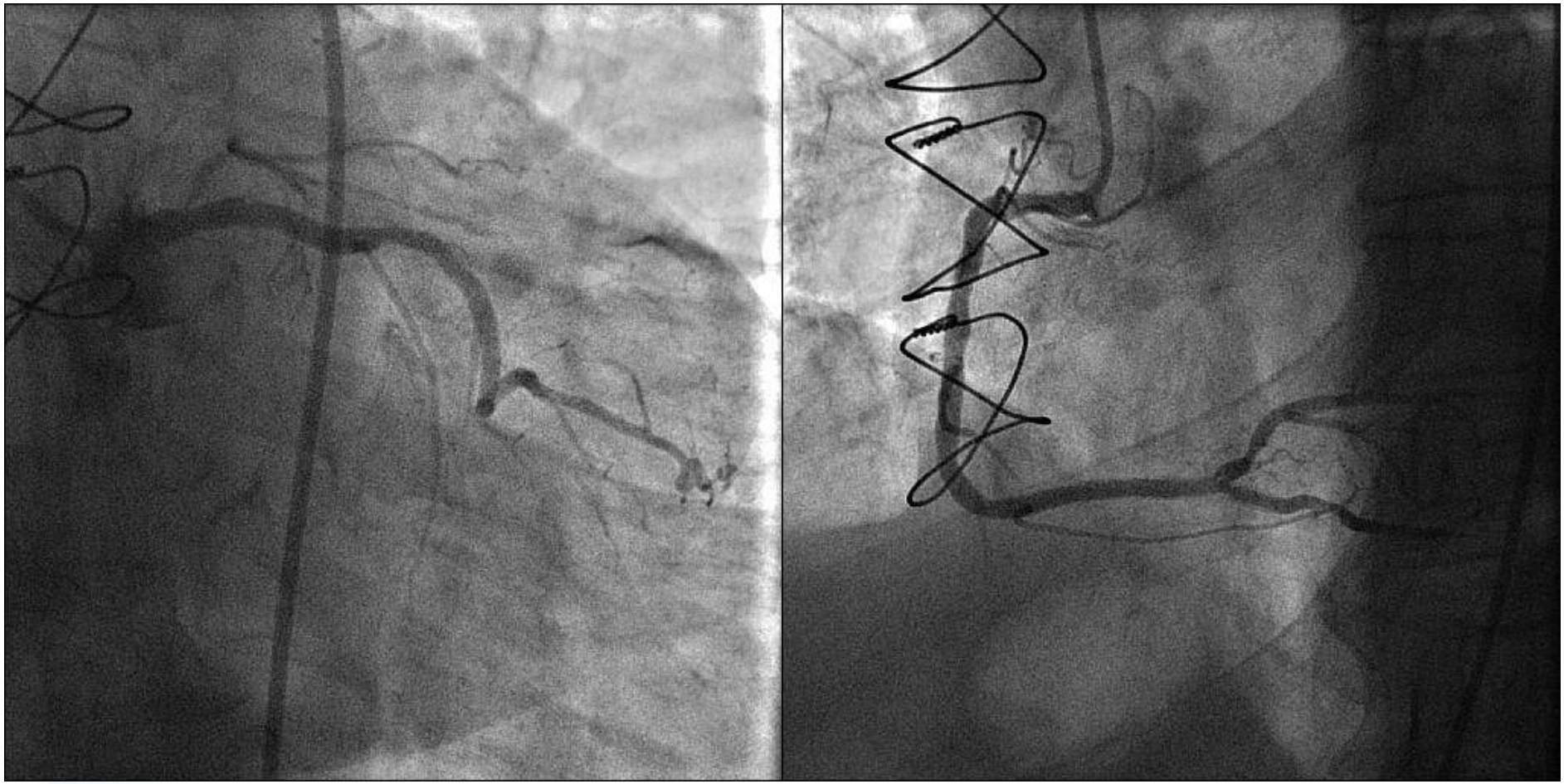


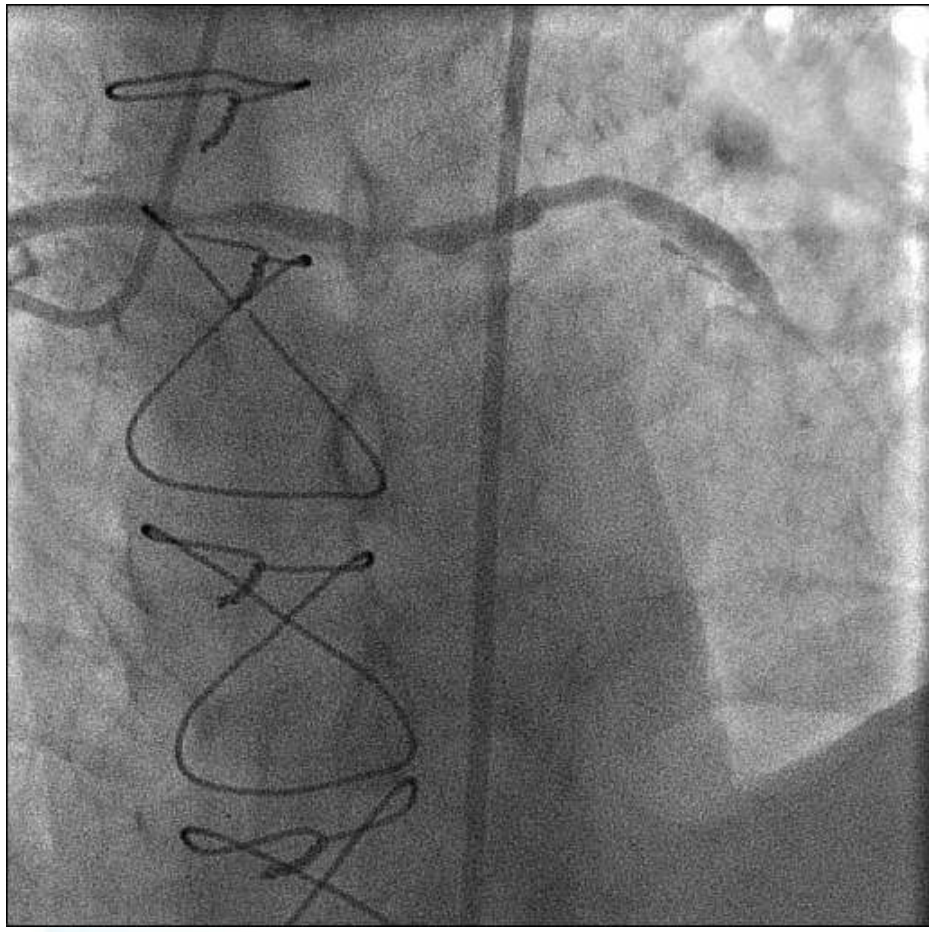
Pre-PCI

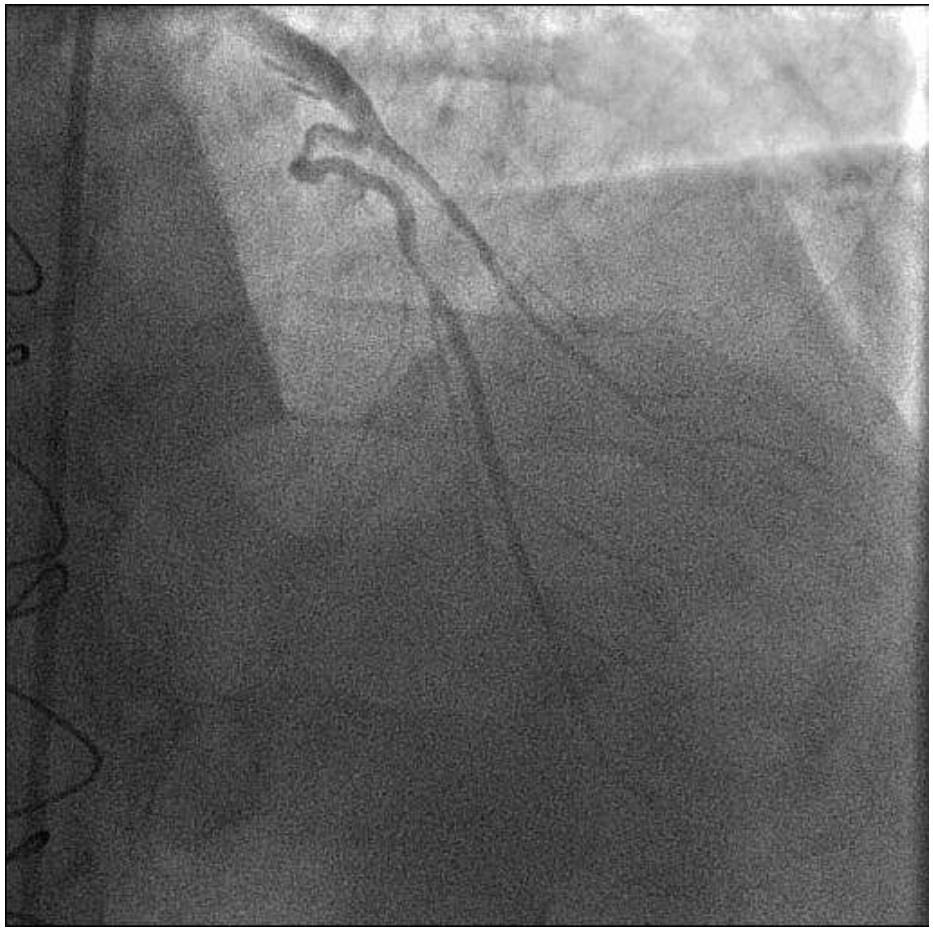
Post-PCI

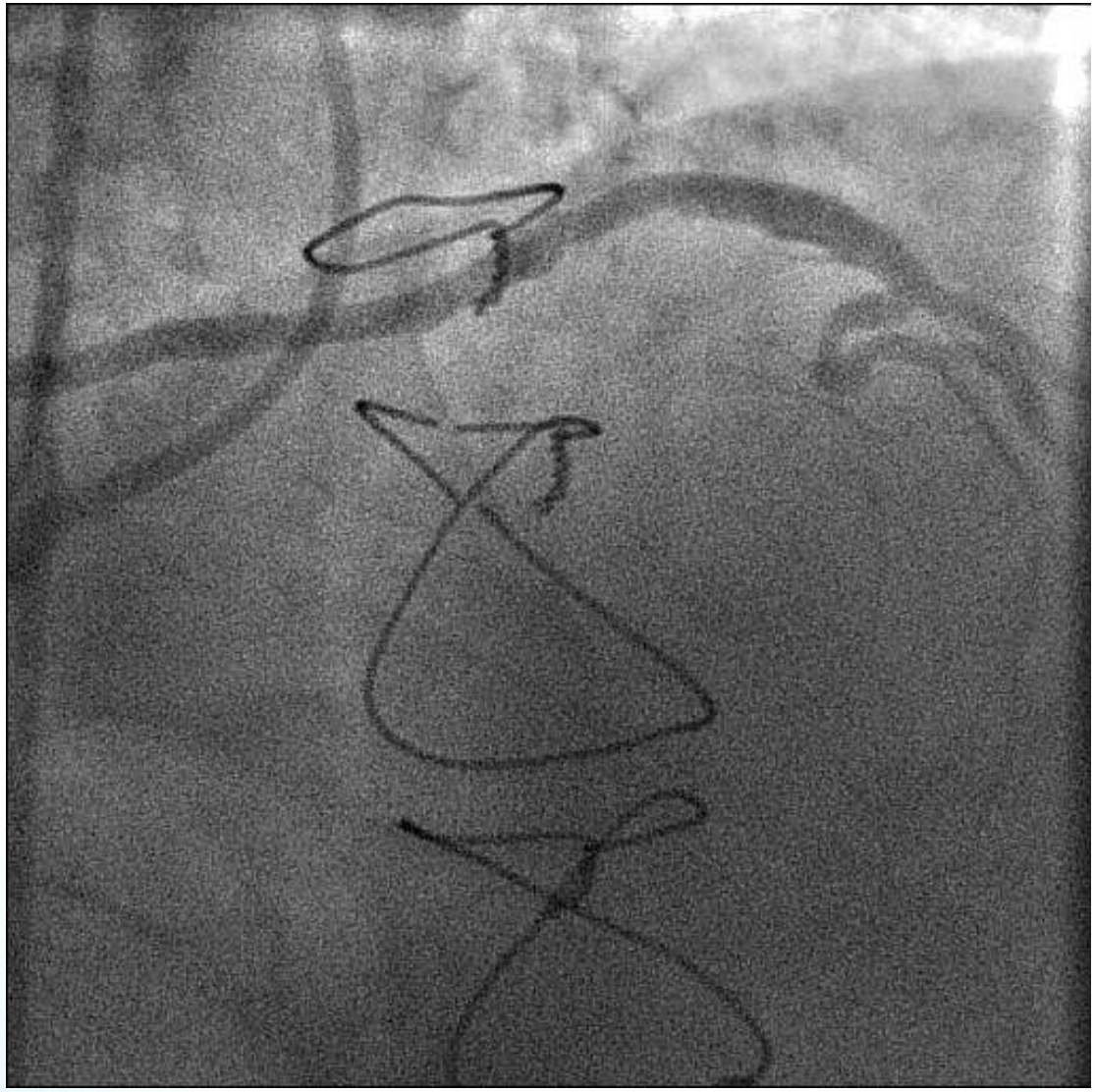
CASE 2

- 72 y.o. male.
- Risk factors for IHD: Hypertension, Dyslipidaemia, Ex-smoker.
- 2005: LIMA-LAD and SVG-D1
- 2012: Unstable angina









Post-PCI

i.v IIb/IIIa
(no reflow)

2 hours after the procedure the patient developed hypovolemic shock due to retroperitoneal hematoma which was treated conservatively.

After 6 hours the patient was hemodynamically unstable with new drop of Ht/Hb due hematemesis. Gastroscopy performed and A.V.L the culprit vessel. Dual antiplatelet therapy was stopped.

2 days later, patient developped a new gastrointestinal bleeding. Colonoscopy had no specific findings.

WHAT WOULD YOU DO NEXT?

1.Stop antiplatelet therapy indefinately?
2. aspirin or clopidogrel only?
3.DAPT?
4. when?

On day sixth, patient was discharged under clopidogrel only and advised to start dual antiplatelet therapy 30 days later.

12 months later patient was asyptomatic and

Nothing else happened!!!!!

The Interventionalists lived happily ever after!!!

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ.