Η αντιαιμοπεταλιακή αγωγή μετά από αγγειοπλαστική των στεφανιαίων αγγείων.

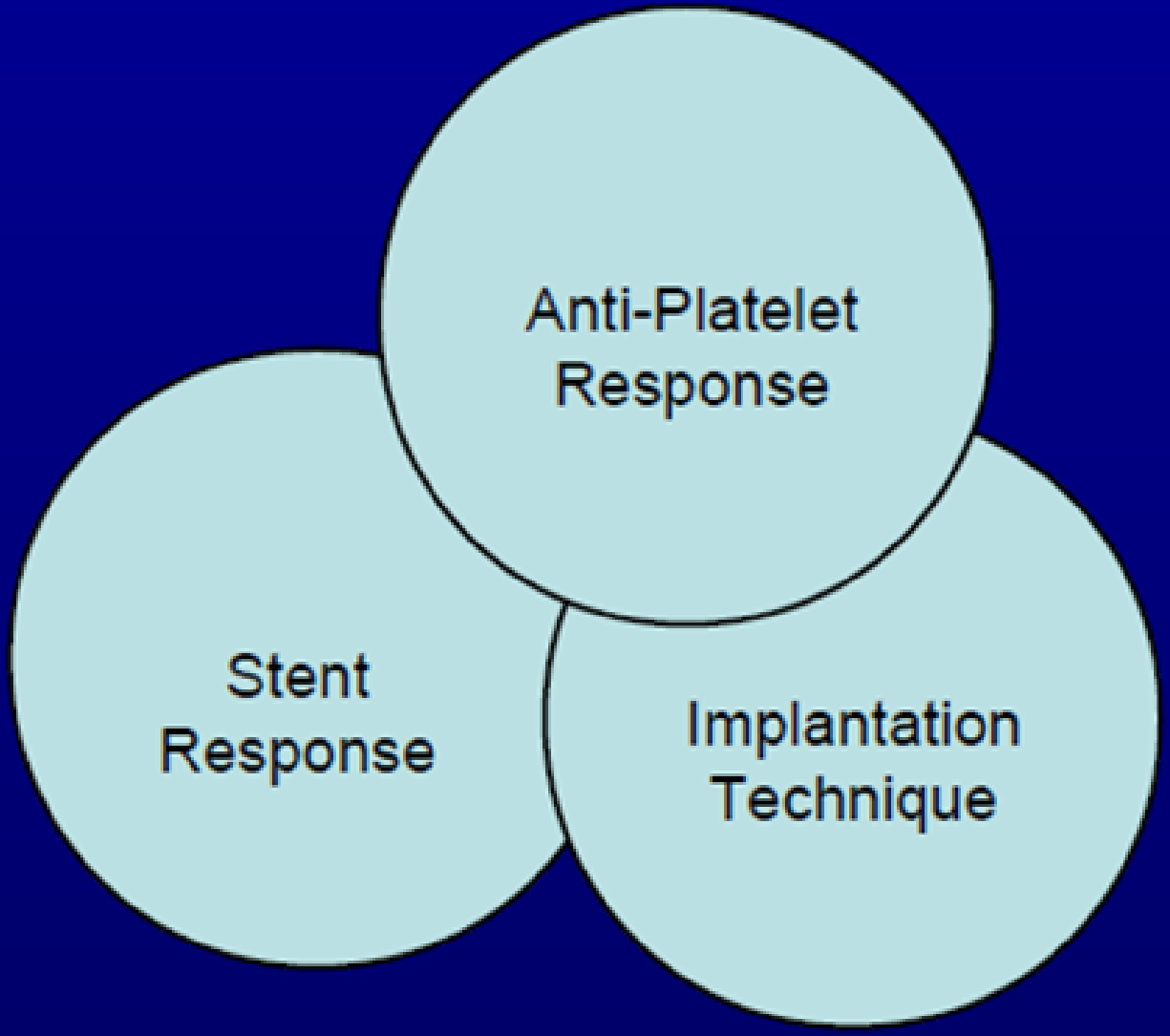
Ευάγγελος Α. Ρέππας

Επεμβατικός καρδιολόγος

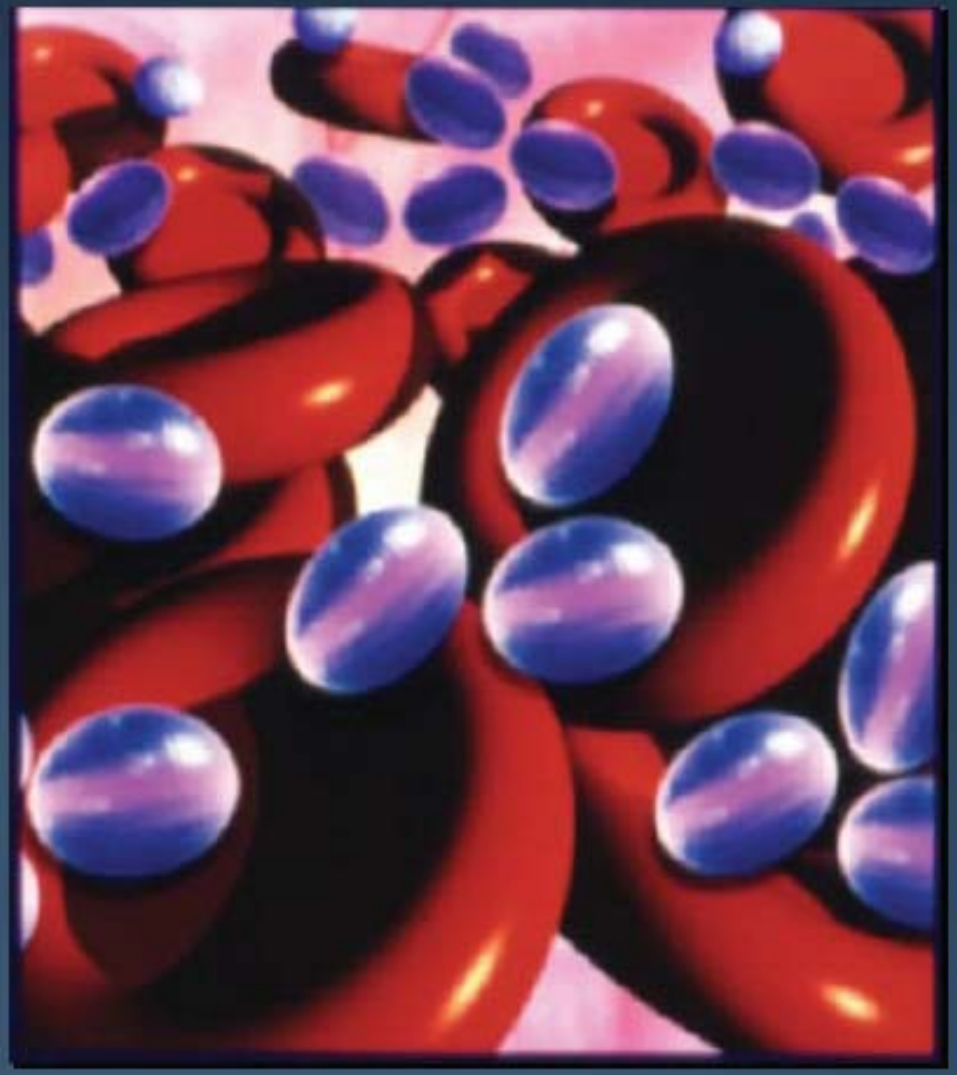
Κλινική Άγιος Λουκάς-Θεσσαλονίκη

10ο Βορειοελλαδικό Καρδιολογικό Συνέδριο
Θεσσαλονίκη 19-21 Μαίου 2011

The Engine of Post PCI Ischemia and Infarction

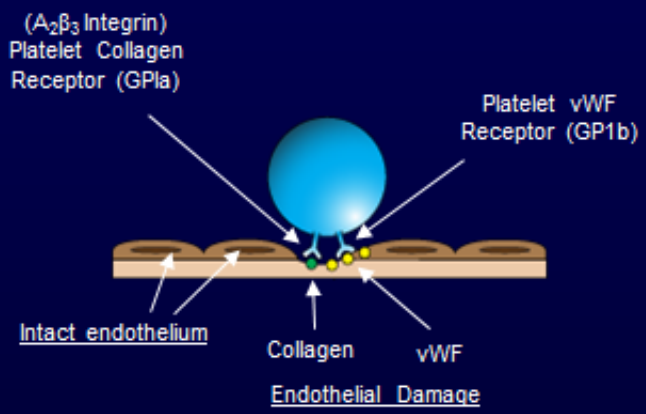


The Platelet

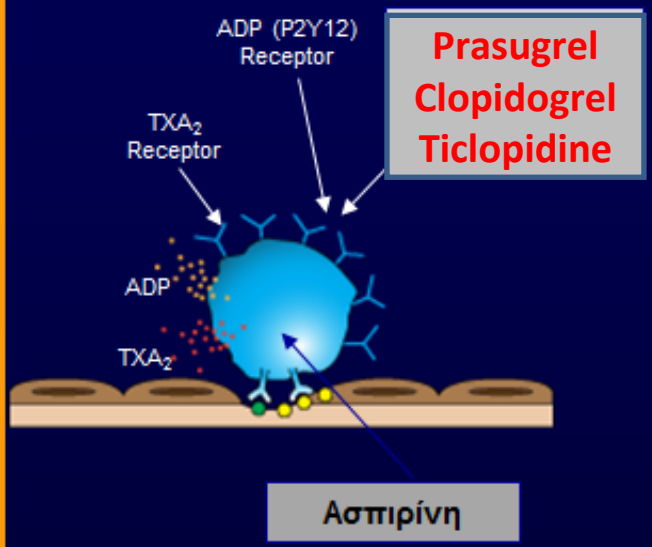


- Small, anucleate blood cell; primary function is to maintain hemostasis
- 1.5 trillion circulating throughout body, with life span of approximately 10 days
- Adheres to breaches in vessel endothelium
- Alters platelet cell membrane and shape upon contact with activating substances
- Secretes clotting factors, vasoconstrictors, and growth factors upon activation

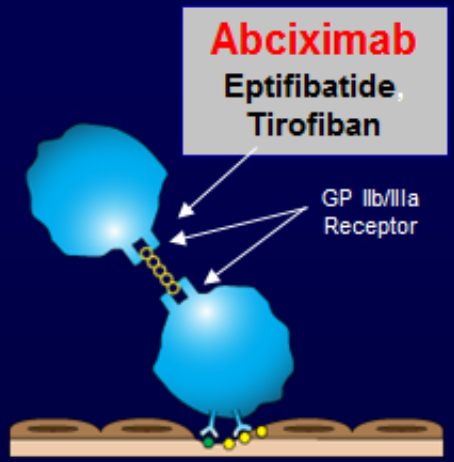
Στοχεύοντας τα αιμοπετάλια



Δεν υπάρχουν αντιαιμοπεταλιακά που στοχεύουν στην **Προσκόλληση**



Τα περισσότερα αντιαιμοπεταλιακά στοχεύουν στην **Ενεργοποίηση**

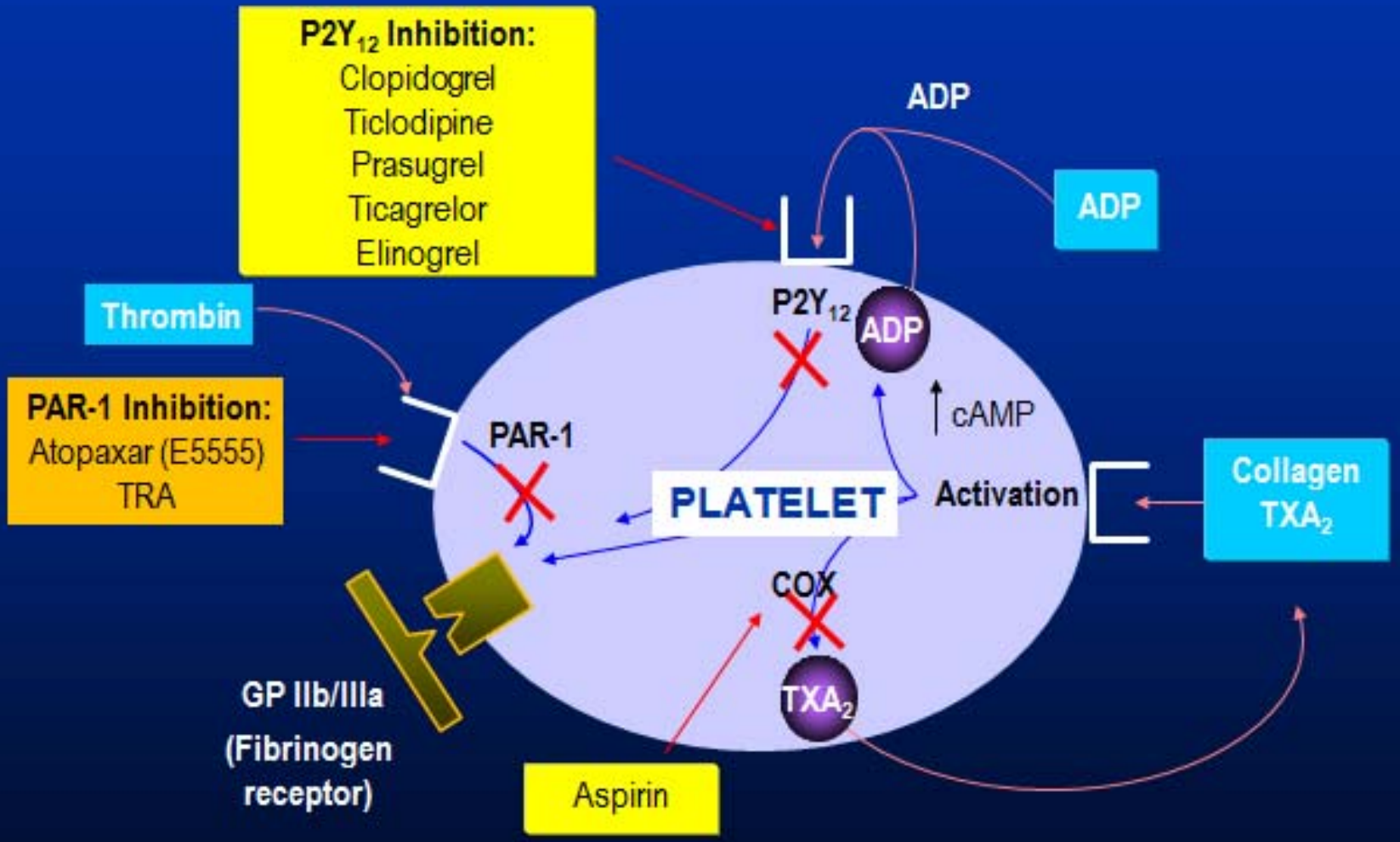


Οι αναστ. GP IIb/IIIa δρουν στο "κοινό τελικό βήμα" **Συσσώρευση**

GP = glycoprotein; vWF = von Willebrand factor; ADP = adenosine diphosphate; TX = thromboxane

Meadows et al. *Circulation Res.* 2007;100:1261-1275

Oral Antiplatelet Therapies



Adapted from Schafer. *Am J Med.* 1996;101:199-209.

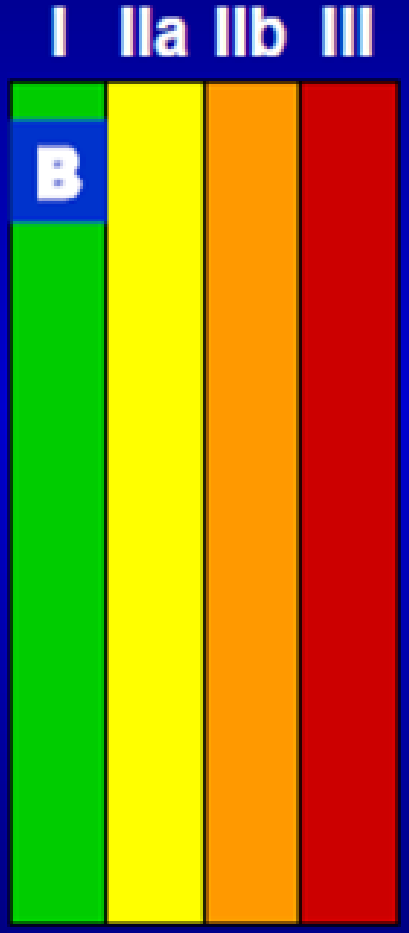
Aspirin

- The simplest drug available in cardiology
  - Old and oral, once a day
- One of the most efficacious
- The cheapest available
- Therefore:
  - The most cost-effective

ACC/AHA/SCAI 2007 Focused Update for PCI

Oral Antiplatelet Adjunctive Therapies

(Modified from 2005 PCI Guideline Recommendation)

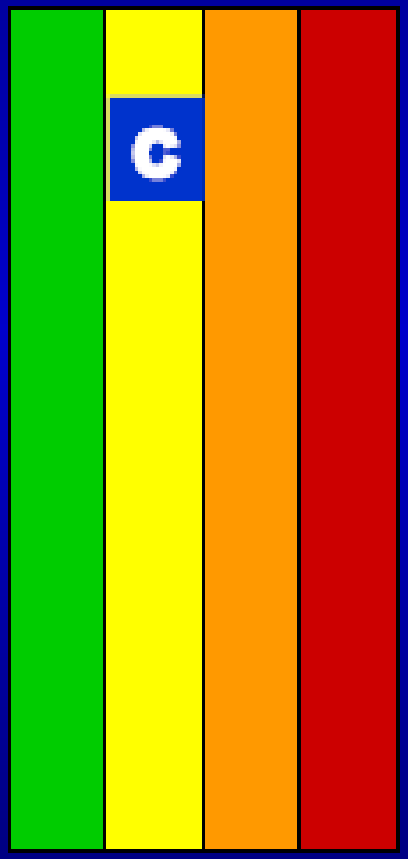


After the PCI procedure, in patients without allergy or increased risk of bleeding, **ASA 162-325 mg** daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, *after* which daily chronic ASA use should be continued indefinitely at a **dose of 75 to 162 mg**.

ACC/AHA/SCAI 2007 Focused Update for PCI

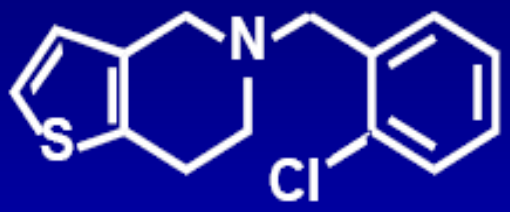
Oral Antiplatelet Adjunctive Therapies

(New Recommendation)



In patients in whom the physician is concerned about risk of bleeding, a lower dose of 75 mg to 162 mg of aspirin is reasonable during the initial period after stent implantation.

The Thienopyridine Family



Ticlopidine

(1st generation)

$P2Y_{12}$ ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting

Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc

Delayed time frame to achieve full antiplatelet effects

Solution to these problems:

Clopidogrel

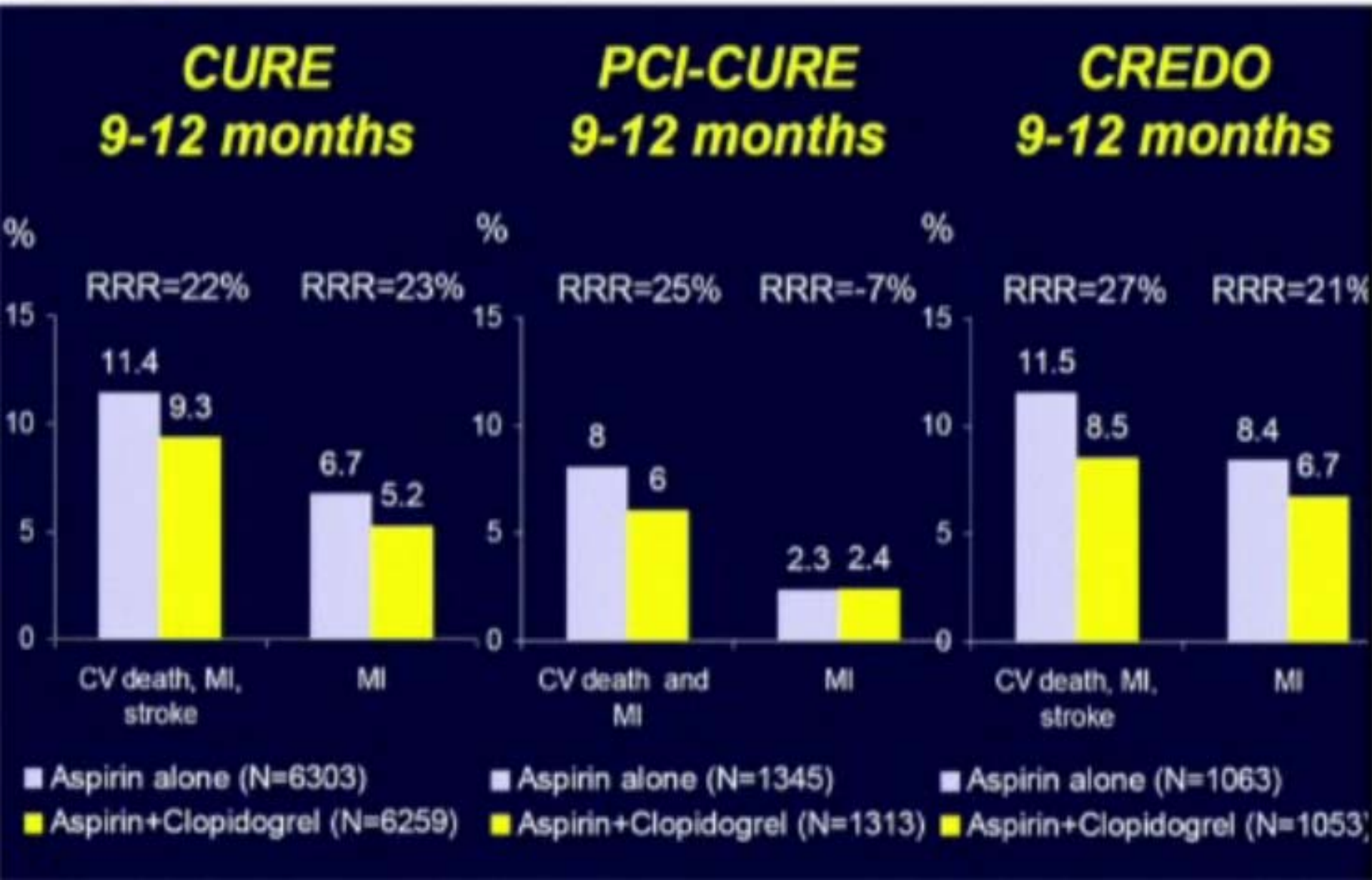
(2nd generation)

Better Safety profile - Fewer side effects
(CLASSICS trial. Bertrand NE *et al. Circulation* 2000; 102: 624–9).

Rapid onset of action with a loading dose
(Cadroy Y *et al. Circulation*. 2000;101:2823-28).

Better clinical outcomes
(Bhatt DL *et al. J Am Coll Cardiol* 2002; 39: 9–14.).

Long-term Benefit of Clopidogrel After BMS



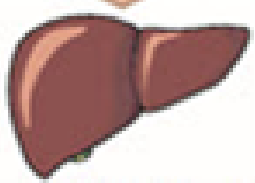
LIMITATIONS OF DAPT WITH CLOPIDOGREL

- High interpatient variation in IPA response
- Irreversible $P2Y_{12}$ receptor binding
- Requirement for metabolic activation
- Suboptimal onset of action for acute setting
- Suboptimal offset of action

Adapted from Schafer. *Am J Med.* 1996;101:199-209.

Clopidogrel Response Variability

20% May Not Have Optimal Antiplatelet Response



Intestinal Absorption ← Poor compliance; Inadequate administration; Variable absorption

Hepatic Metabolism Cytochrome P450 pathway ← Genetic polymorphisms: CYP2C19PMs, CYP2C9*3, ABCB1; Drug-drug interactions

Active Metabolite

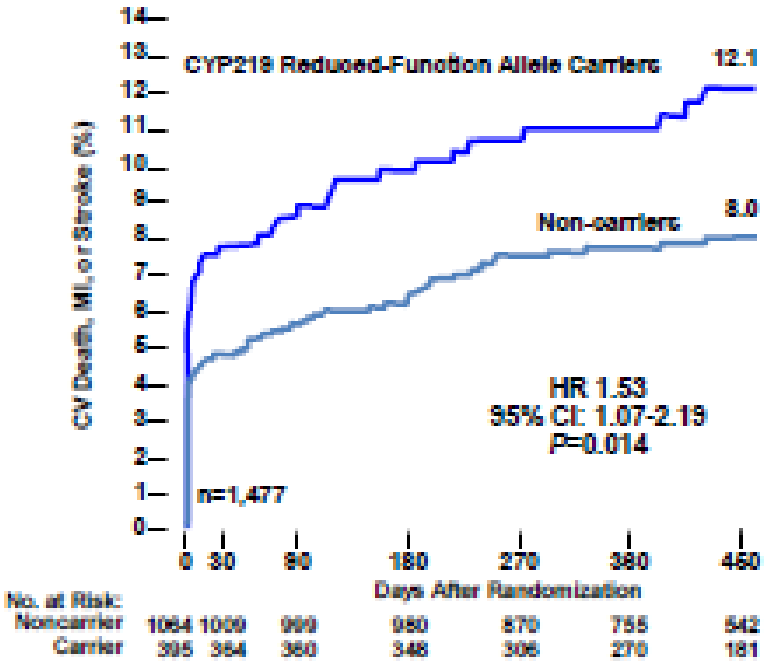
$P2Y_{12}$ Receptor (irreversible inhibition) ← Genetic polymorphisms: $P2Y_{12}$ receptor; Alternate platelet activation pathways

GP IIb/IIIa receptor expression ← Genetic polymorphisms

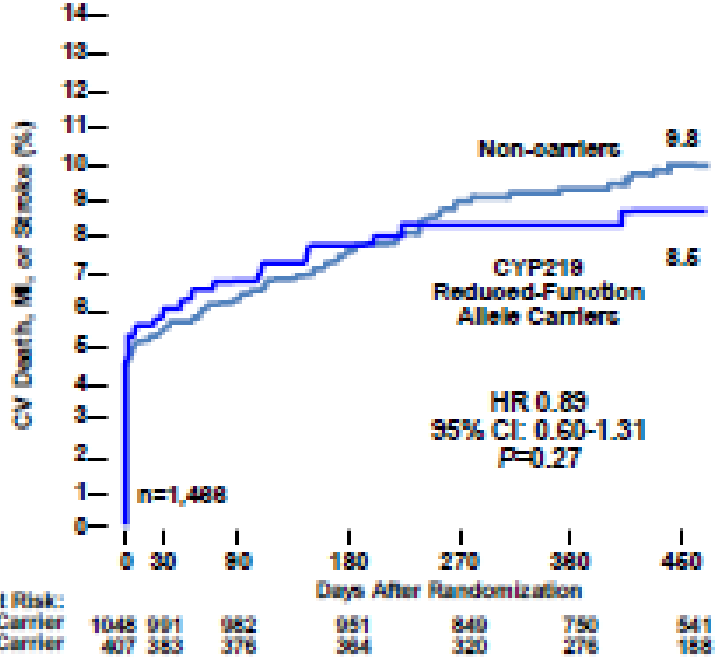
O'Donoghue et al. *Circulation*. 2008;114:e600-e606; Simon T et al. *N Engl J Med*. 2009;360:363-375; Feher G et al. *Clin Genetics*. 2009;75:1-18.

Cytochrome P450 Polymorphisms and Response to Clopidogrel and Prasugrel

Clopidogrel*[1,2]



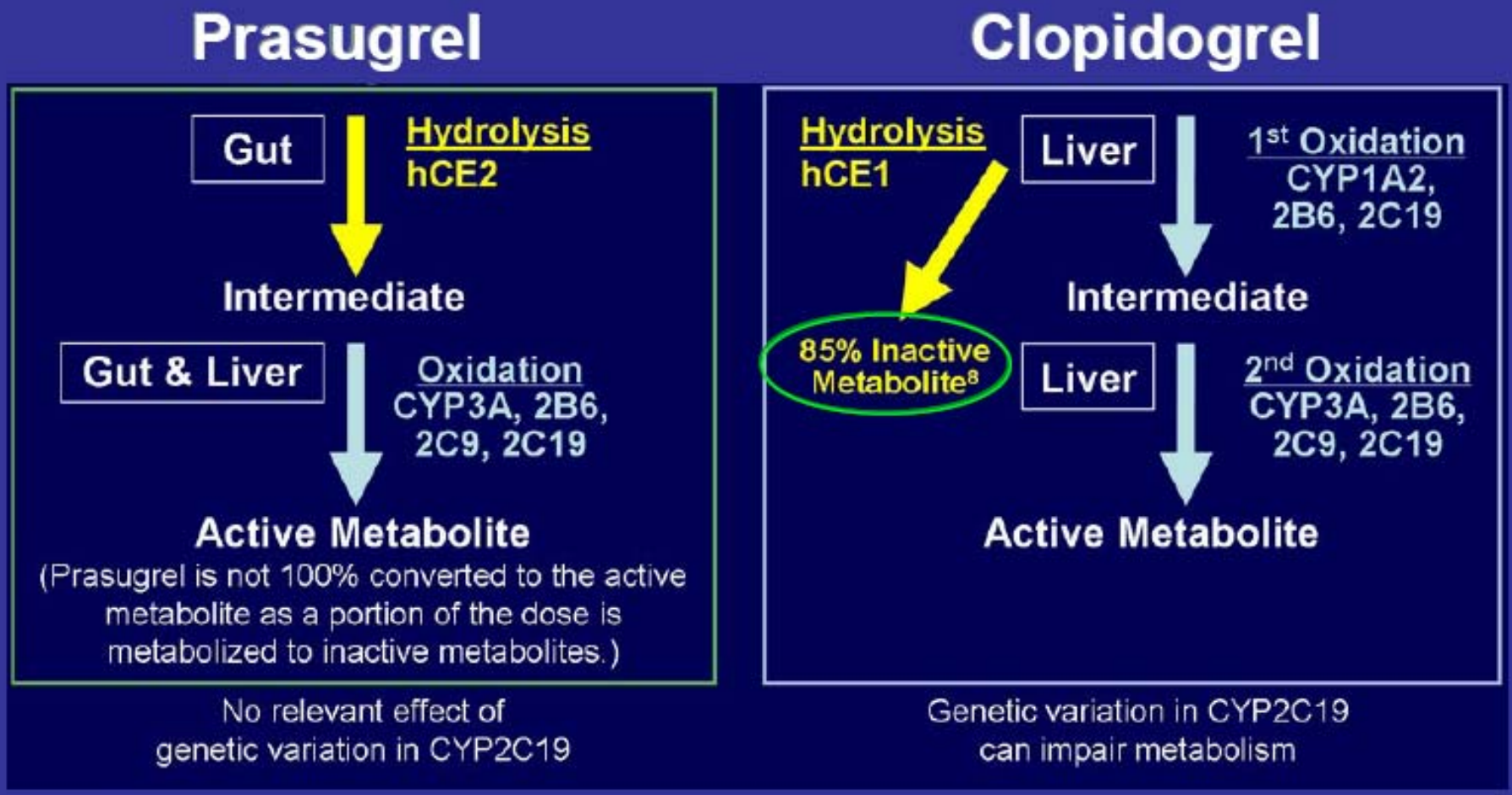
Prasugrel[1]



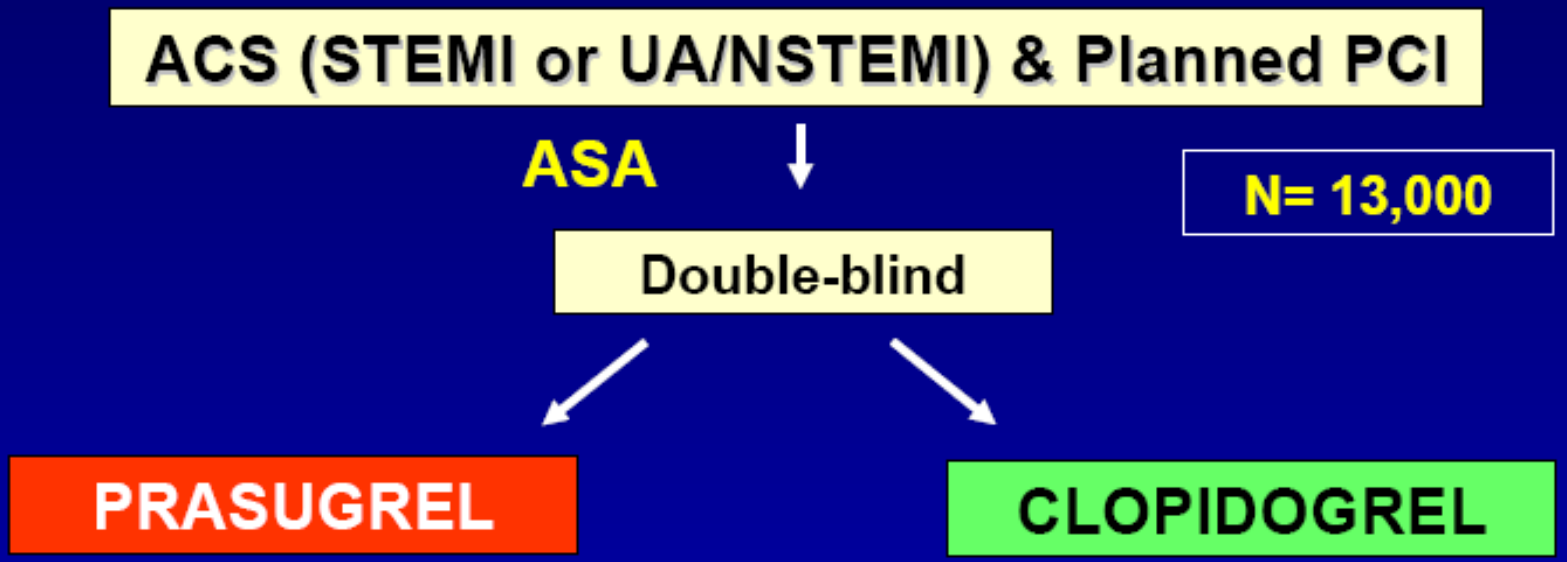
* Carriers 27.1% of the population.

1. Mega JL et al. AHA 2008.
2. Mega JL et al. *N Engl J Med*. 2008;360.

Prasugrel and Clopidogrel Active Metabolite Formation



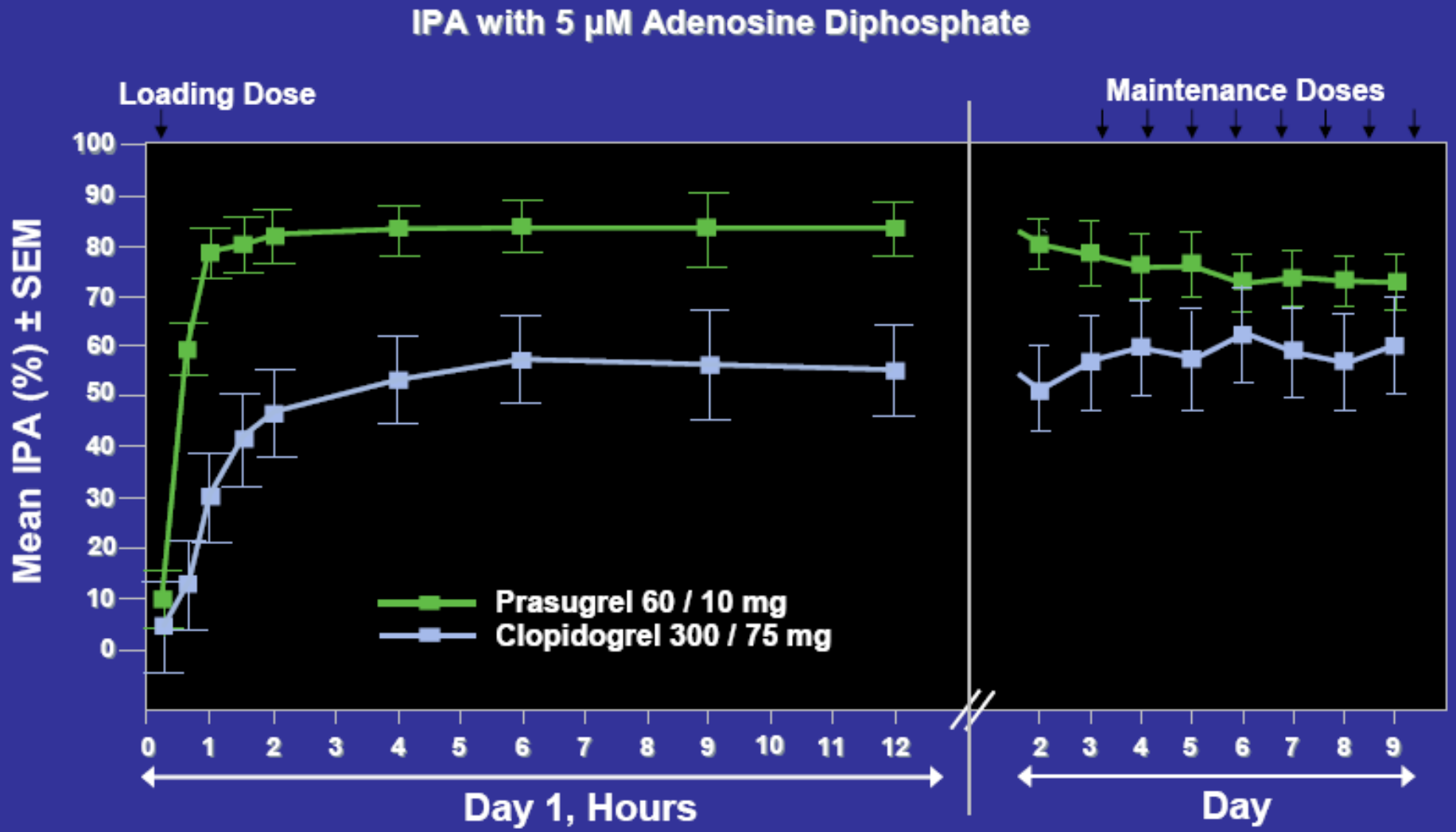
TRITON–TIMI 38 Study Design



1° end point:	CV death, MI, stroke
2° end points:	CV death, MI, stroke, re-ischemia
	CV death, MI, UTVR

TIMI, thrombolysis in myocardial infarction; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; UTVR, urgent target vessel revascularization

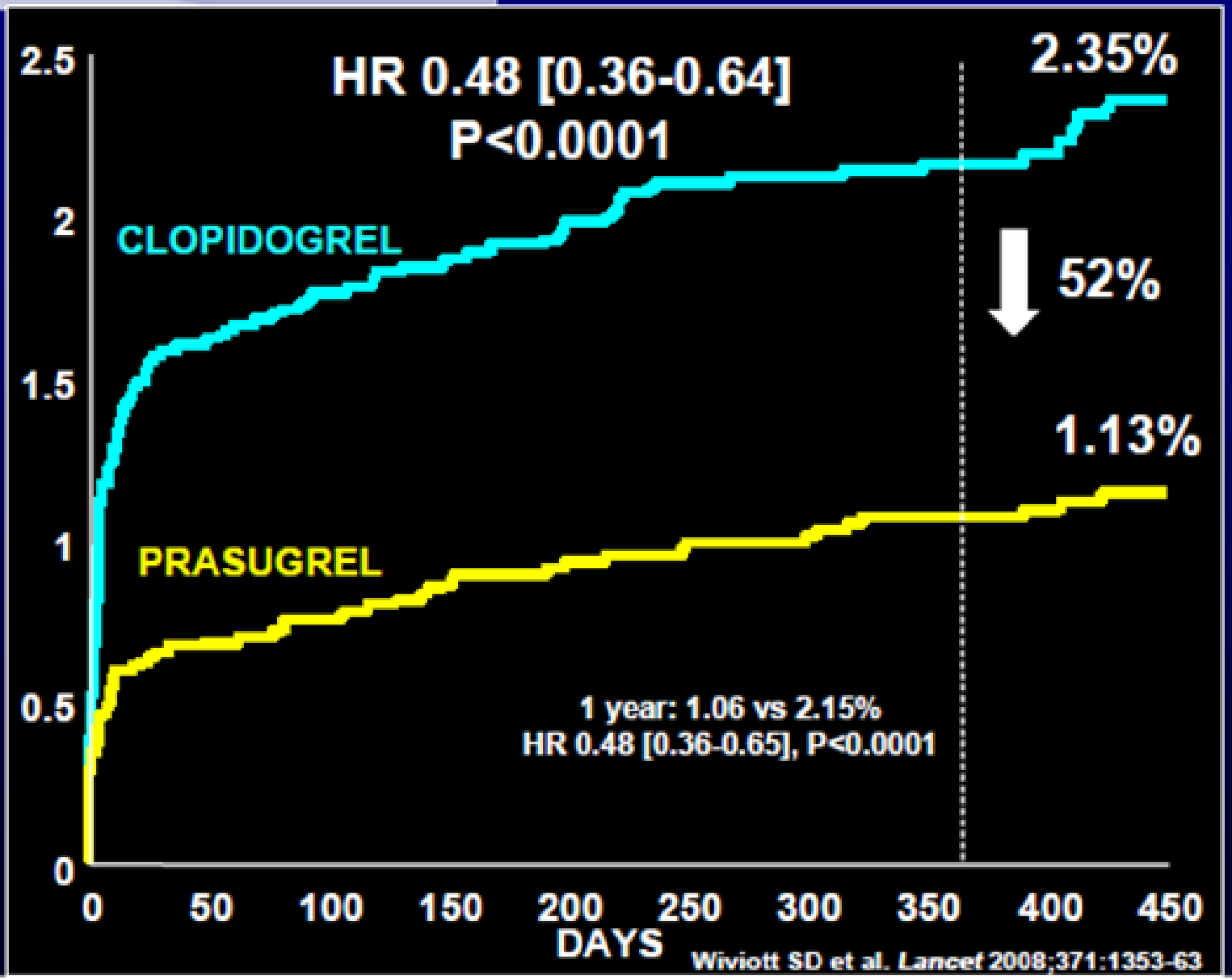
Inhibition of Platelet Aggregation (IPA): Prasugrel and Clopidogrel



J Cardiovasc Pharmacol. 2007;50:555-562

TRITON TIMI-38
STENT ANALYSIS

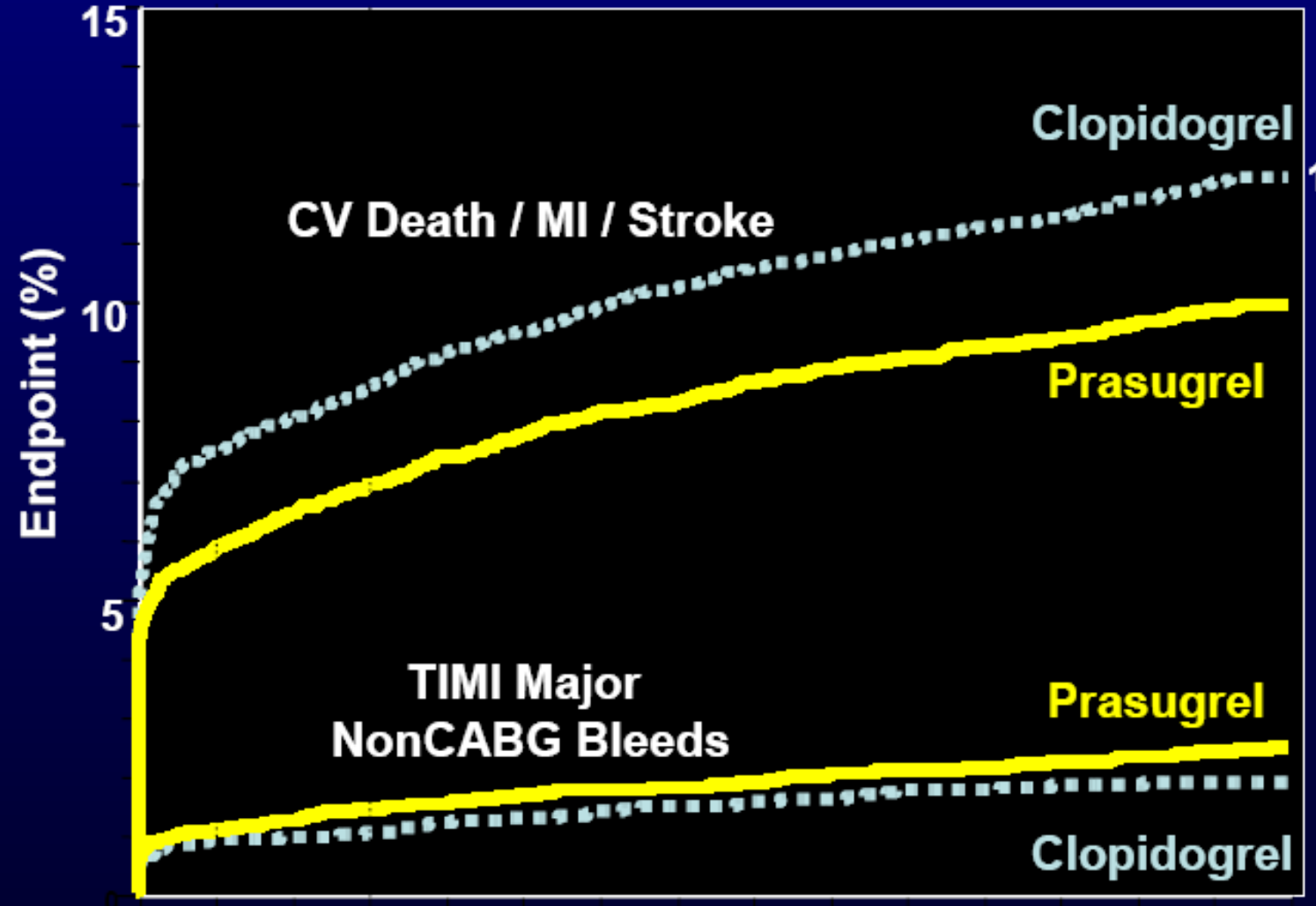
Definite/Probable ST: Any Stent (N=12844)



Wiviott SD et al. *Lancet* 2008;371:1353-63

TRITON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

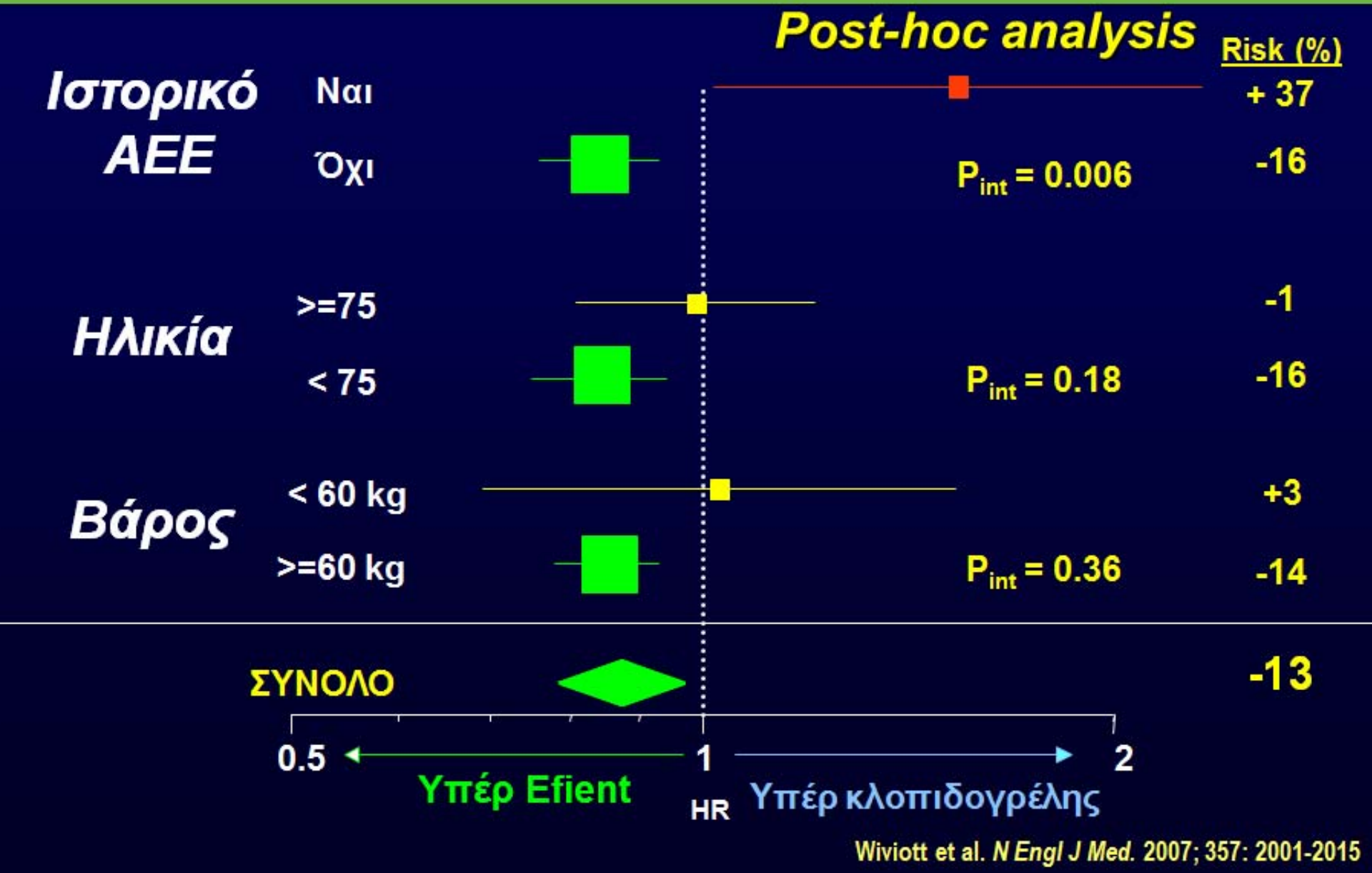
↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

Wiviott et al. NEJM 2007

Καθαρό κλινικό όφελος: αιμορραγίες/πληθυσμό



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

Prasugrel vs Clopidogrel

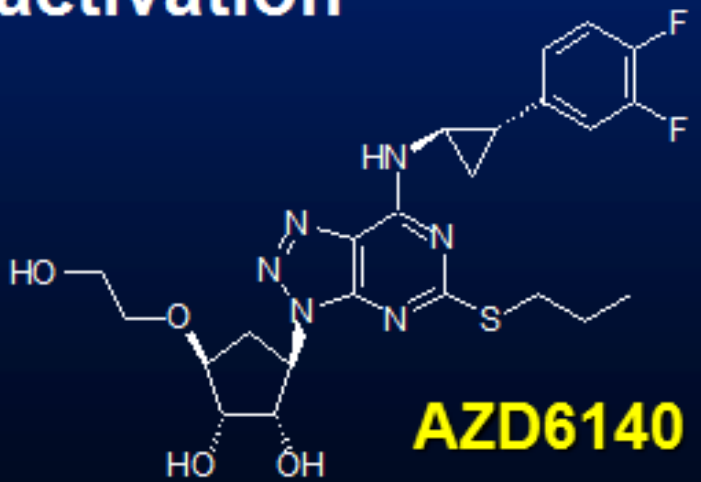
Summary

- Prasugrel provides
  - greater inhibition of ADP-induced platelet aggregation
  - Faster onset of action
  - More consistent IPA response
  - BUT: Greater bleeding risk-patient selection is key

Ticagrelor (AZD6140) Characteristics

- Class: CPTP* (non-thienopyridine)
- Reversible platelet $P2Y_{12}$ receptor antagonist
- Orally active
- Rapid onset of action (2 h) with or without a loading dose
- Acts directly (no metabolic activation required)
- Plasma $t_{1/2}$ ~12 h (BID Drug)

*cyclo-pentyl-triazolo-pyrimidine



AZD6140

PLATO study design

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

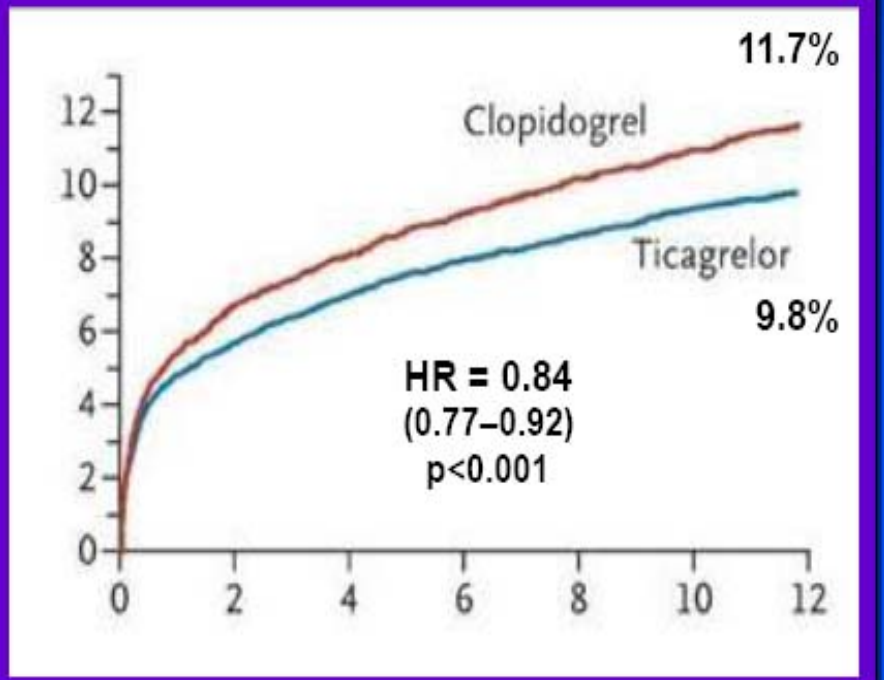
Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

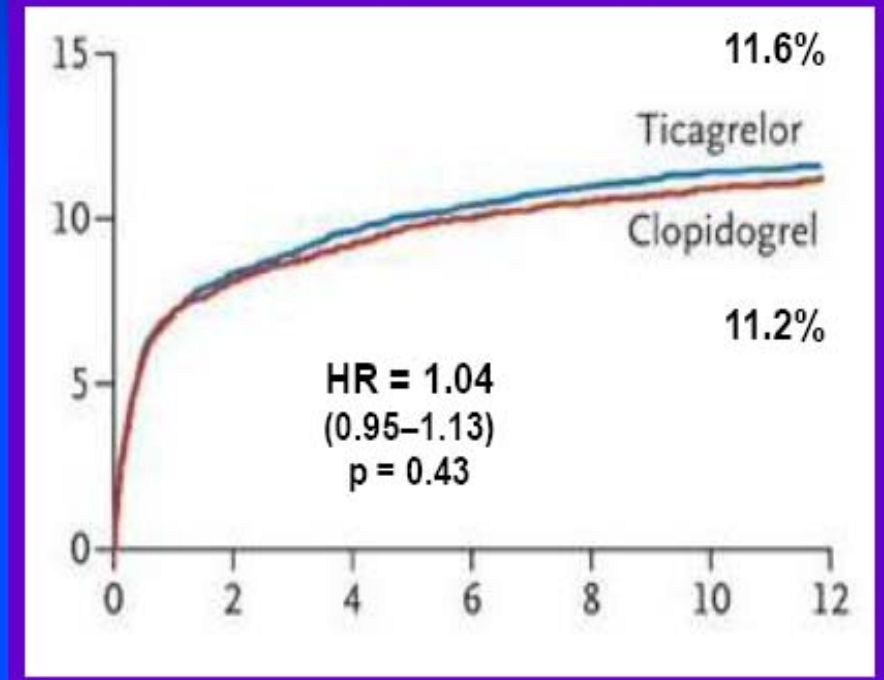
PLATO Trial

Ticagrelor vs Clopidogrel in ACS

Ischemic Endpoint

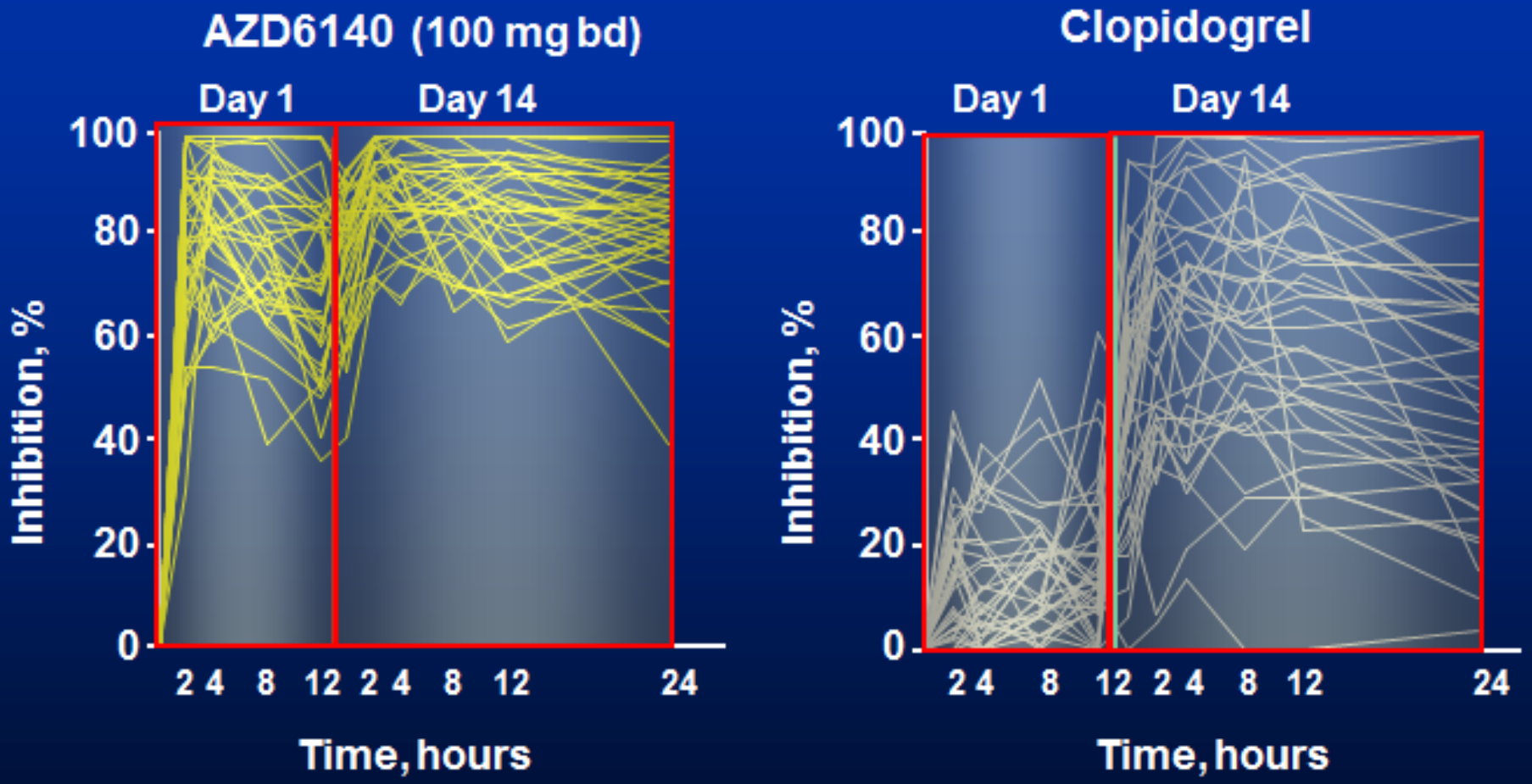


Bleeding Endpoint



Wallentin L et al. NEJM 2009;361:1045

DISPERSE: Faster, Greater and More Consistent IPA with AZD6140 vs clopidogrel



Husted SE et al Eur Heart J 2006; 27: 1038-1047

Comparison of Antiplatelet Agents

	clopidogrel	prasugrel	ticagrelor
STEMI indication	Yes	Yes	Not FDA Approved
Potency	++	+++	+++
Rapidity of onset	+	+++	++++
Variable response	Very variable	No	No
CYP2C19 loss of function impact	Yes	No	No
Reversibility	Not reversible	Not reversible	Reversible
Hold before CABG	5-7 days	7-10 days	2-3 days
Clinical experience	++++	++	0
Bleeding risk	+	++	+
Side effects	Rare	Rare	More common

ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΑ ΠΟΥ ΕΡΧΟΝΤΑΙ

- ✓ Elinogrel (Chronic CHD Trial)
- ✓ Atopaxar (Lancelot –CHD Trial)
- ✓ TRA or Vorapaxar (TRACER-TRA 2nd Prevention)

Guideline recommendations for duration of DAPT after PCI

		AHA/ACC	ESC
STEMI			
Thienopyridine	≥ 12 months	IB	IIaC
Ticagrelor	12 months	-	IB
UA-NSTEMI			
Thienopyridine	DES≥ 12 months	IB	IB
	BMS≥ 1 month ideally≥ 12 months	IB	IB
Ticagrelor	12 months	-	IB
ELECTIVE PCI			
Thienopyridine	DES≥ 12 months	IB	IC
	BMS≥ 1 month ideally≥ 12 months	IB	IA

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paxlitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

See Comment 466

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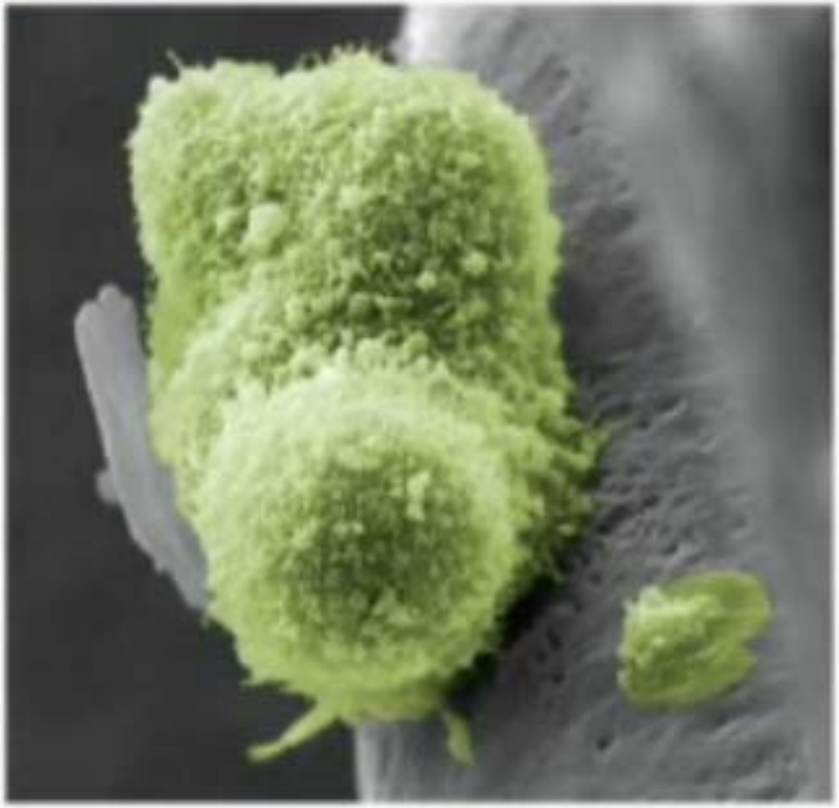
Netherlands
(E P McFadde...
E Regar MD, A... FRACP,
Prof P W Serr... nd
Washington H... enter,
Washington ...U
(E Stabile ... MD,
T Kinnaird MD, W O Suddath MD,

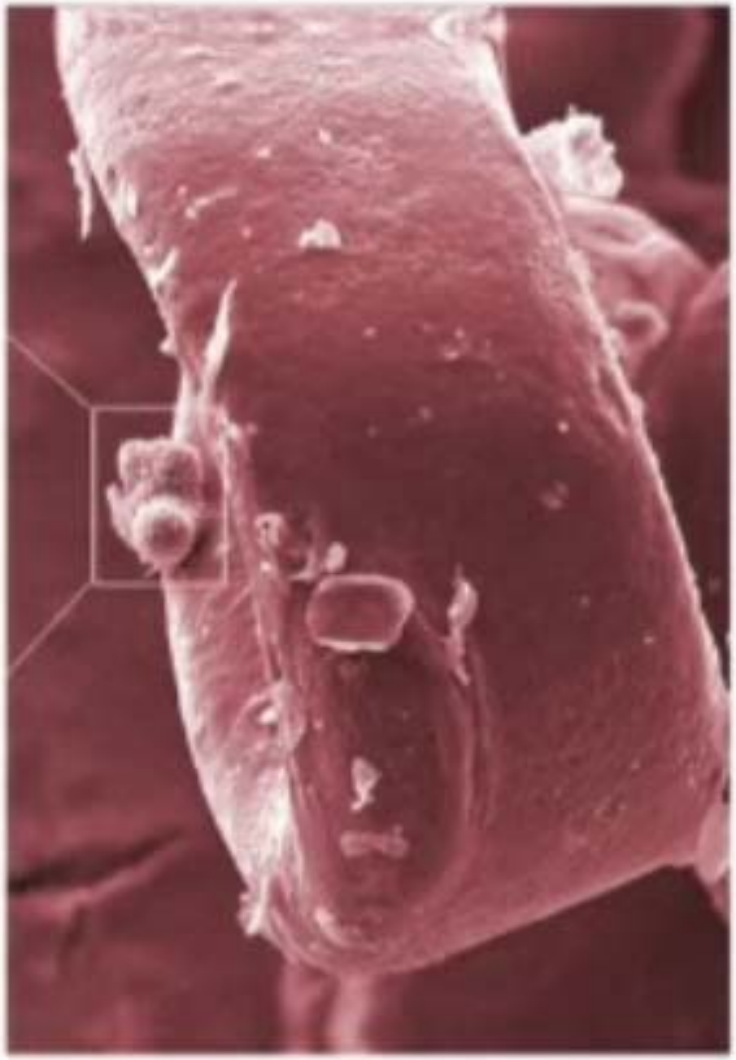
Clopidogrel for >1-year?

Stent Thrombosis

Some Observations

- **Stent thrombosis rates**
  - Annual rate after PCI – 0.5% to 3% per year
  - Highest rate after STEMI – but about half are silent
- **Symptomatic stent thrombosis is associated with high morbidity and mortality**
  - Mortality – 30% to 50%
  - CHF – 30% to 80%
- **Prevention is key for success**
  - Strategies will need to combine pharmacological and mechanical approaches

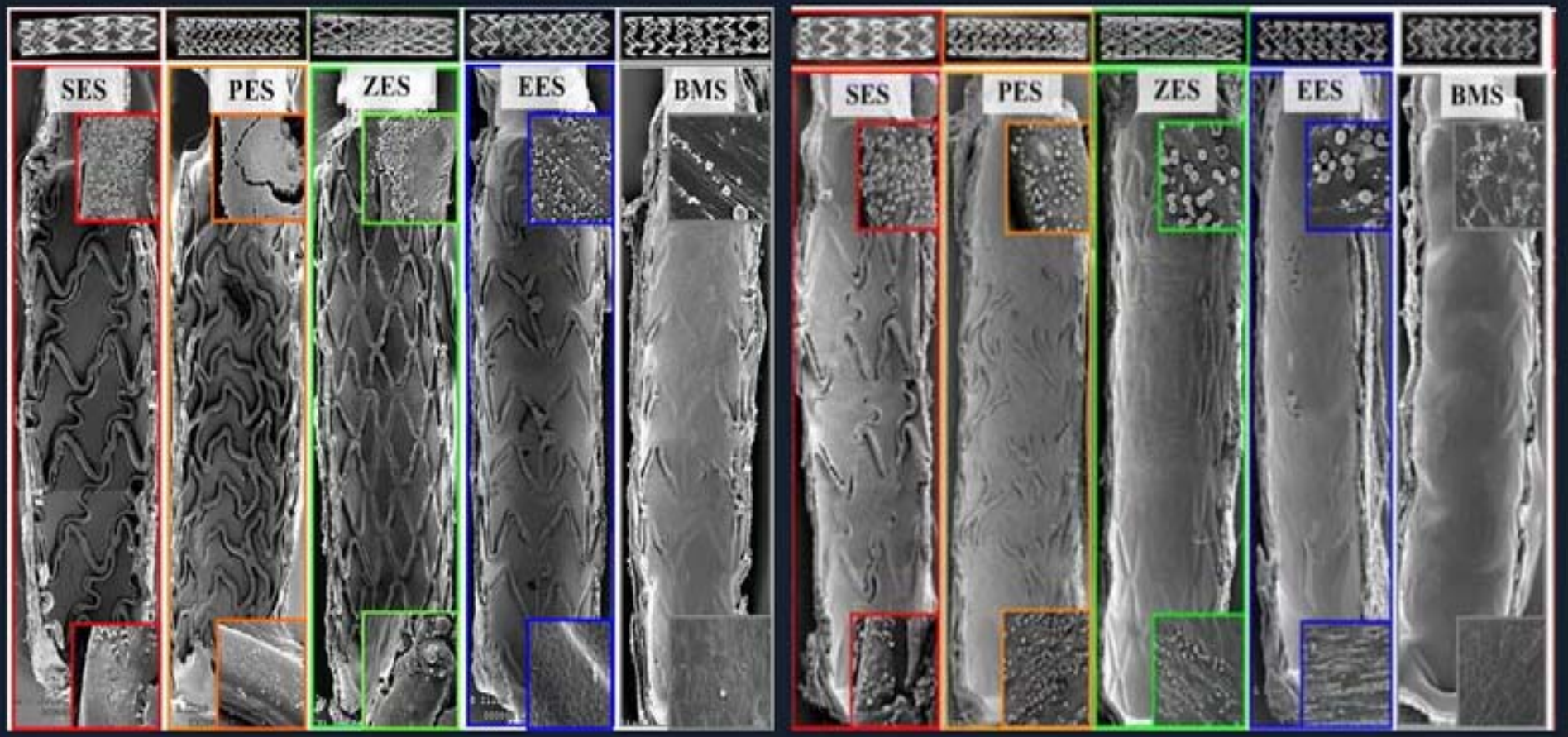




Platelet aggregation on a stent

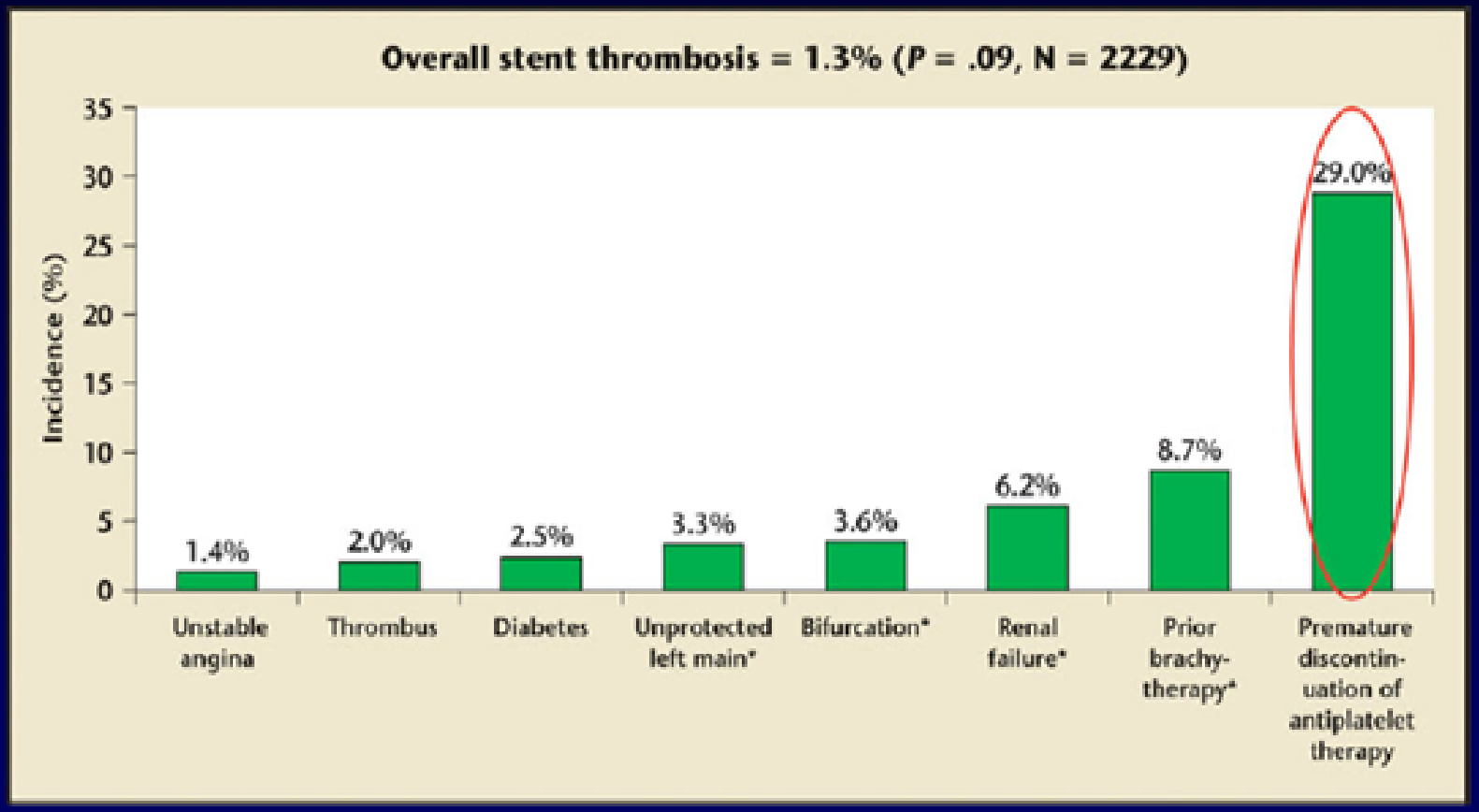
Adapted from D Erlinge

Endothelial Coverage by SEM after 14 and 28 Days: Different DES versus BMS Control



Healing of DES (Cypher and Taxus) versus BMS in Humans

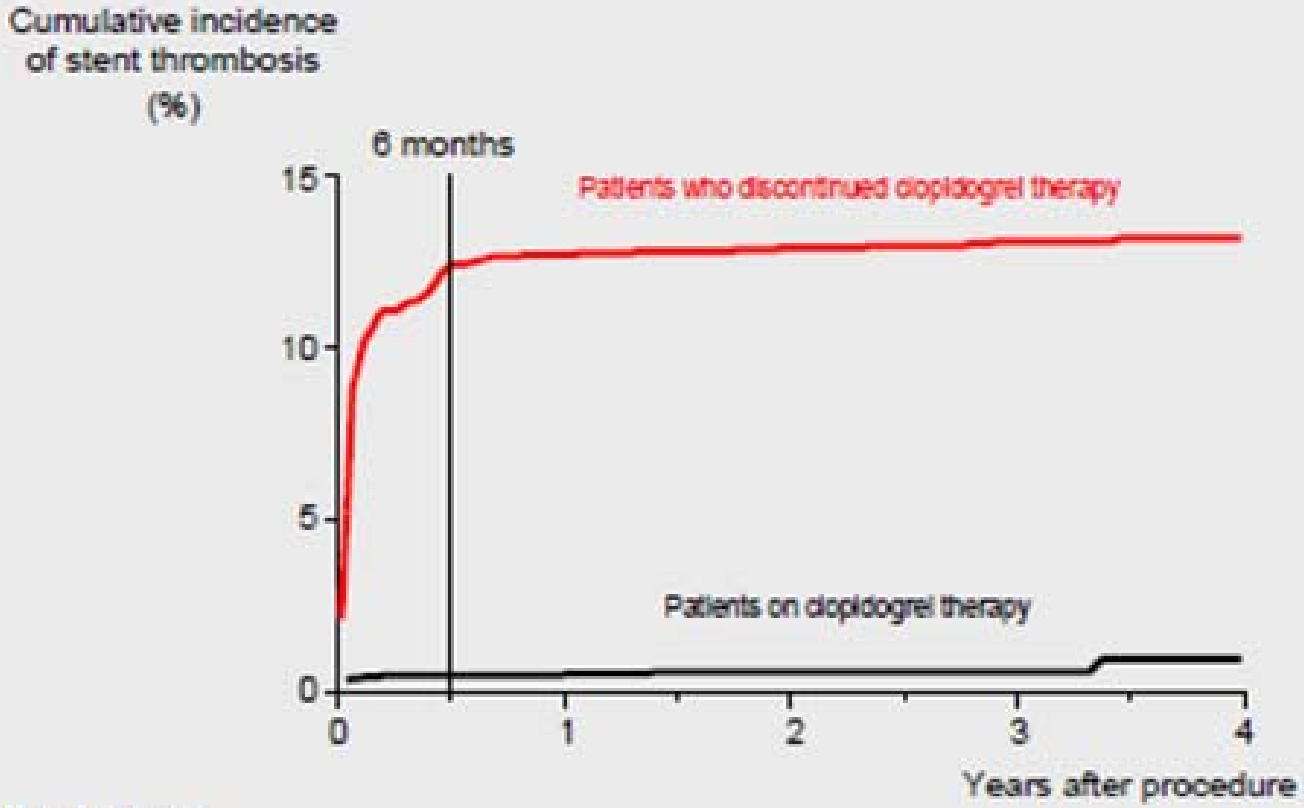
Predictors of Thrombosis after DES Implantation



Holmes DR. Rev Cardiovasc Med. 2007;8:S11
Iakovou I, et al. JAMA. 2005;293:2126.

ISAR

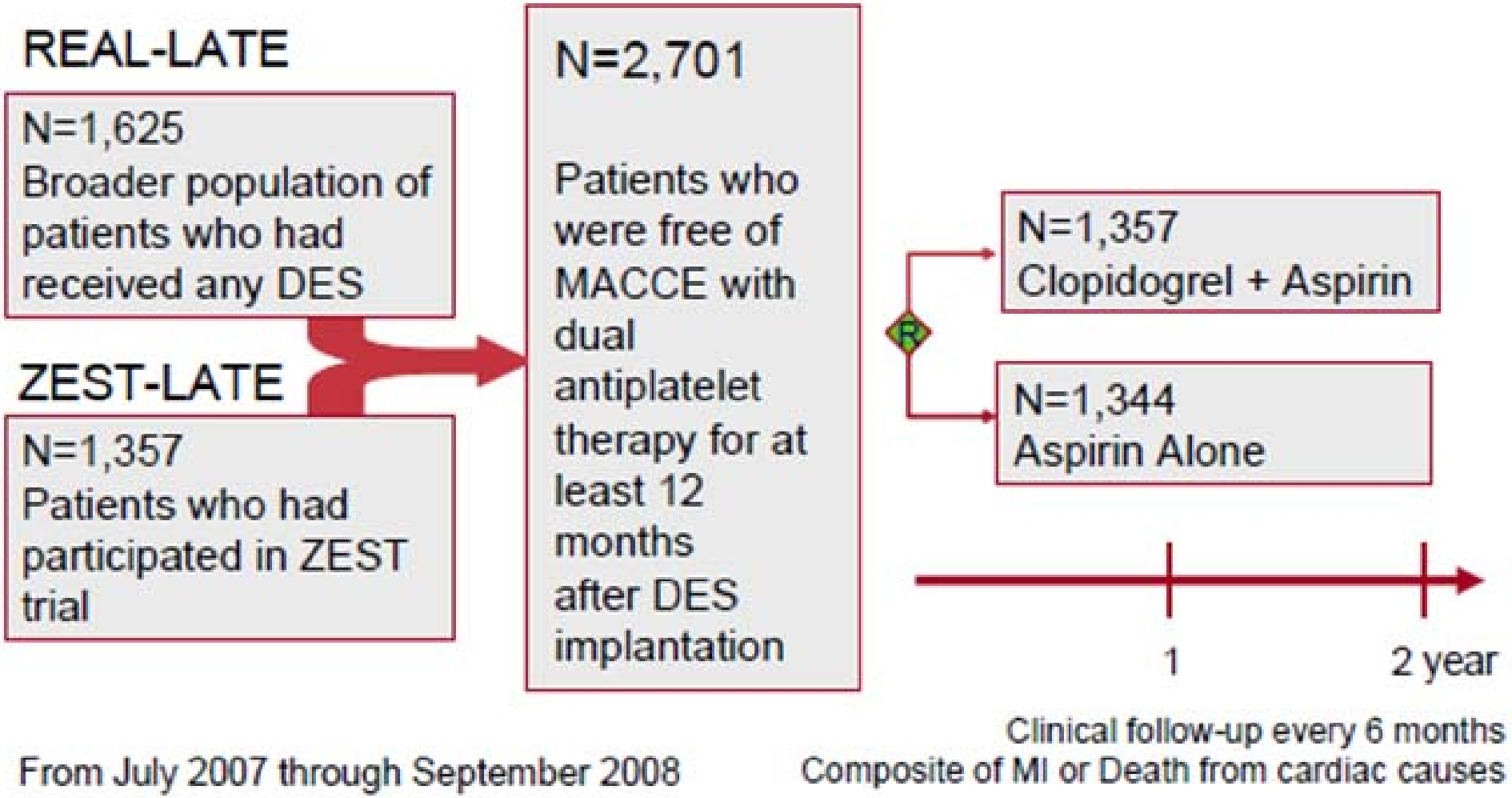
Relationship Between DAPT and ST over 4 year Follow-up, N=6,816



No. of patients					
Discont. clopidogrel	0	1,277	3,934	2,539	1,373
On clopidogrel	6,816	5,181	1,074	398	116

Schulz S, Kastrati A, et al. Eur Heart J 2009

DES LATE

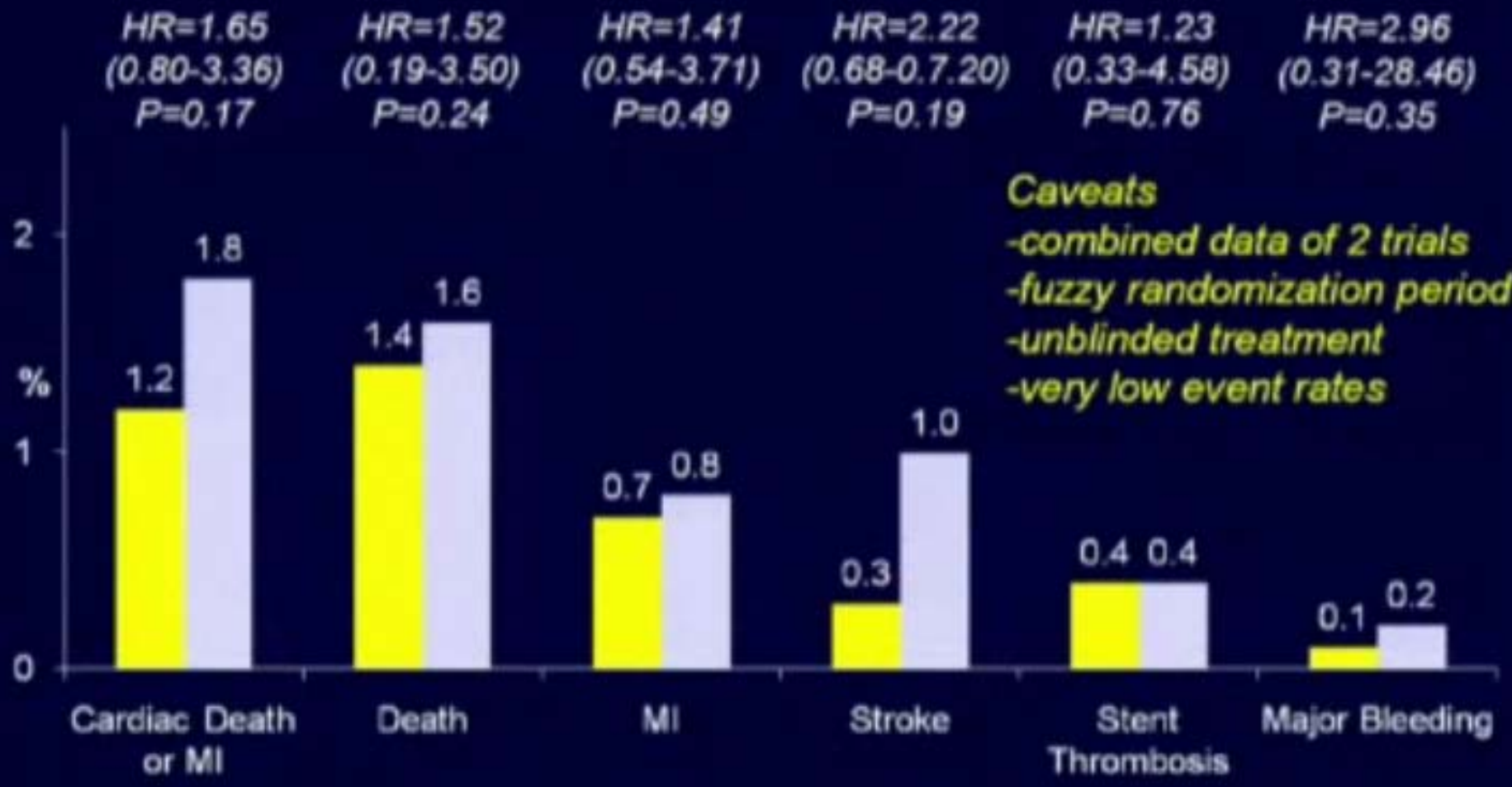


Park et al. N Engl J Med 2010; ACC 2010

euro PCR

DAPT Beyond 12 Months - Real/Zest Late

Clinical Outcomes @ 24 Months



Thienopyridines

MODIFIED Recommendation

Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing drug-eluting stent placement .
(*prior stated to consider continuation beyond 12 months*)

ΣΥΧΝΑ ΠΡΟΒΛΗΜΑΤΑ ΚΑΘΗΜΕΡΙΝΗΣ ΠΡΑΚΤΙΚΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕΤΑ ΑΠΟ ΑΓΓΕΙΟΠΛΑΣΤΙΚΗ

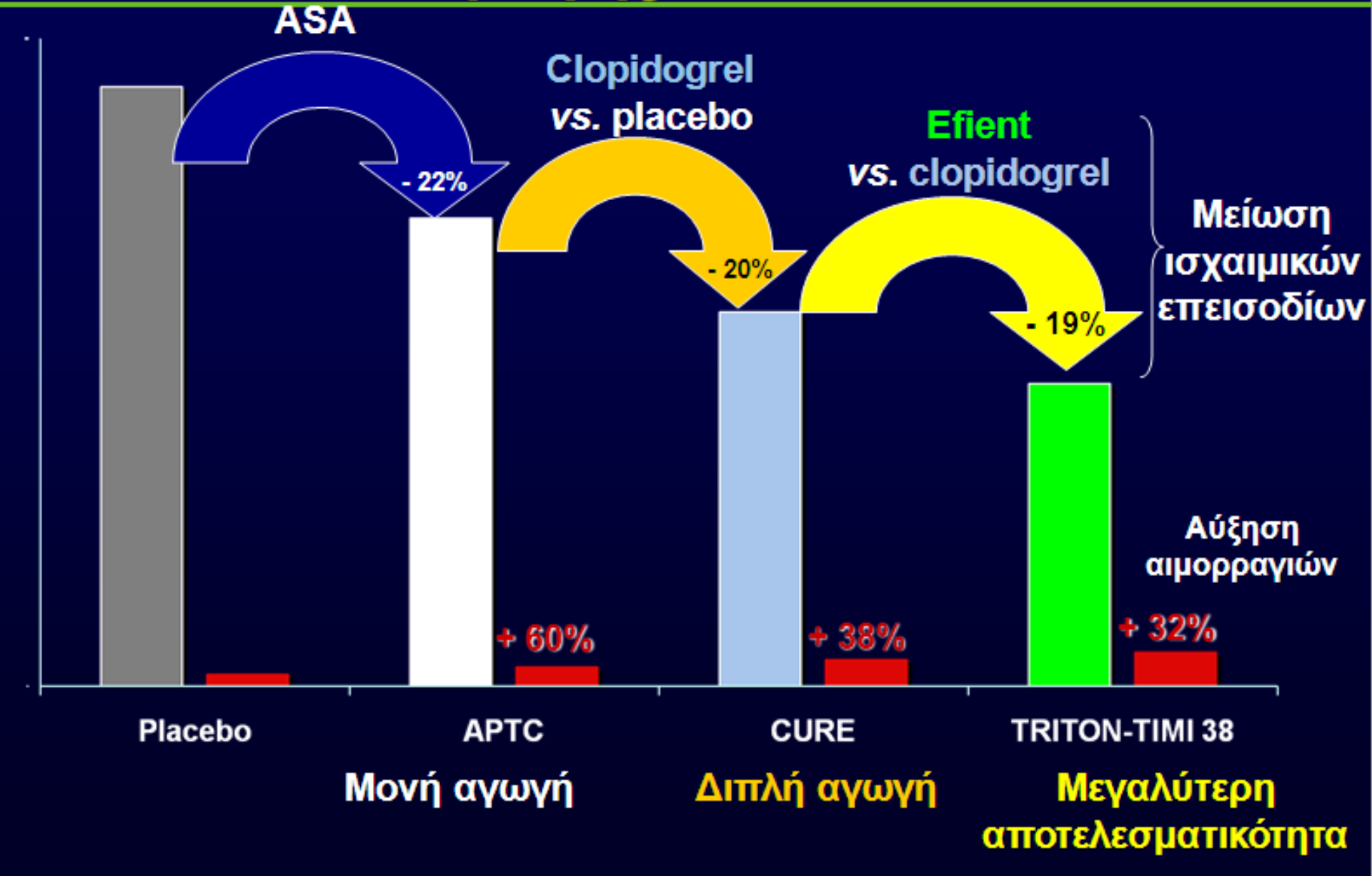
ΑΙΜΟΡΡΑΓΙΕΣ

ΚΛΟΠΙΔΟΓΡΕΛΗ ΚΑΙ PPIs

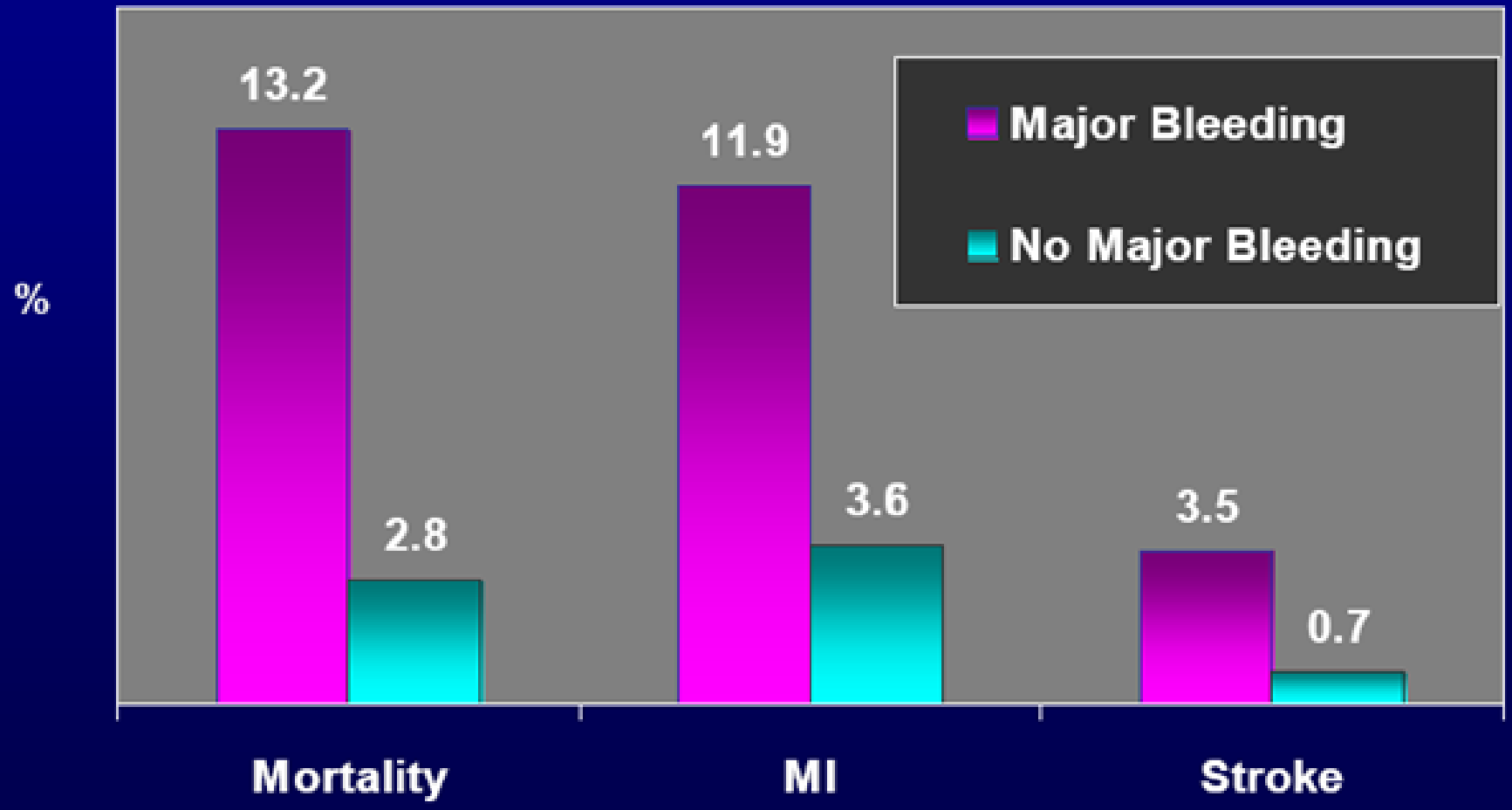
ΑΝΑΓΚΗ ΓΕΝΙΚΟΥ ΧΕΙΡΟΥΡΓΕΙΟΥ

ΑΝΑΓΚΗ ΤΡΙΠΛΗΣ ΑΝΤΙΠΗΚΤΙΚΗΣ ΑΓΩΓΗΣ

Η εξέλιξη της Αντιαιμοπεταλιακής αγωγής στα ΟΣΣ

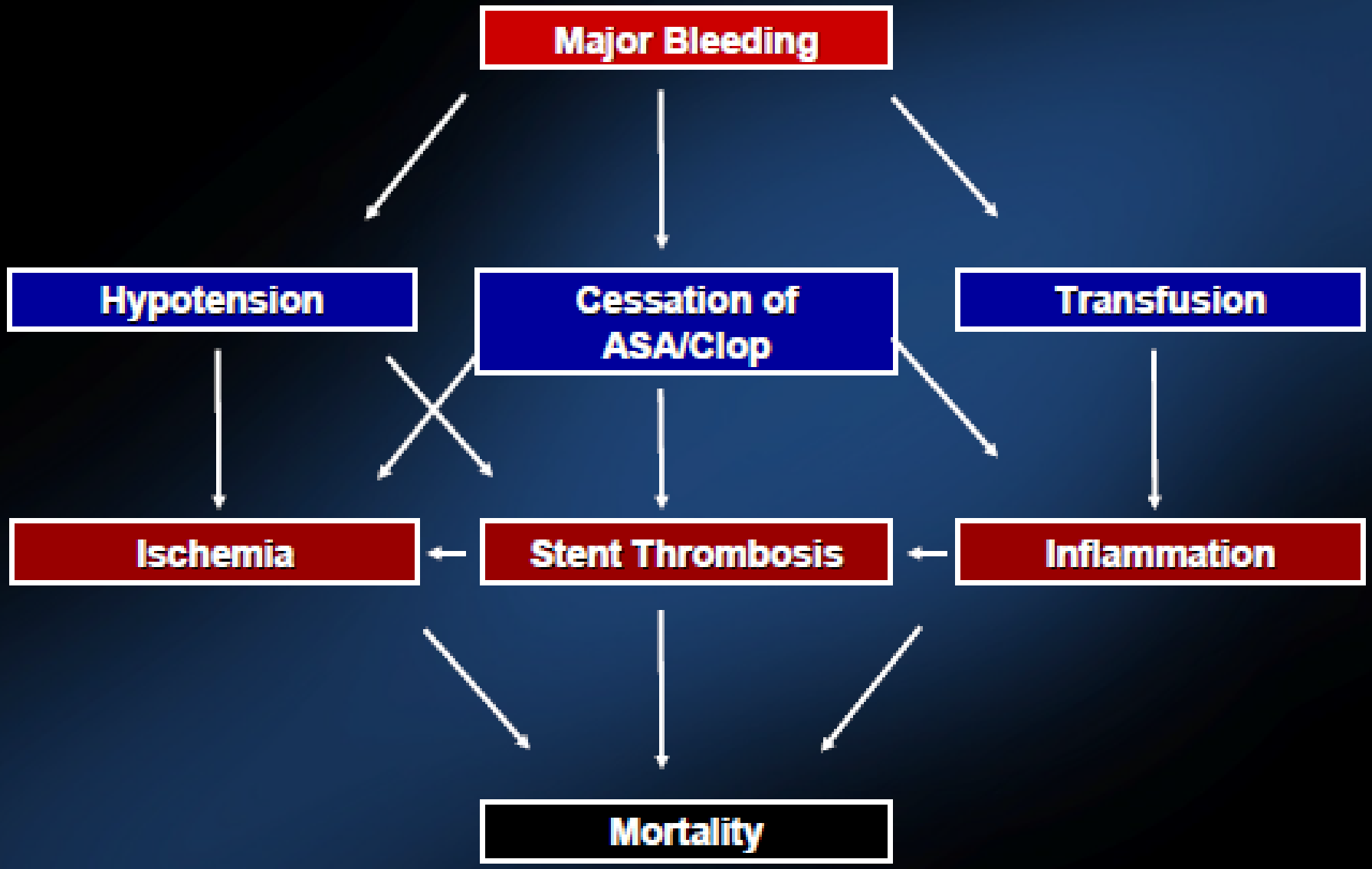


Interaction of Major Bleeding with Mortality: OASIS 5



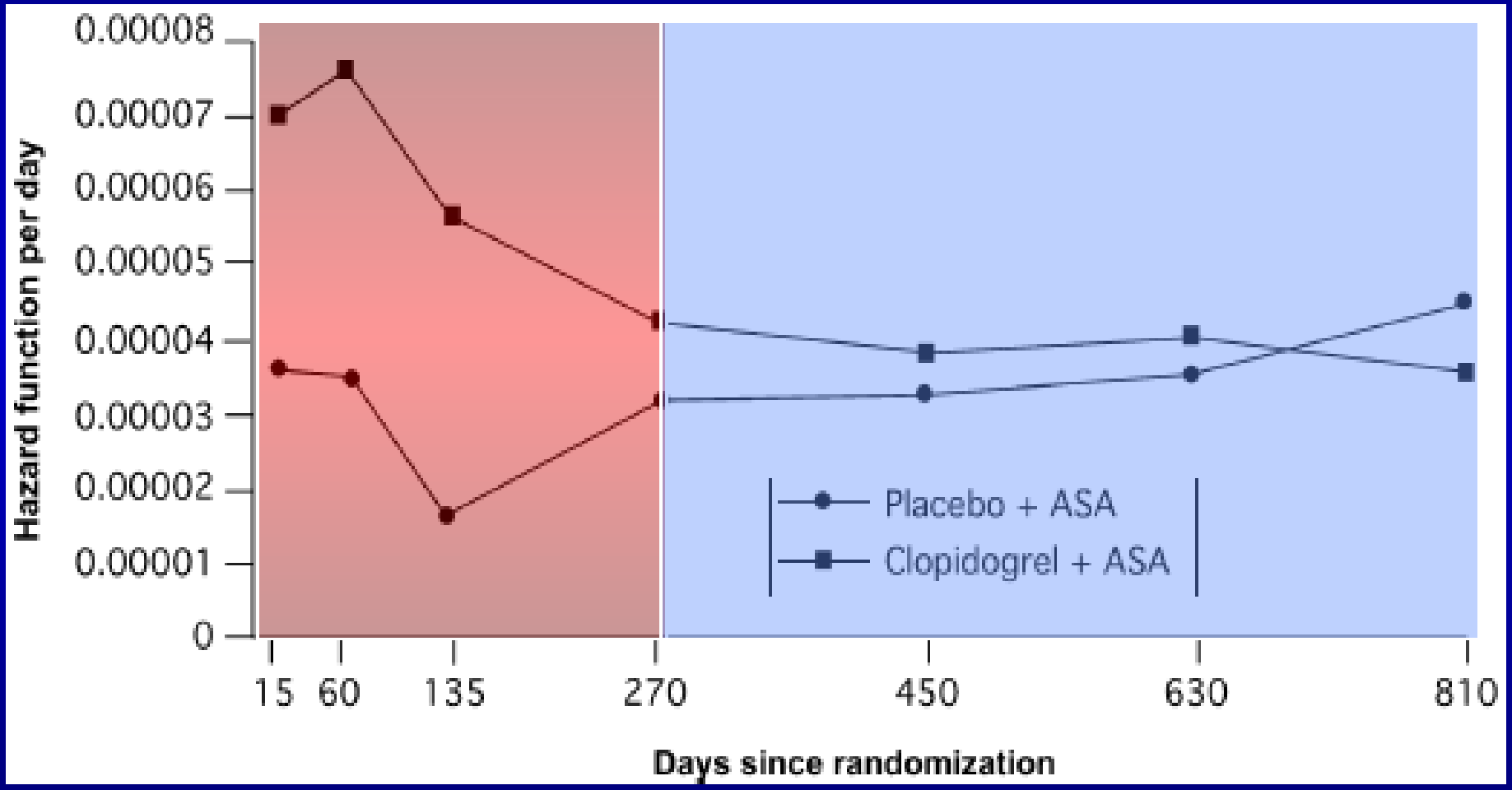
The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, N Engl J Med 2006;354:1464-1476

Potential Relationship Between Bleeding and Mortality



Bhatt DL. In Braunwald: Harrison's Online 2005.

Insights from CHARISMA: Timing of Severe or Moderate Bleeding



Bhatt DL, Flather MD, Hacke W, et al. JACC 2007; 49: 1982-8

ΣΥΧΝΑ ΠΡΟΒΛΗΜΑΤΑ ΚΑΘΗΜΕΡΙΝΗΣ ΠΡΑΚΤΙΚΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕΤΑ ΑΠΟ ΑΓΓΕΙΟΠΛΑΣΤΙΚΗ

ΑΙΜΟΡΡΑΓΙΕΣ

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ΑΝΑΓΚΗ ΤΡΙΠΛΗΣ ΑΝΤΙΠΗΚΤΙΚΗΣ ΑΓΩΓΗΣ

2009 Updated Labeling for Clopidogrel–PPI Interaction

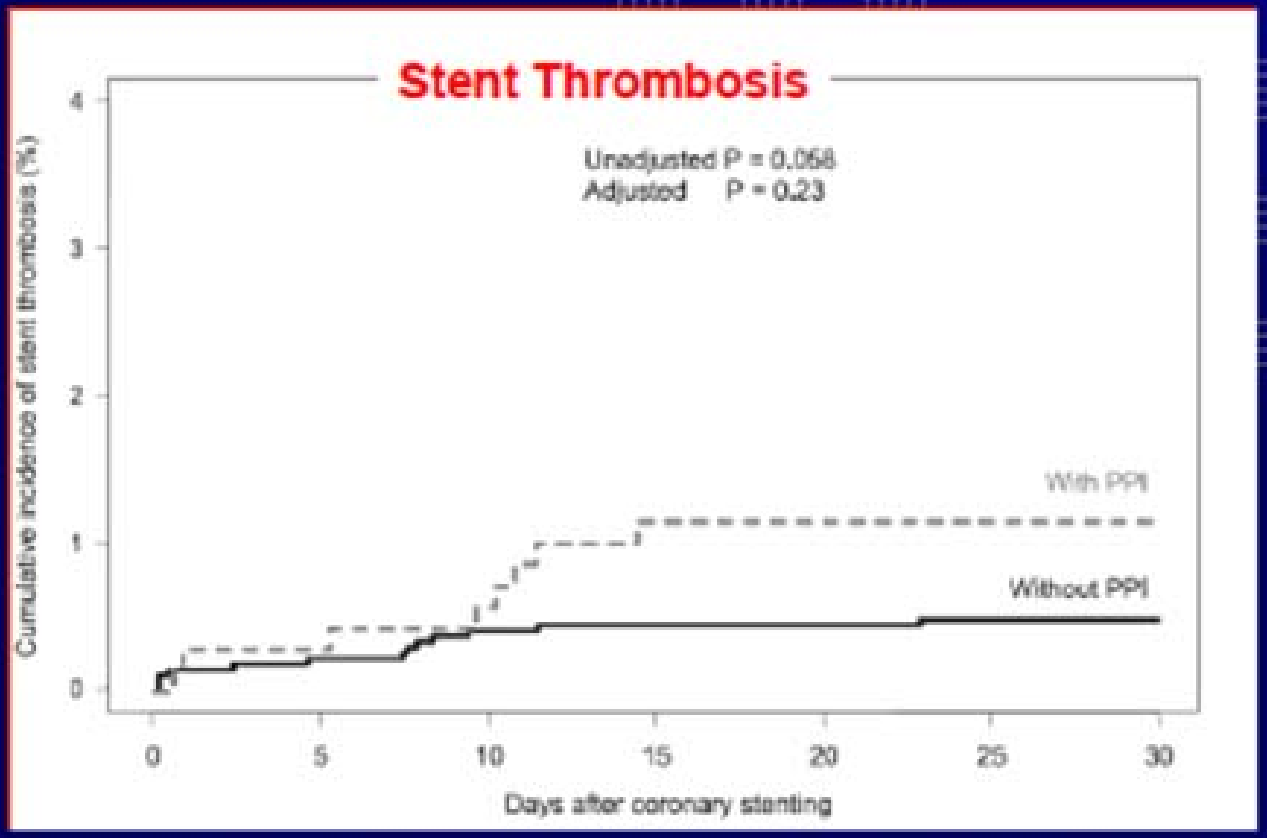
- FDA-required label changes:[2]
  - Warning: "Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of *CYP2C19*, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart"
  - Drug-Drug Interactions: "Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine"
  - Based on PK/PD studies showing concomitant omeprazole reduced clopidogrel active metabolite and effect on platelets[1]
    - Did not include COGENT study data[2]
- EMEA warning extends to discourage concomitant use of all PPIs[3]
  - Concomitant use of drugs that inhibit CYP2C19 discouraged; concomitant use of <u>any</u> PPI "should be avoided unless absolutely necessary"[4]

EMEA=European Medicines Agency; FDA=Food and Drug Administration; PD=pharmacodynamic; PK=pharmacokinetic.

[1]Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafety InformationforHeathcareProfessionals/ucm190787.htm. Published November 17, 2009. Accessed January 22, 2010. [2]Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2009. [3]Wathion N. http://www.emea.europa.eu/humandocs/PDFs/ EPAR/Plavix/32895609en.pdf. Published May 29, 2009. Accessed January 22, 2010. [4]Plavix [summary of product characteristics]. Paris, France: Sanofi Pharma Bristol-Myers Squibb SNC; 2009.

Stent Thrombosis (within 30 days) and PPI Use

3,338 patients with DES – 698 (21%) treated with PPI
All treated with clopidogrel



30-day mortality w PPI 2.6% vs w/o 0.9%; adjusted p=0.02

Sarafoff, Sibbing et al. Thromb Haemost 2010

ΠΡΑΚΤΙΚΕΣ ΟΔΗΓΙΕΣ ΓΙΑ ΑΣΘΕΝΕΙΣ ΠΟΥ ΧΡΗΖΟΥΝ ΓΑΣΤΡΟΠΡΟΣΤΑΣΙΑΣ ΜΕ ΤΑΥΤΟΧΡΟΝΗ ΔΙΠΛΗ ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΗ ΑΓΩΓΗ

- Συνταγογραφήστε Η2Β αποκλειστές
- Συνταγογραφήστε παντοπραζόλη (CYP 2C9)
- Αντικαταστήστε την κλοπιδογρέλη με πρασουγρέλη ή Ticagrelor

ΣΥΧΝΑ ΠΡΟΒΛΗΜΑΤΑ ΚΑΘΗΜΕΡΙΝΗΣ ΠΡΑΚΤΙΚΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕΤΑ ΑΠΟ ΑΓΓΕΙΟΠΛΑΣΤΙΚΗ

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Perioperative Management for Non-Cardiac Surgery Following Coronary Stent Deployment

	Clopidogrel	Prasugrel	Ticagrelor
Stop Drug	≥ 5 days	≥ 7 days	≥ 3 days
Restart Drug	≤ 2-3 days	≤ 2-3 days	≤ 2-3 days
Reload	300-600mg*	No	No
Continue ASA 81g/day	Yes	Yes	Yes

** High Risk Strata (Prior ACS; Diabetes Mellitus; Stent*

ΣΥΧΝΑ ΠΡΟΒΛΗΜΑΤΑ ΚΑΘΗΜΕΡΙΝΗΣ ΠΡΑΚΤΙΚΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕΤΑ ΑΠΟ ΑΓΓΕΙΟΠΛΑΣΤΙΚΗ

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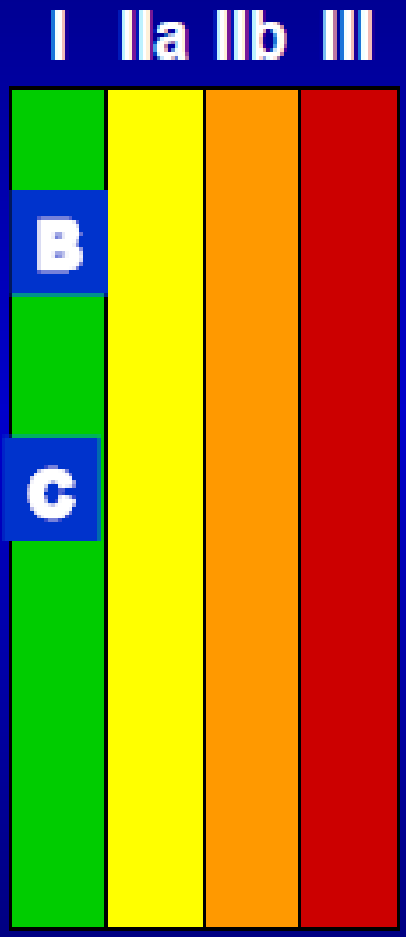
ACC/AHA/SCAI 2007 Focused Update for PCI

Oral Antiplatelet Adjunctive Therapies

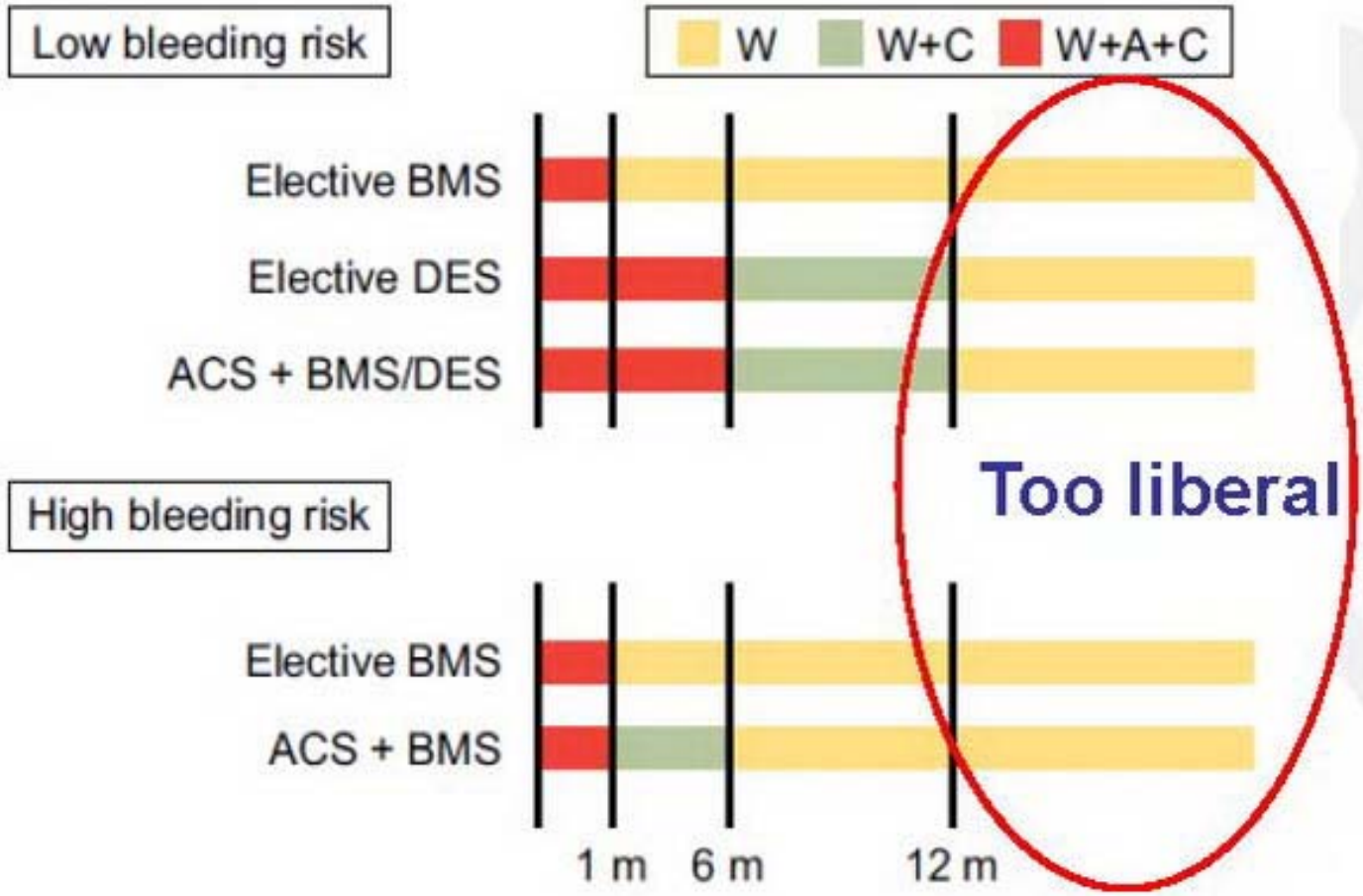
(New Recommendation)



Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.

In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75-mg dose of clopidogrel.

Triple antithrombotic therapy:
no guidelines / no recommendation



Pipilis et al. Hellenic J Cardiol 2010.

Συνοψίζοντας

- Οι νεώτεροι αποκλειστές των P2Y12 υποδοχέων παρουσιάζουν μεγαλύτερη μείωση στα ισχαιμικά επεισόδια, αλλά και περισσότερες αιμορραγίες.
- Όταν σχεδιάζετε μια θεραπευτική στρατηγική μετά από αγγειοπλαστική λάβετε υπ όψιν:

✓ Το συνολικό ισχαιμικό κίνδυνο του ασθενούς

✓ Τον κίνδυνο αιμορραγιών

✓ Τη διάρκεια της θεραπείας

✓ Τις συνυπάρχουσες φαρμακευτικές αγωγές