FELLOWS COURSE – AUG / 07

Anticoagulant and antithrombotic therapy in the PCI of NSTE-ACS

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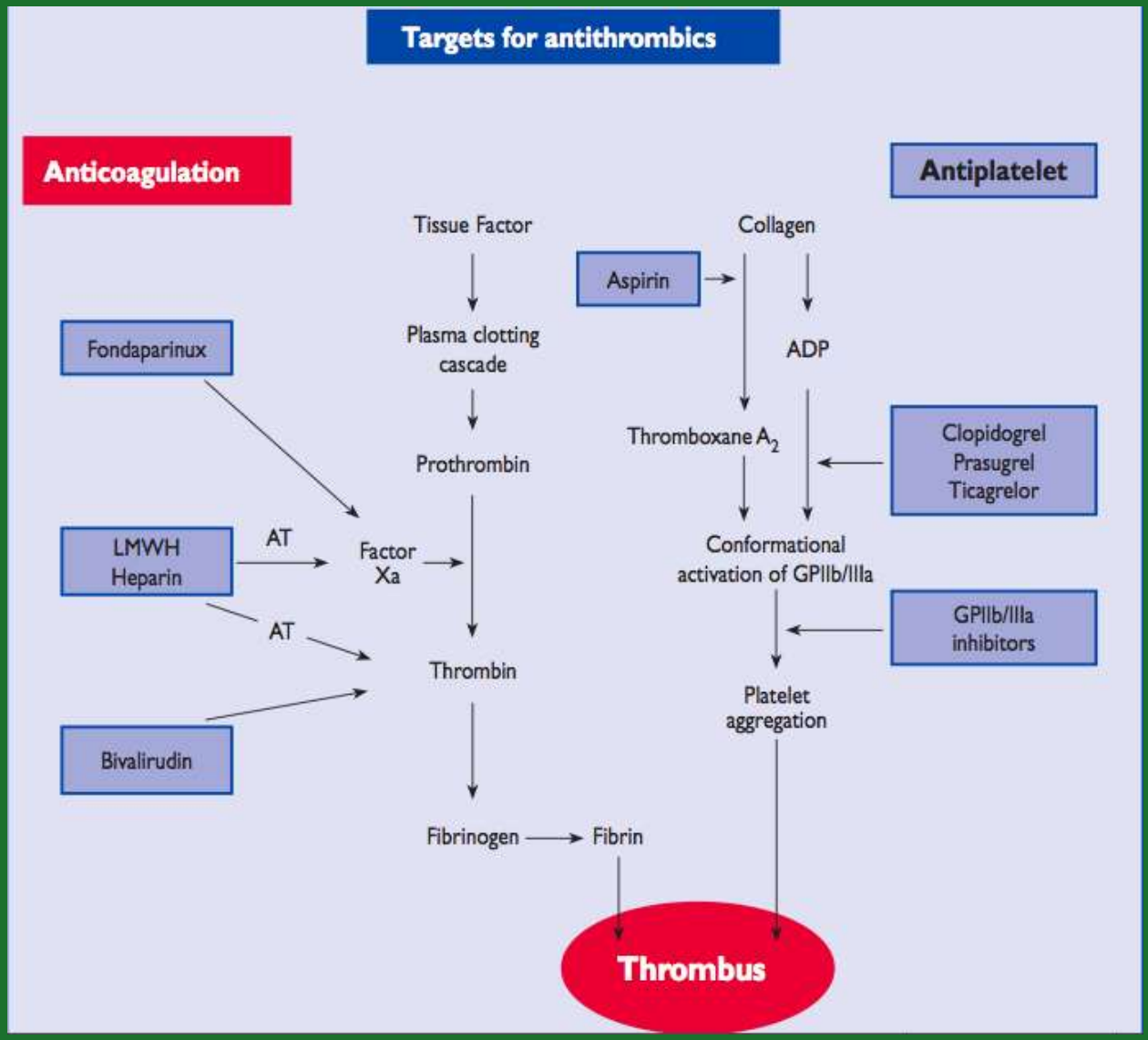
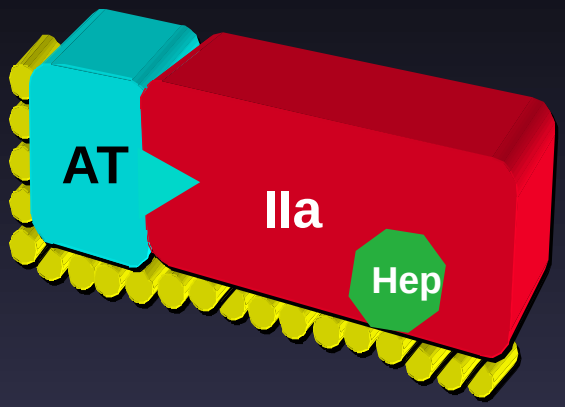
Anticoagulant and antithrombotic therapy in the PCI of NSTE-ACS

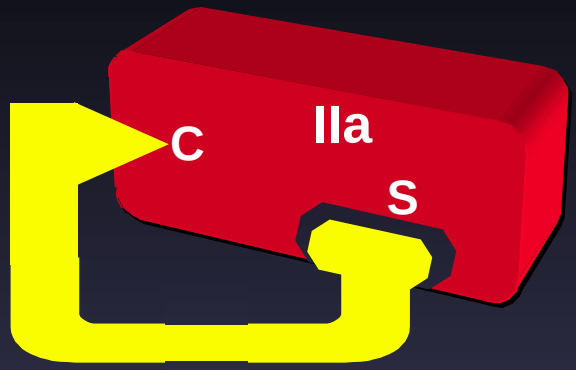
1. Drugs available – Mechanism of action
2. Drugs association
3. RCT
4. Guidelines
5. Conclusions


Targets for antithrombics
Anticoagulation
Antiplatelet
Tissue Factor
Collagen
Aspirin
Plasma clotting cascade
ADP
Fondaparinux
Thromboxane A2
Clopidogrel
Prasugrel
Ticagrelor
Prothrombin
LMWH
Heparin
AT
Factor Xa
Conformational activation of GPIIb/IIIa
AT
GPIIb/IIIa inhibitors
Thrombin
Platelet aggregation
Bivalirudin
Fibrinogen
Fibrin
Thrombus

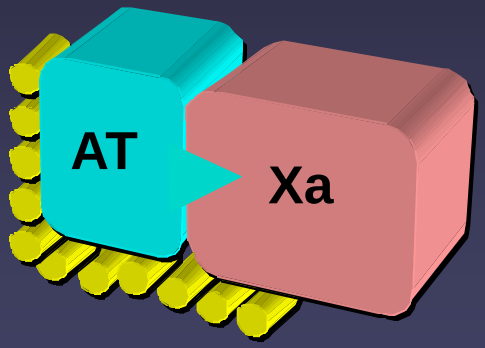
Four Anticoagulant Choices



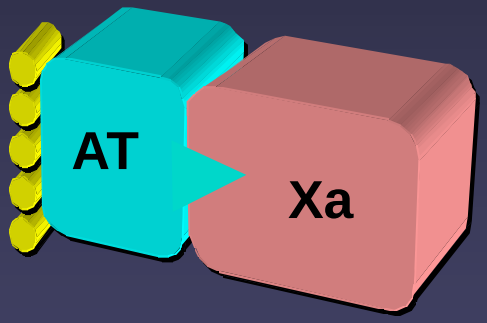
UFH



Direct antithrombin



LMWH



Pentasaccharide

Konkle BA, Schafer AI. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Braunwald's Heart Disease*. Vol 2. 7th ed. Philadelphia: Elsevier Saunders; 2005:2067-2092.

= saccharide unit.

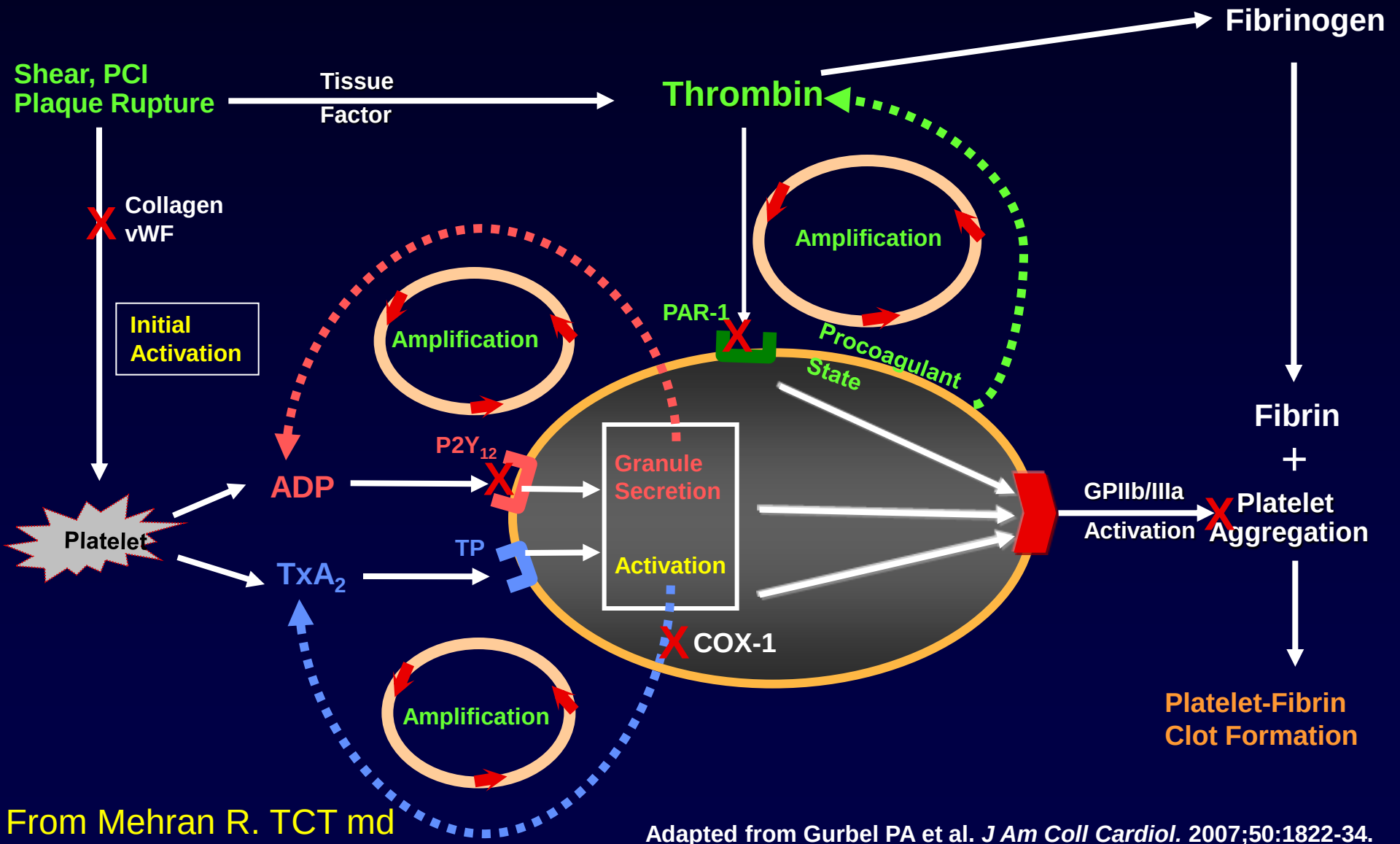
From Mehran R. TCT md

Initial Medical Treatment: Anticoagulant Dosing

Bivalirudin	0.1 mg/kg bolus, 0.25 mg/kg/h infusion
Enoxaparin	30 mg IV bolus may be given 1 mg/kg SC every 12 h; extend dosing interval to 1 mg/kg every 24 h if estimated creatinine clearance <30 mL/min
Fondaparinux	2.5 mg SC once daily Avoid for creatinine clearance <30 mL/min
Unfractionated heparin	60 U/kg (max 4000 U) as IV bolus IV infusion of 12 U/kg/h (max 1000 U/h) to maintain aPTT at 1.5-2.0 times control (approx. 50-70 s)

Adapted from Anderson JL, et al. *J Am Coll Cardiol.* 2007;50(7):e1-e157.

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



From Mehran R. TCT md

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

$P2Y_{12}$ Receptor Antagonists

Agent	Class	IPA (20 *uM* ADP) mean	Time to peak onset	Reversibility (d/c before CABG)
Ticlopidine 250 mg bid	thienopyridine (pro-drug)	25%	48 hrs	non reversible 5 days
Clopidogrel 300 mg LD Clopidogrel 600 mg LD Clopidogrel 75 mg qd Clopidogrel 150 mg qd	thienopyridine (pro-drug)	30% - 40% 35% - 50% 30% - 35% 45% - 50%	12 hrs 6 hrs - -	non reversible 5 days
Prasugrel 60 mg LD* Prasugrel 10 mg qd* Prasugrel 5 mg qd*	thienopyridine (pro-drug)	80% 60% 40%	1-2 hrs - -	non reversible 7 days
Ticagrelor 180 mg LD* Ticagrelor 90 mg bid*	cyclo-pentyl-triazolo-pyrimidine**	80% 70%	1-2 hrs -	reversible 2-5 days

*Less affected by genetic polymorphisms and drug interactions (e.g. PPIs)

**not a pro-drug

Factor Xa inhibitors

FONDAPARINUX IN NSTE-ACS

- Fondaparinux is a synthetic analog of the pentasaccharide sequence in heparin
- **The efficacy and safety of subcutaneous fondaparinux** 2.5 mg daily was **compared with routine treatment with enoxaparin** 1 mg/kg body weight for 8 days or until hospital discharge in the **OASIS-5** trial and was found to be superior to UFH
- Importantly, long-term mortality after 6 months was lower with fondaparinux 5.8% compared with 6.5% with enoxaparin.
- **During the trial, there were observations of catheter related thrombi occurring more frequently with the use of fondaparinux**
- In addition, there tended to be more clinical PCI-related coronary complications with fondaparinux.

Catheter Thrombus

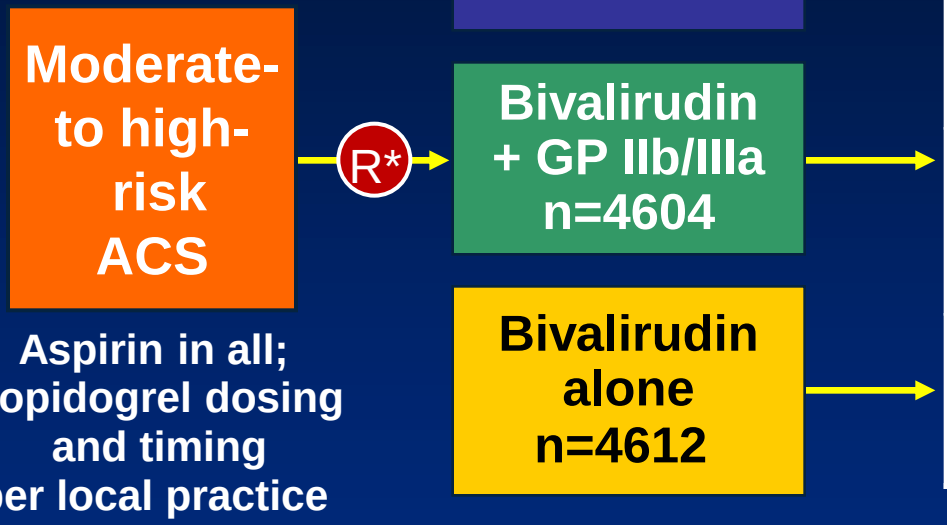
- Unfractionated heparin added to fondaparinux prevents catheter thrombus
- GP IIb IIIa inhibitors are likely not effective at preventing catheter thrombus
- Guidelines recommend a dose of 50-60u/kg of Heparin in conjunction with GPIIb/IIIa and 85u/Kg if not (OASIS 8)

Direct thrombin inhibitors (DTIs)

- The DTIs act by binding to thrombin and blocking its interaction with substrates
- DTIs directly block the formation of fibrin from fibrinogen by the action of thrombin
- DTIs are available for use in the setting of arterial thrombosis**: lepirudin, argatroban, and bivalirudin;**
- **Bivalirudin is a synthetic bivalent inhibitor**.
- Multiple trials have firmly established that bivalirudin is a reasonable therapy in ACS.
- **Dabigratan-Oral Direct Thrombin Inhibitor-REDEEM trial was released at AHA**

ACUITY Study: 30-Day Results

Moderate- to high-risk patients with UA or NSTEMI undergoing an invasive strategy (N=13,819)



Ischemic Composite	Bleeding	Net Clinical Outcome
7.3%	5.7%	11.7%
7.7%	5.3%	11.8%
7.8%	3.0%	10.1%

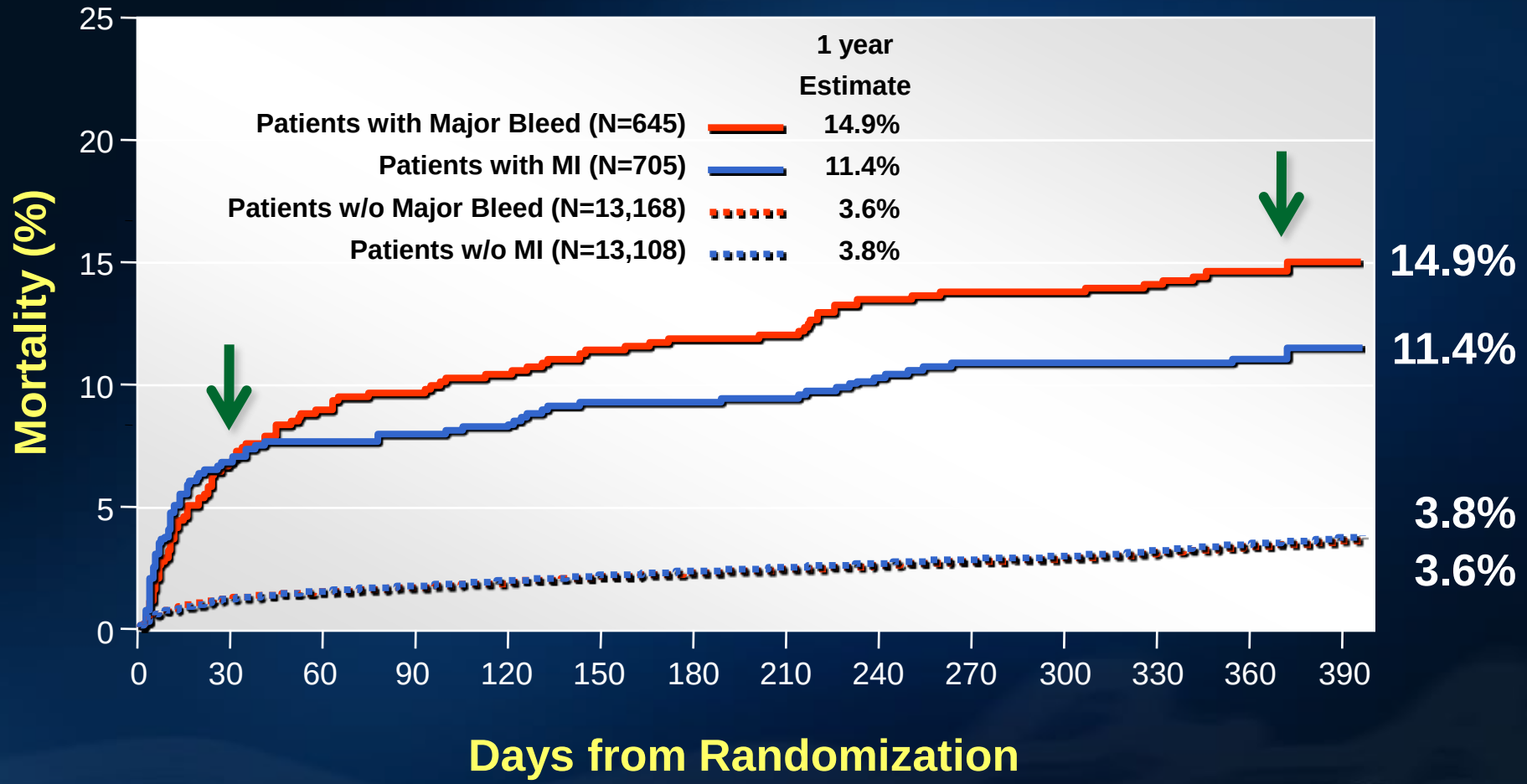
End points: death, MI, and unplanned revascularization for ischemia (30 days and 1 year); major bleeding (30 days); composite of the above (30 days)

*Stratified by preangiography thienopyridine use or administration.

Stone GW, et al. *N Engl J Med*. 2006;355(21):2203-2216.

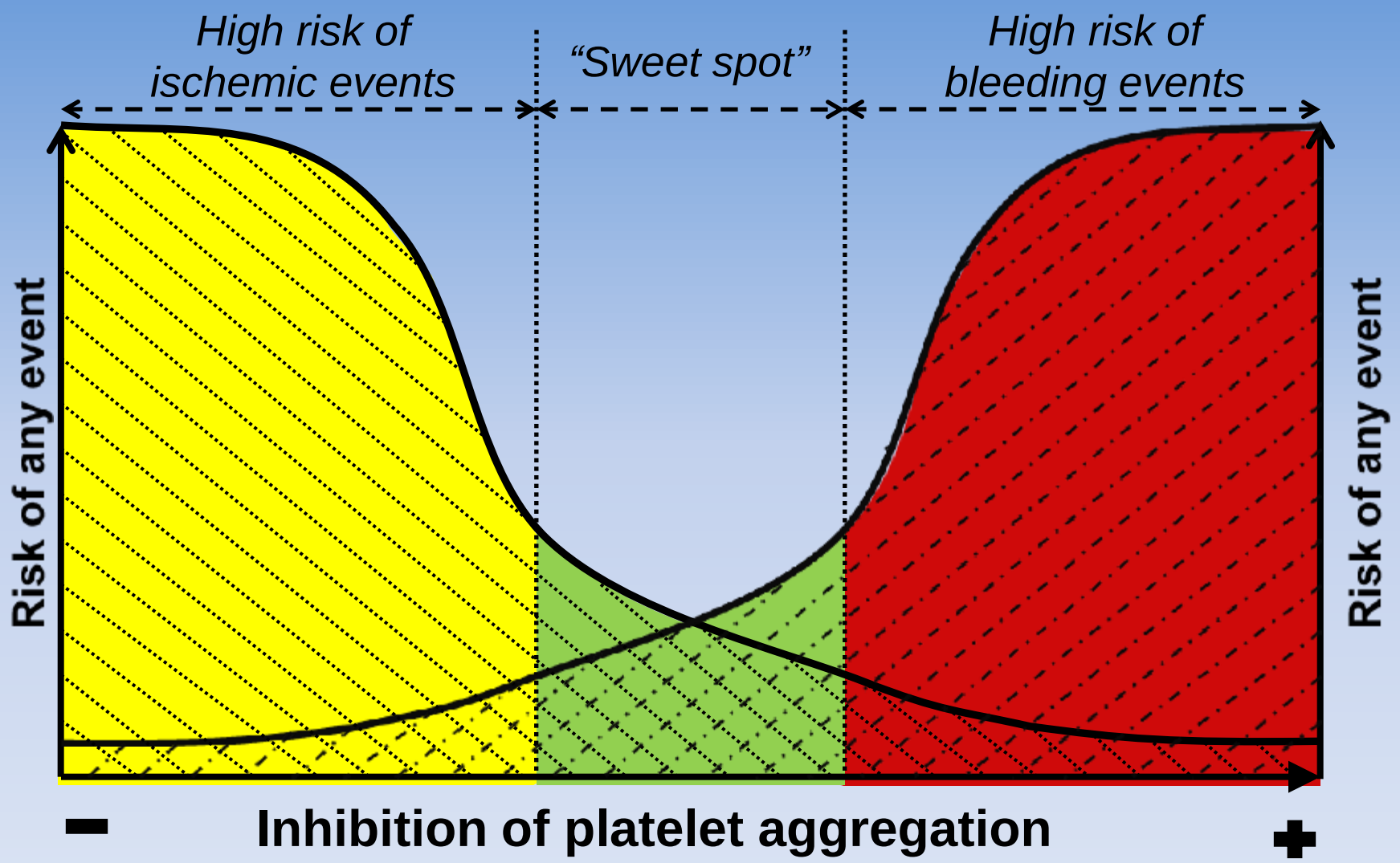
ACUITY (N=13,819)

Impact of MI and Major Bleeding in the First 30 Days on Risk of Death Over 1 Year



ACUITY

Balancing Safety and Efficacy



From Mehran R. TCT md

Ferreiro & Angiolillo. Thromb Haemost 2010 (in press)

CURRENT Study Design, Flow and Compliance

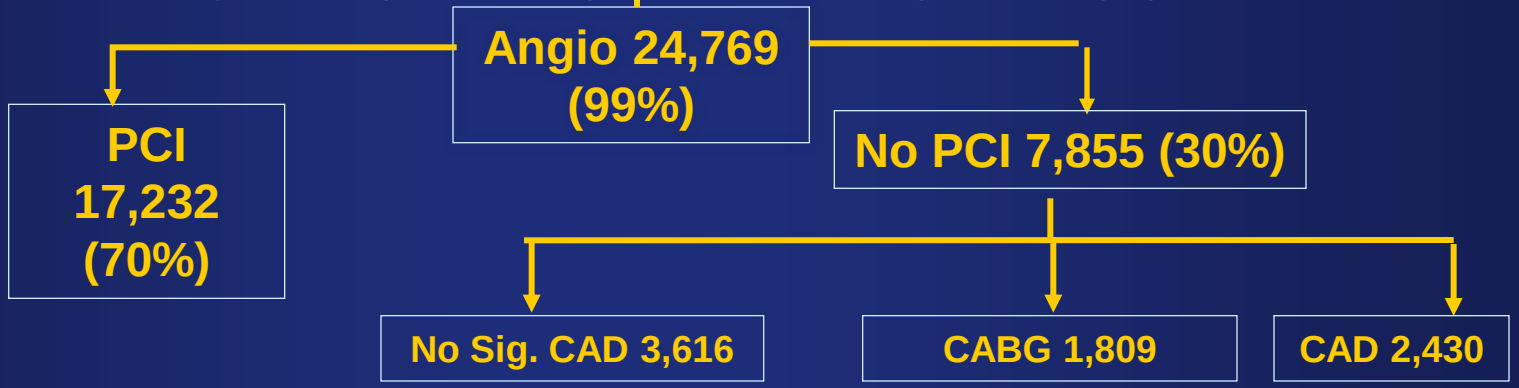
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

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

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

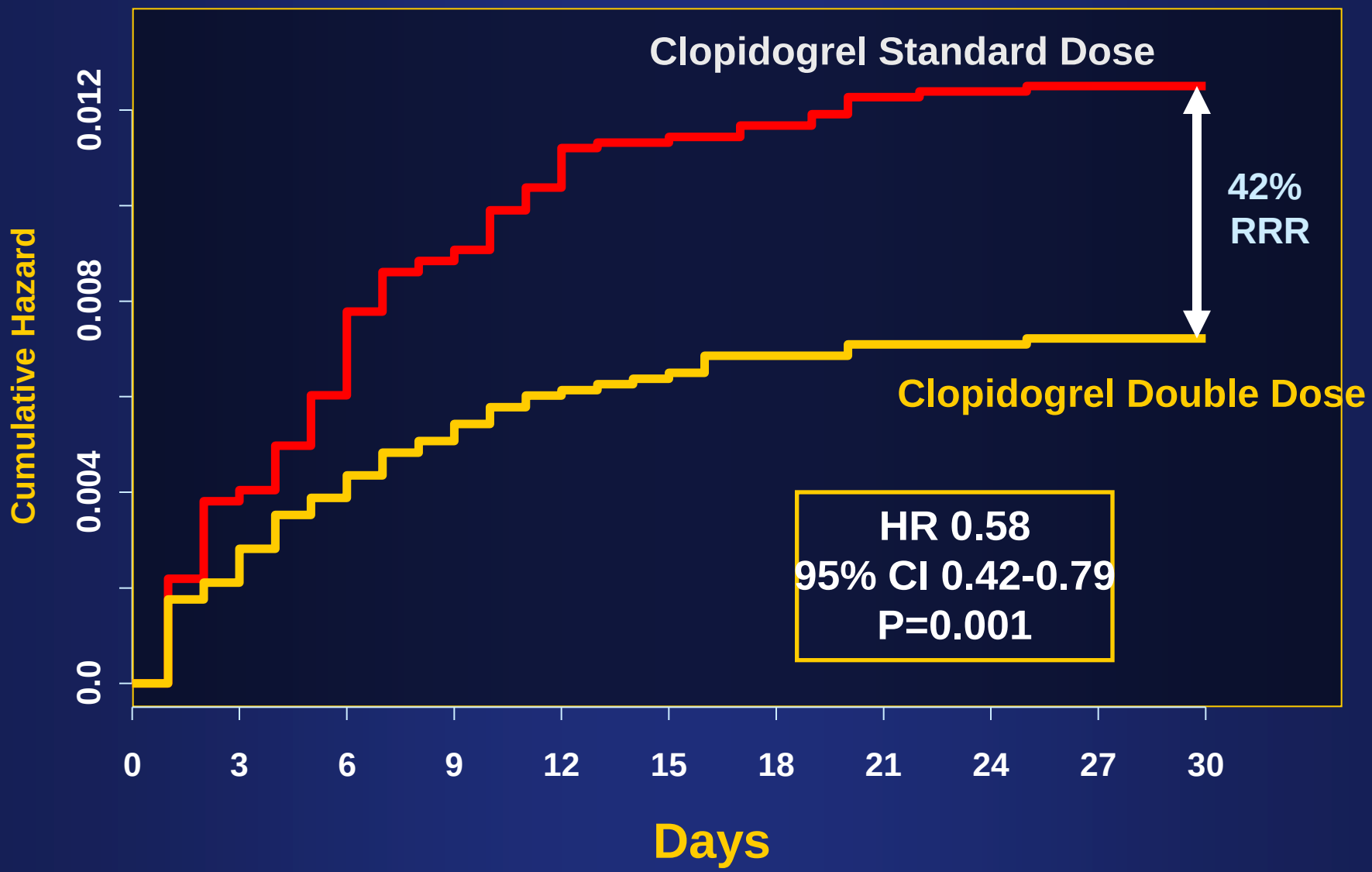
ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)



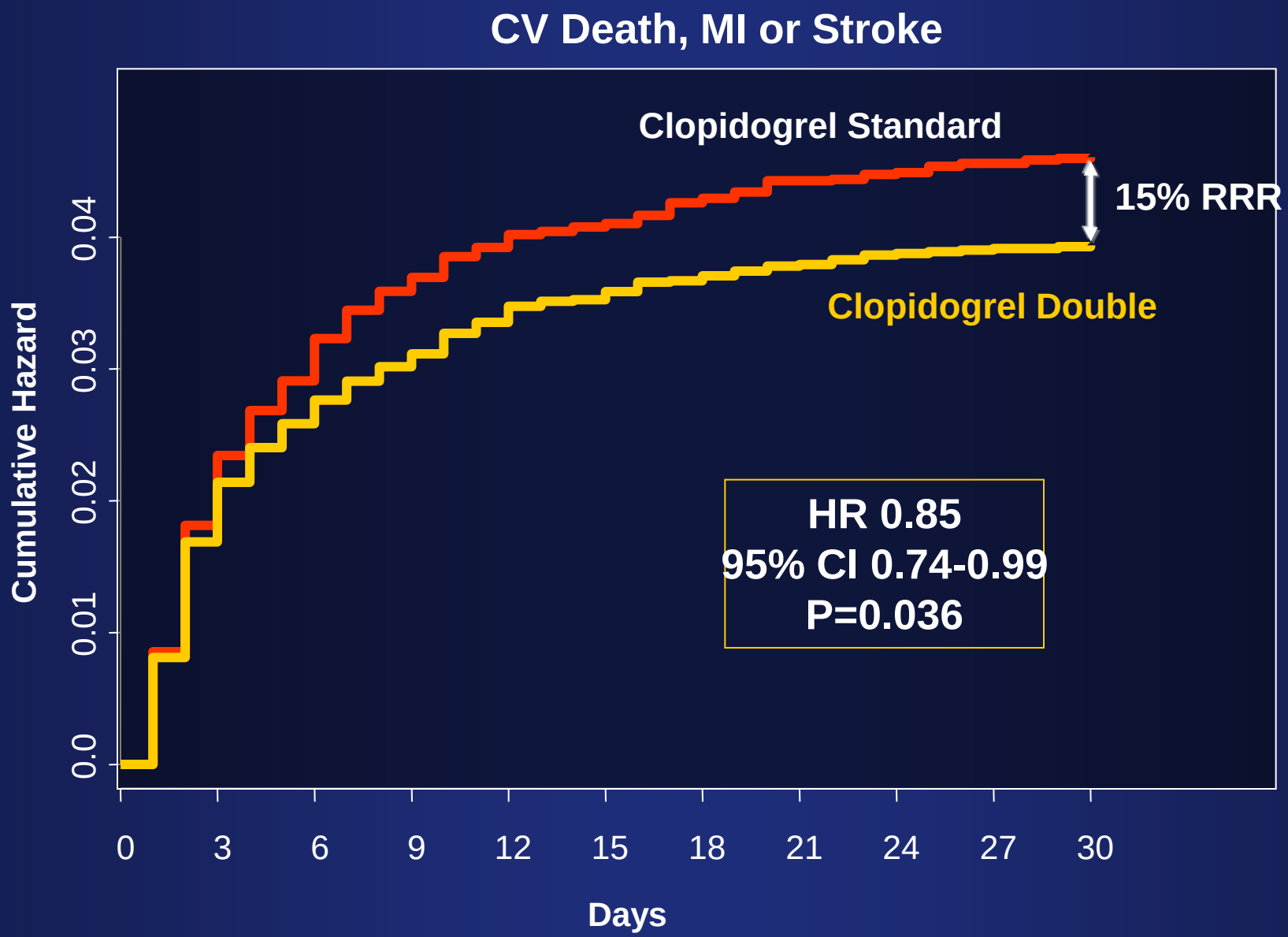
Efficacy Outcomes:	CV Death, MI or stroke at day 30
	Stent Thrombosis at day 30
Safety Outcomes:	Bleeding (CURRENT defined Major/Severe and TIMI Major)
Key Subgroup:	PCI v No PCI

CURRENT

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



Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients

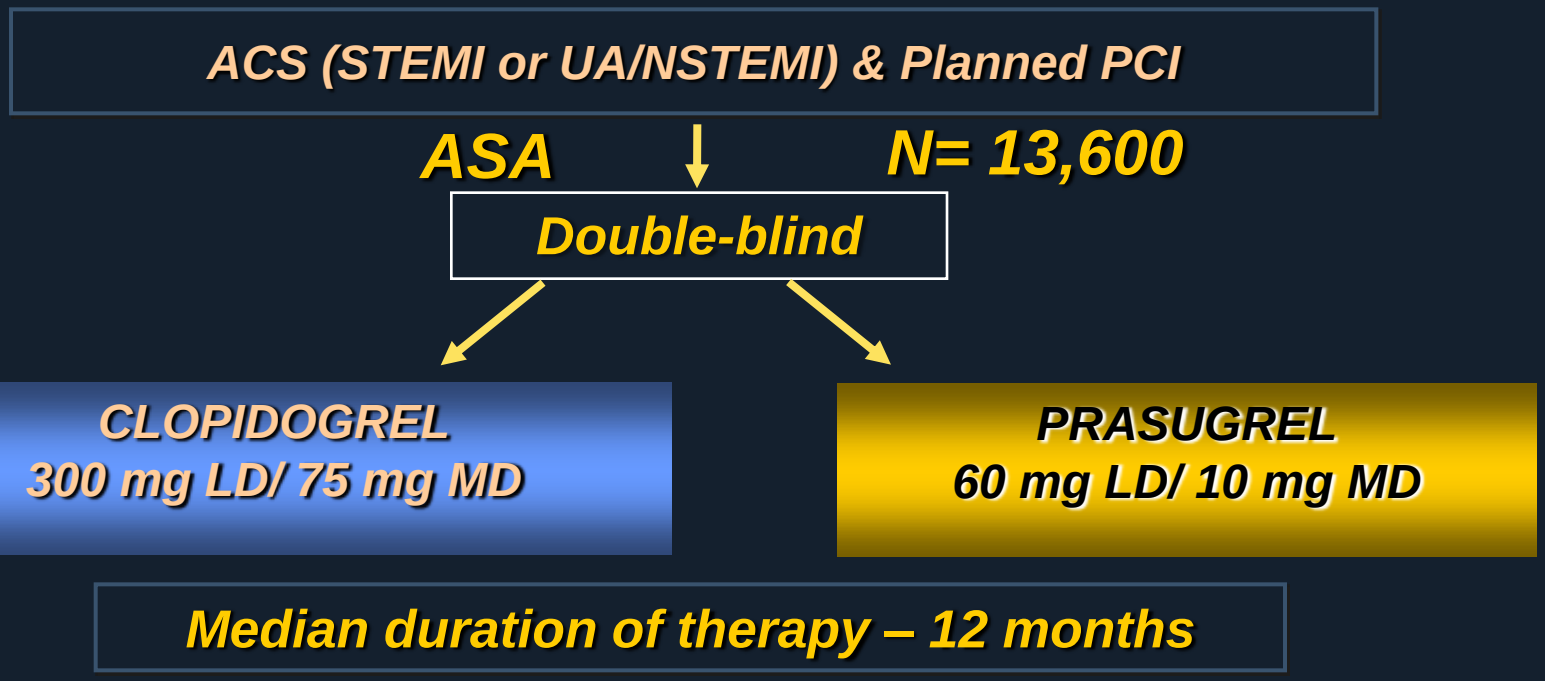


Clopidogrel Double vs Standard Dose Bleeding PCI Population

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

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

TRITON-Study Design



1º endpoint: CV death, MI, Stroke

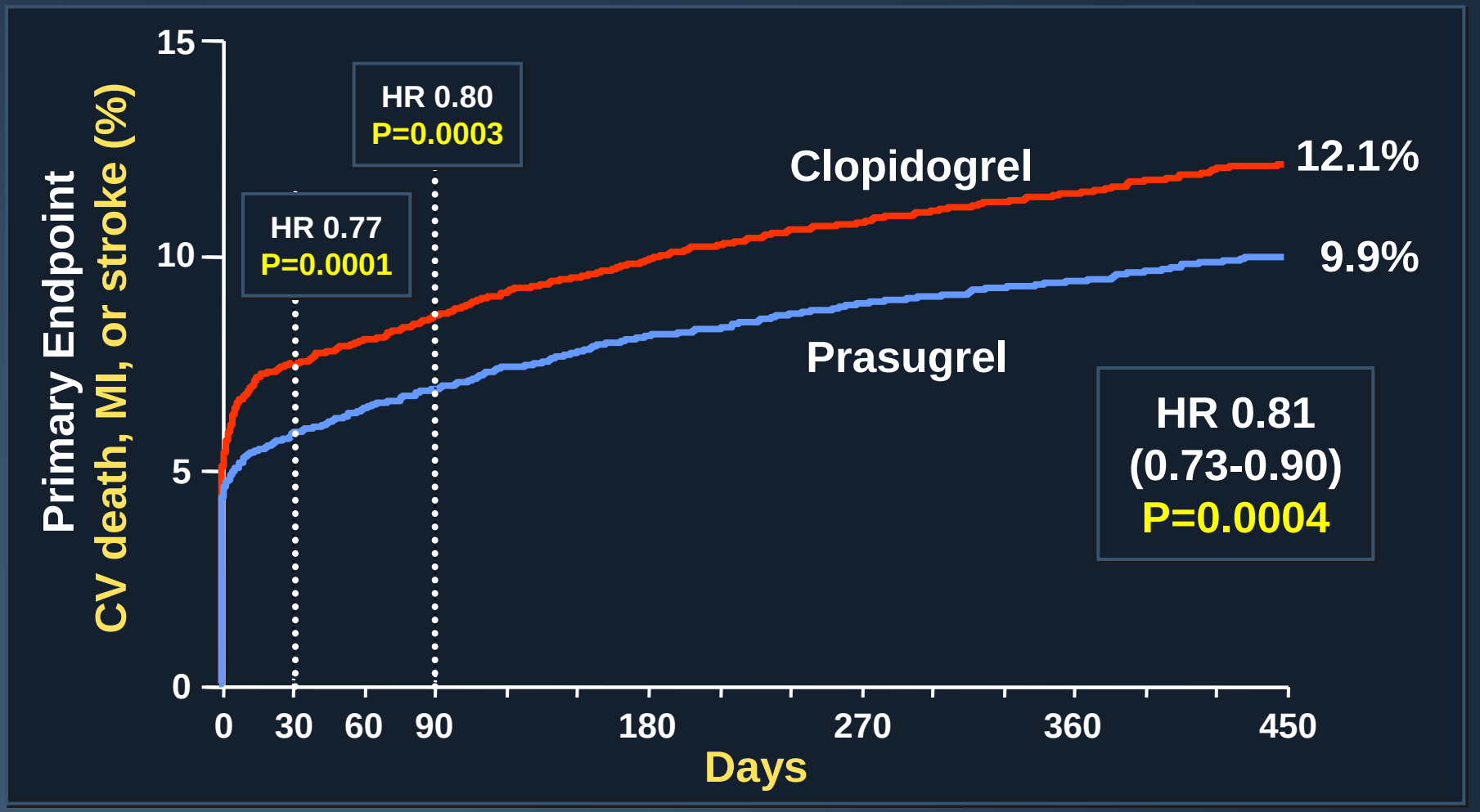
2º endpoints: CV death, MI, Stroke, Rehosp-Rec Isch, CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

TRITON-TIMI-38

13,608 pts with ACS (unstable angina, NSTEMI, acute STEMI, or recent STEMI) undergoing PCI with known coronary anatomy (except for primary PCI pts) were treated with aspirin and randomized to clopidogrel 300 mg load + 75 mg qd vs. prasugrel 60 mg load + 10 mg qd and followed for 6-15 mos (median 12 mos)

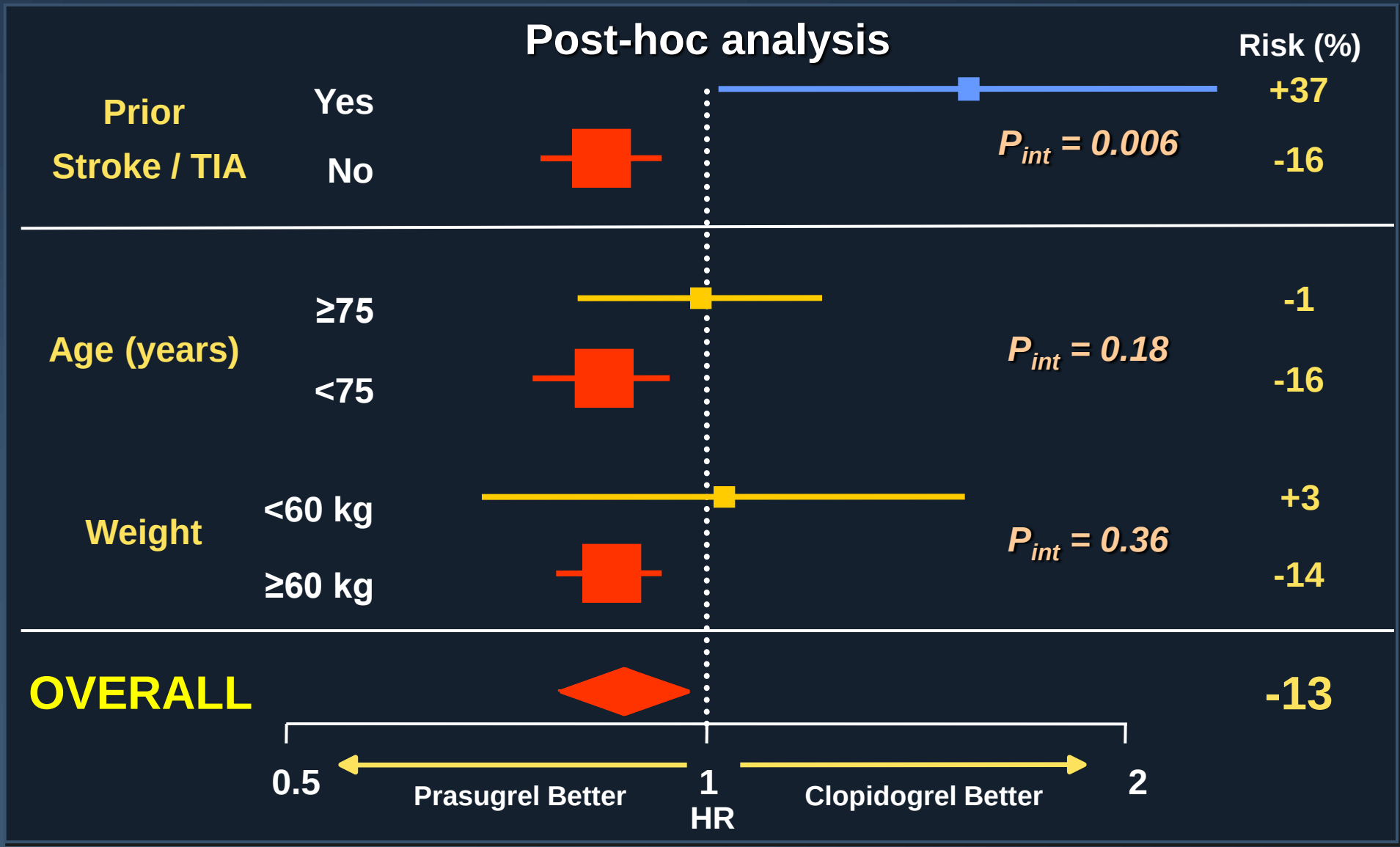


Wiviott SD et al. NEJM 2007;357:2001-15

TRITON TIMI-38

Net Clinical Benefit

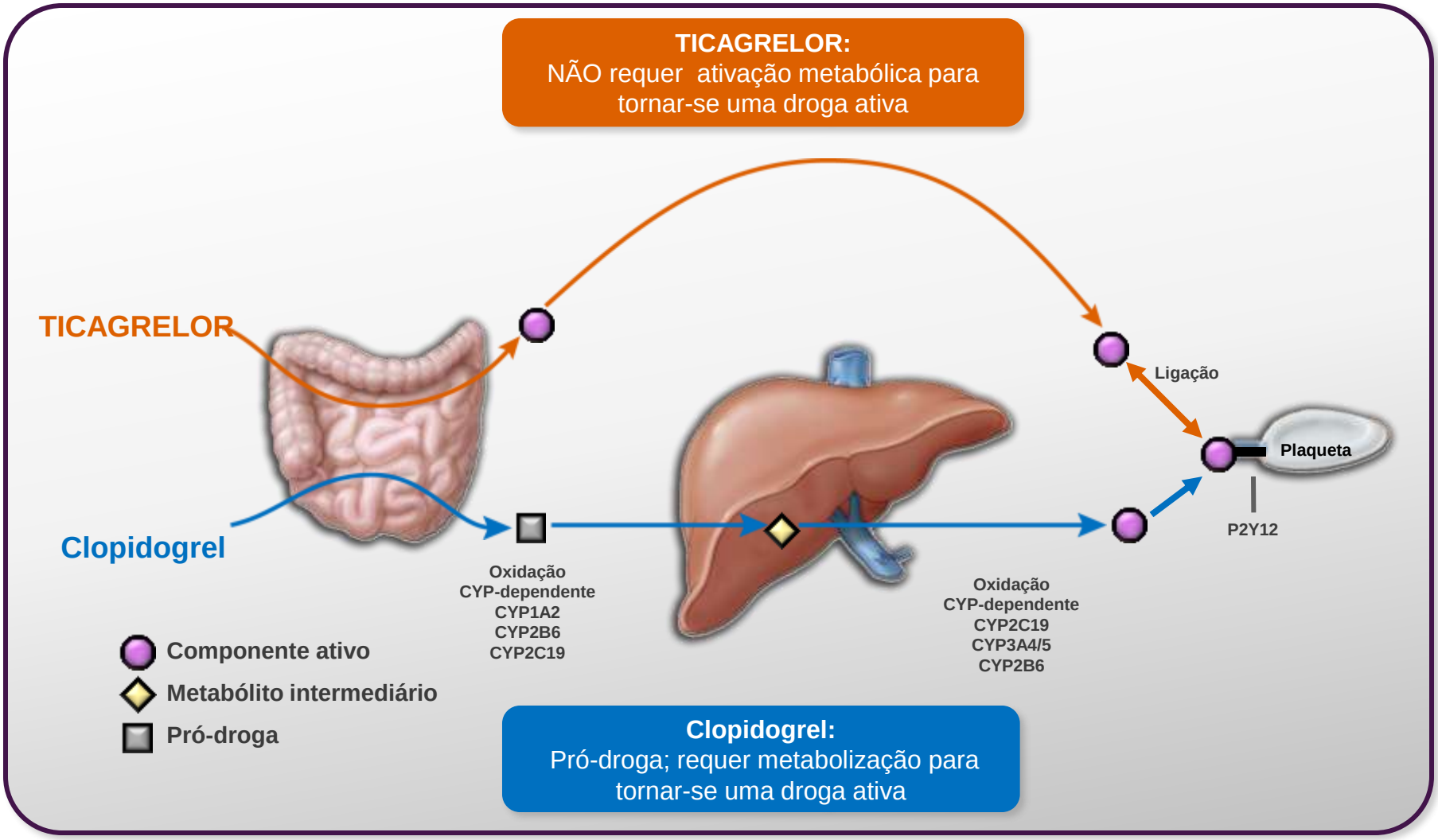
CV Death / MI / CVA / TIMI Major Bleeding



Wiviott SD et al. NEJM 2007;357:2001-15

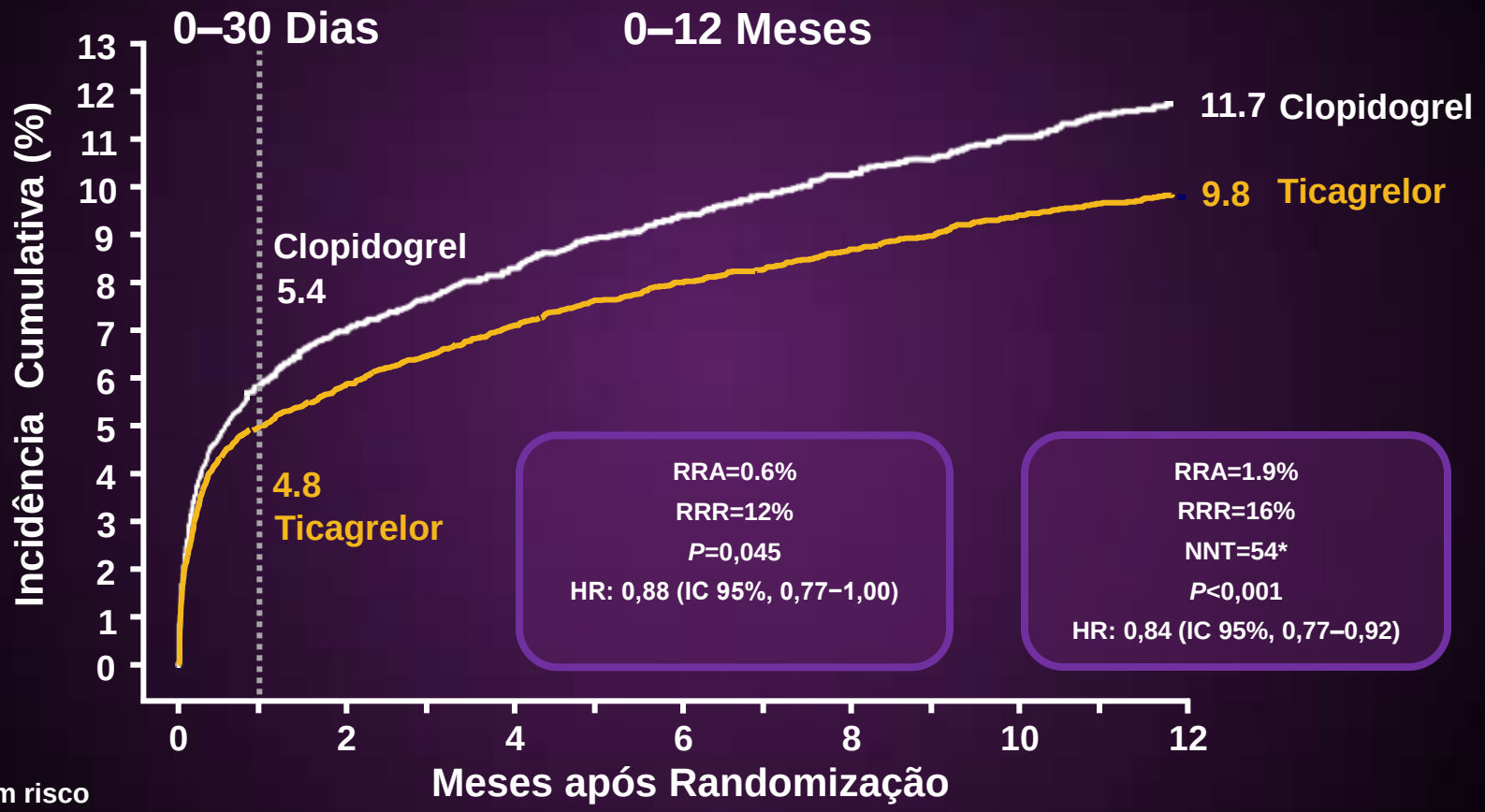

PLATO
TM

Ticagrelor :
Não requer metabolização hepática para ativação



Adaptado de Schomig A. *N Engl J Med*. 2009;361:1108–1111.

PLATO: Desfecho Primário de Eficácia
(Composto de Morte CV, IM ou AVC)

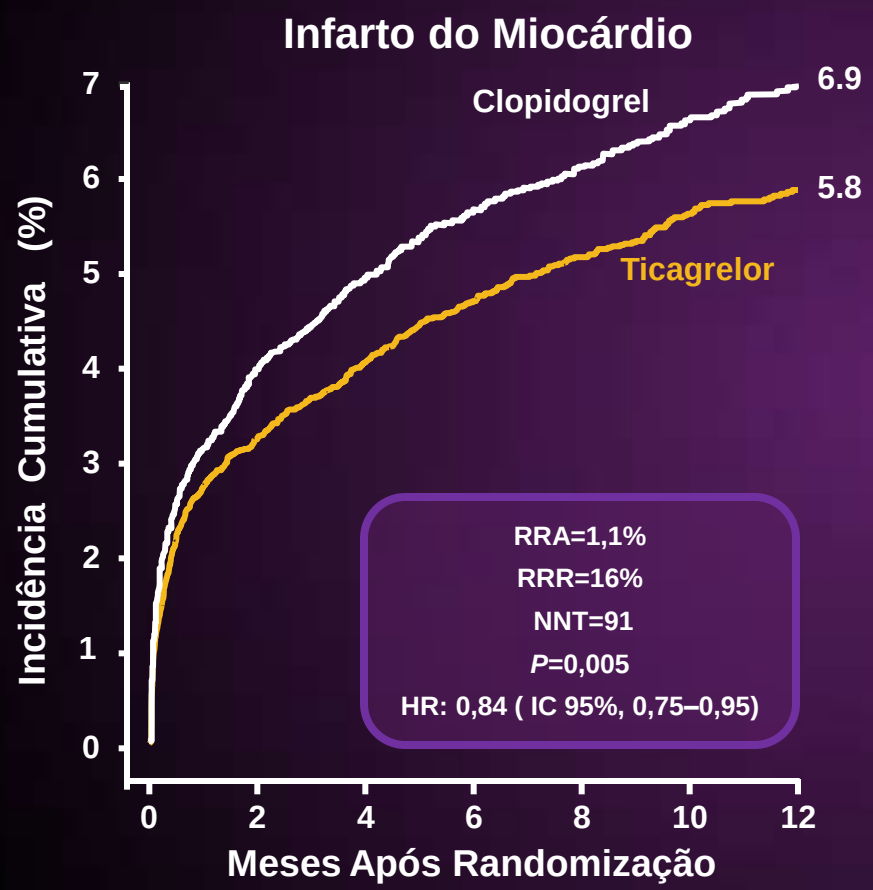


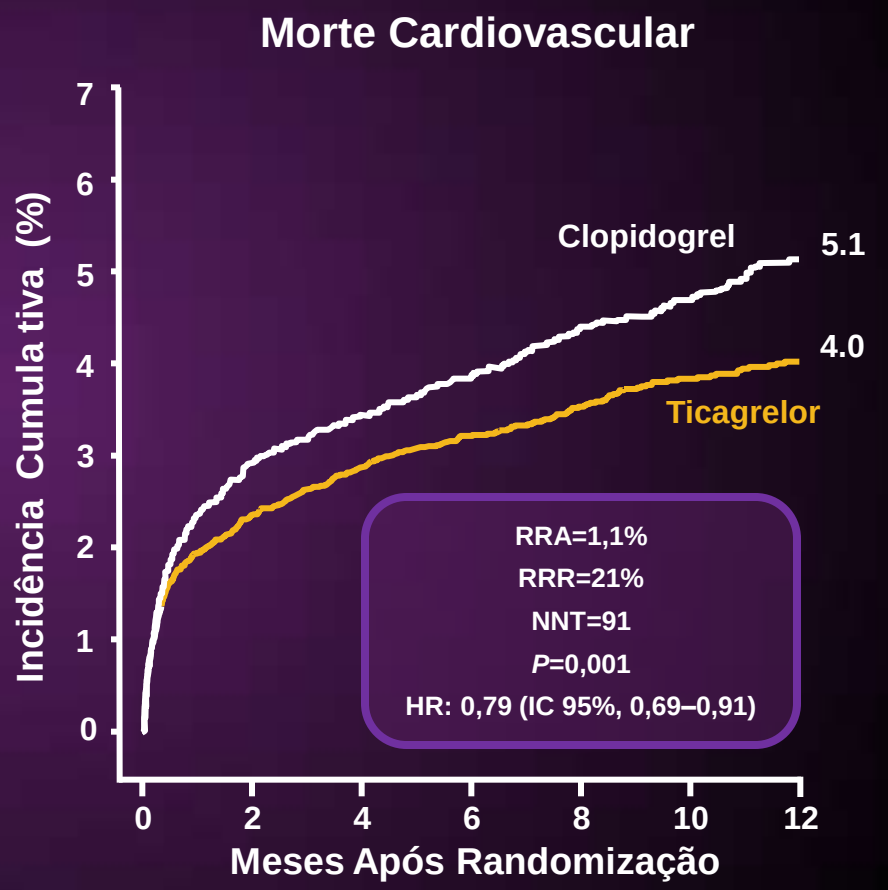
No. em risco							
Ticagrelor	9.333	8.628	8.460	8.219	6.743	5.161	4.147
Clopidogrel	9.291	8.521	8.362	8.124	6.650	5.096	4.047

Ambos os grupos incluem AAS.
*NNT em um ano.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

PLATO: Desfechos Secundários de Eficácia



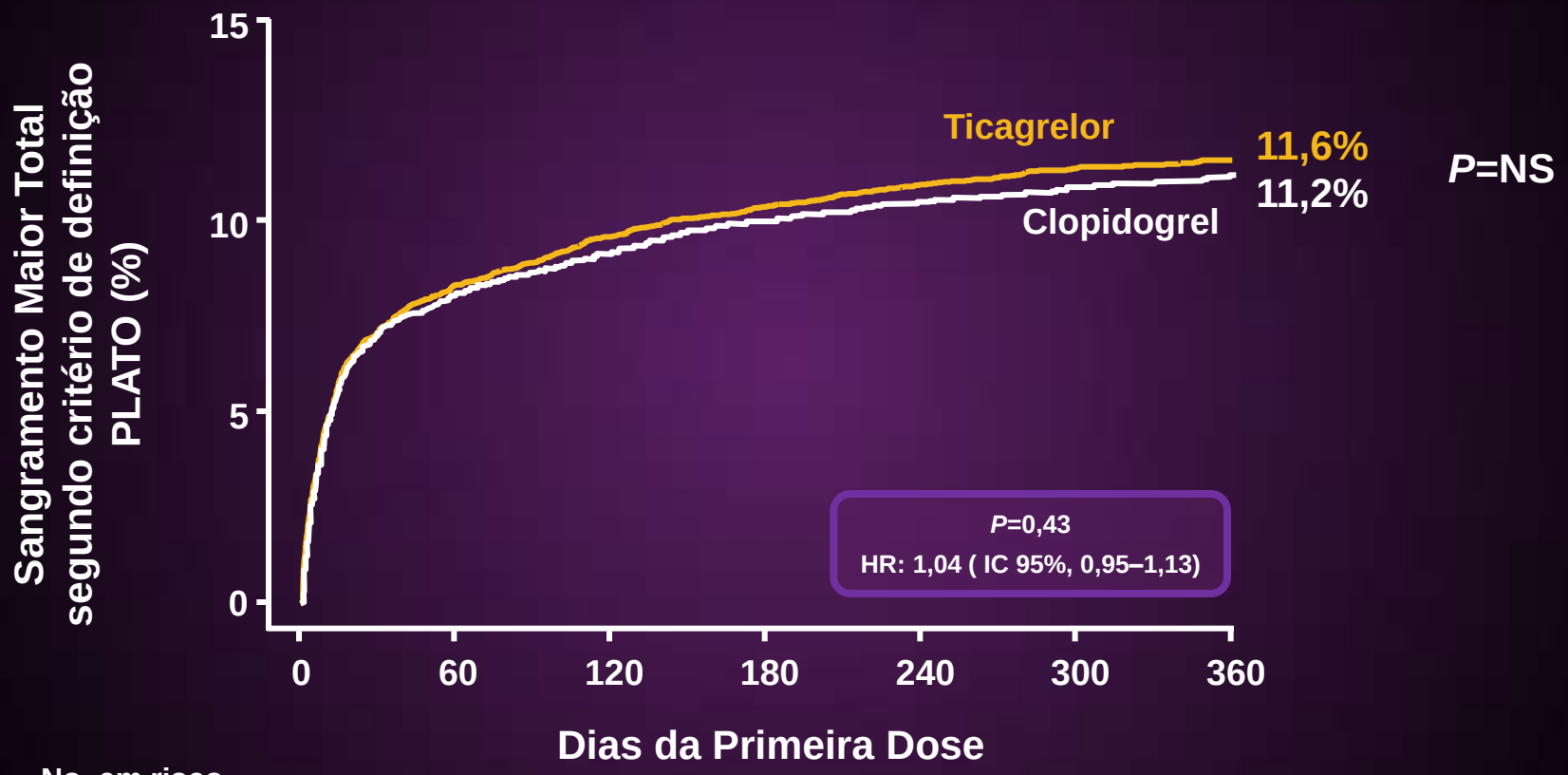


Taxa de AVC para ticagrelor não foi diferente de clopidogrel (1,3% vs 1,1%), *P*=0,225

Ambos os grupos incluiram AAS

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057. Supplement.
BRILIQUE: Summary of Product Characteristics, 2010.

PLATO: Desfecho Primário de Segurança

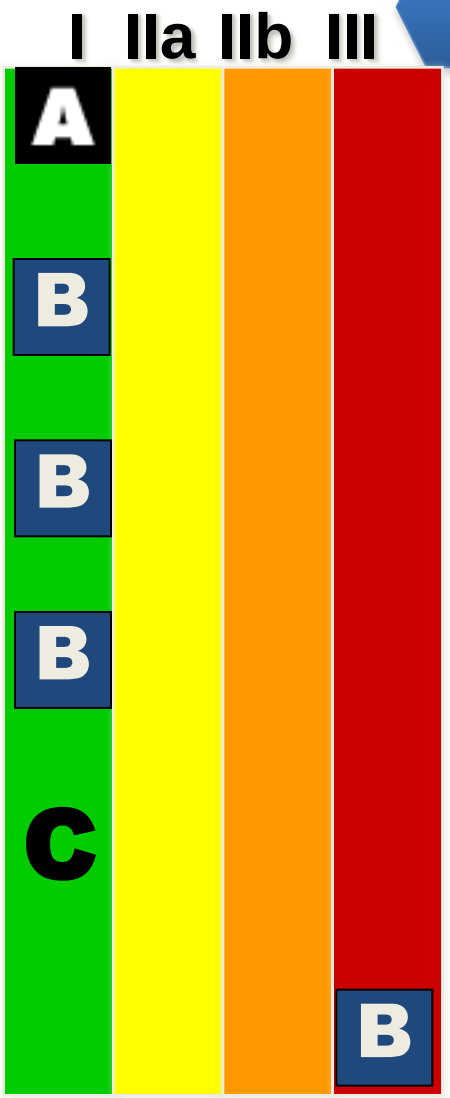


No. em risco							
Ticagrelor	9.235	7.246	6.826	6.545	5.129	3.783	3.433
Clopidogrel	9.186	7.305	6.930	6.670	5.209	3.841	3.479

Ambos os grupos incluiram AAS

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

Guidelines ESC 2010 –Anticoagulant



Fondaparinux (safety/efficacy)

Fondaparinux + UFH (PCI)

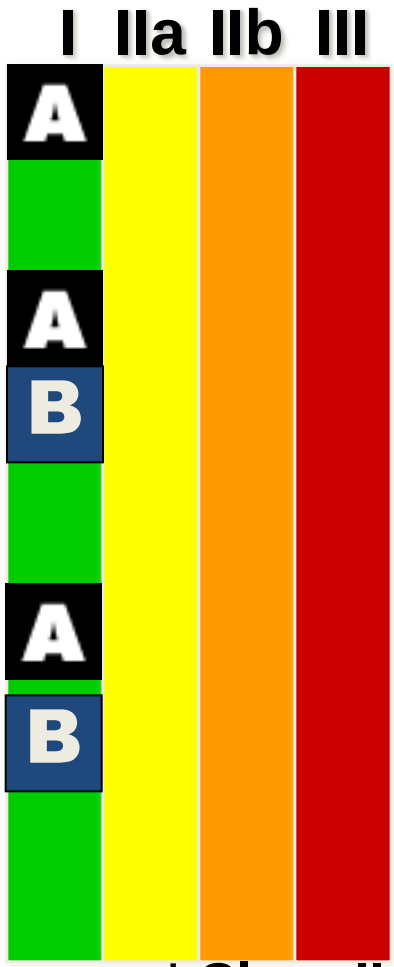
Enoxaparin (if Fdpx not available)

Bivalirudin+ GPIIb/IIIa (Emerg + ↑ Bleeding)

UFH* (if only available)

Heparins crossover

ACC-AHA Guidelines 2007 + 2011 -Anti-Platelet



Anticoagulant therapy added ASAP

For an invasive strategy-

Enoxaparin or UFH

Bivalirudin

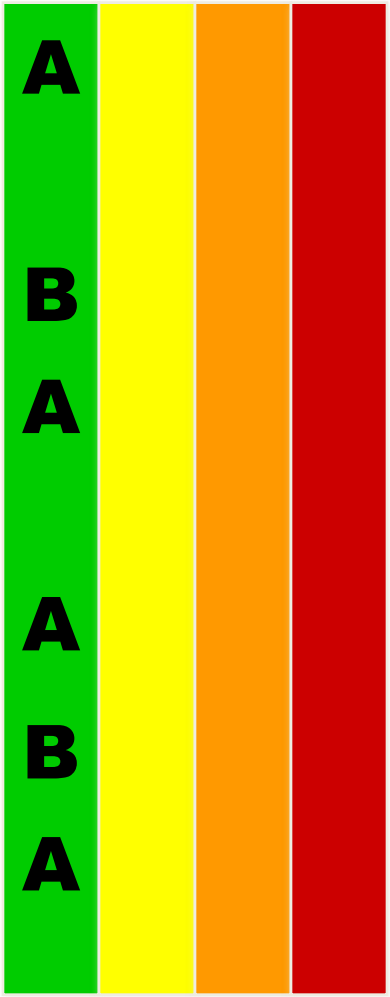
For a conservative strategy-

Enoxaparin, or UFH*

Fondaparinux, esp. if increased risk of bleeding

*** Class IIA: Enoxaparin or fondaparinum preferred over UFH**

ACC-AHA Guidelines 2007 + 2011 -Anti-Platelet



Aspirin ASAP

Before PCI

Clopidogrel

GP IIb/IIIa (small molecule preferred)

During PCI

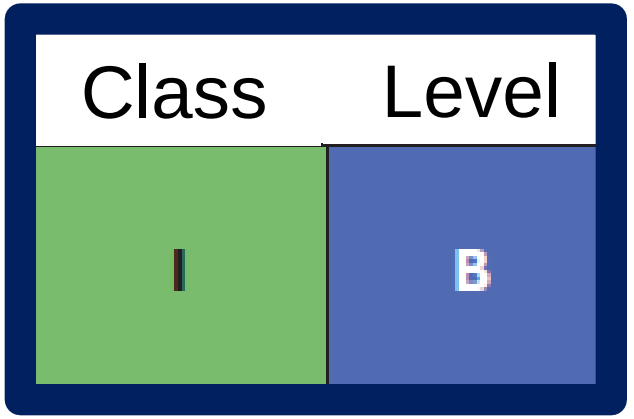
Clopidogrel

Prasugrel

GP IIb/IIIa inhibitor

Prasugrel

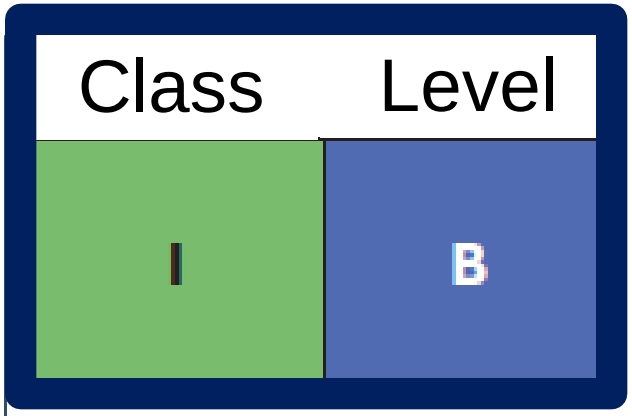
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of lifethreatening bleeding or other contraindications



Diretrizes(SCA) - ESC 2010

Ticagrelor

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)



Diretrizes(SCA) - ESC 2010

Upstream GPIIb/IIIa antagonism

In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low

Class	Level
IIb	C

GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy

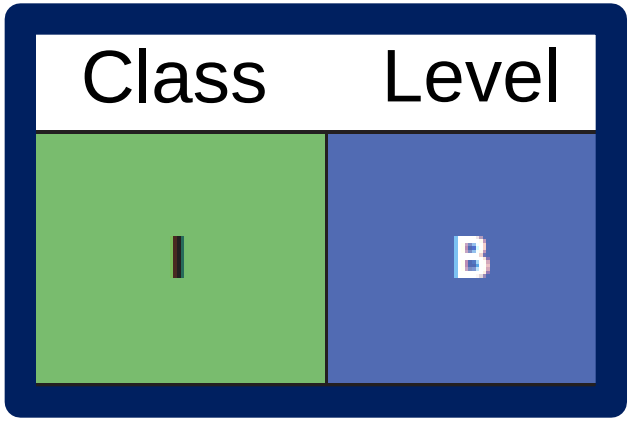
Class	Level
III	A

GP IIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively

Class	Level
III	A

Bivalirudin vs GPIIb/IIIa antagonists

Bivalirudin plus provisional GP IIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GPIIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding



Conclusions:

1- Association of anticoagulants and ASA are basic principle in treating ACS patients

2- Depending on the current local practice dual anti-platelet therapy should be given prior to angiographic definition; if so ticagrelor or clopidogrel should be preferable over prasugrel.

3- The balance between ischemia prevention and bleeding risk is mandatory in choosing a more powerfull drug combination.

4-Fondaparinux (anti-Xa) and bivalirudin(DTI) not associated to GPI, showed a bleeding risk reduction in RCT and are potentially options when considering a good balance risk/benefit ratio.

5- The “upstream”use of GPI is an exception and reserved for high risk ischemia and low bleeding risk group.