SOLACI CACI '14
ARGENTINA
In partnership with TCT

Actividade Pré-Congresso
PROEDUCAR
SOCIEDAD LATINOAMERICANA DE CARDIOLOGIA INTERVENCIONISTA

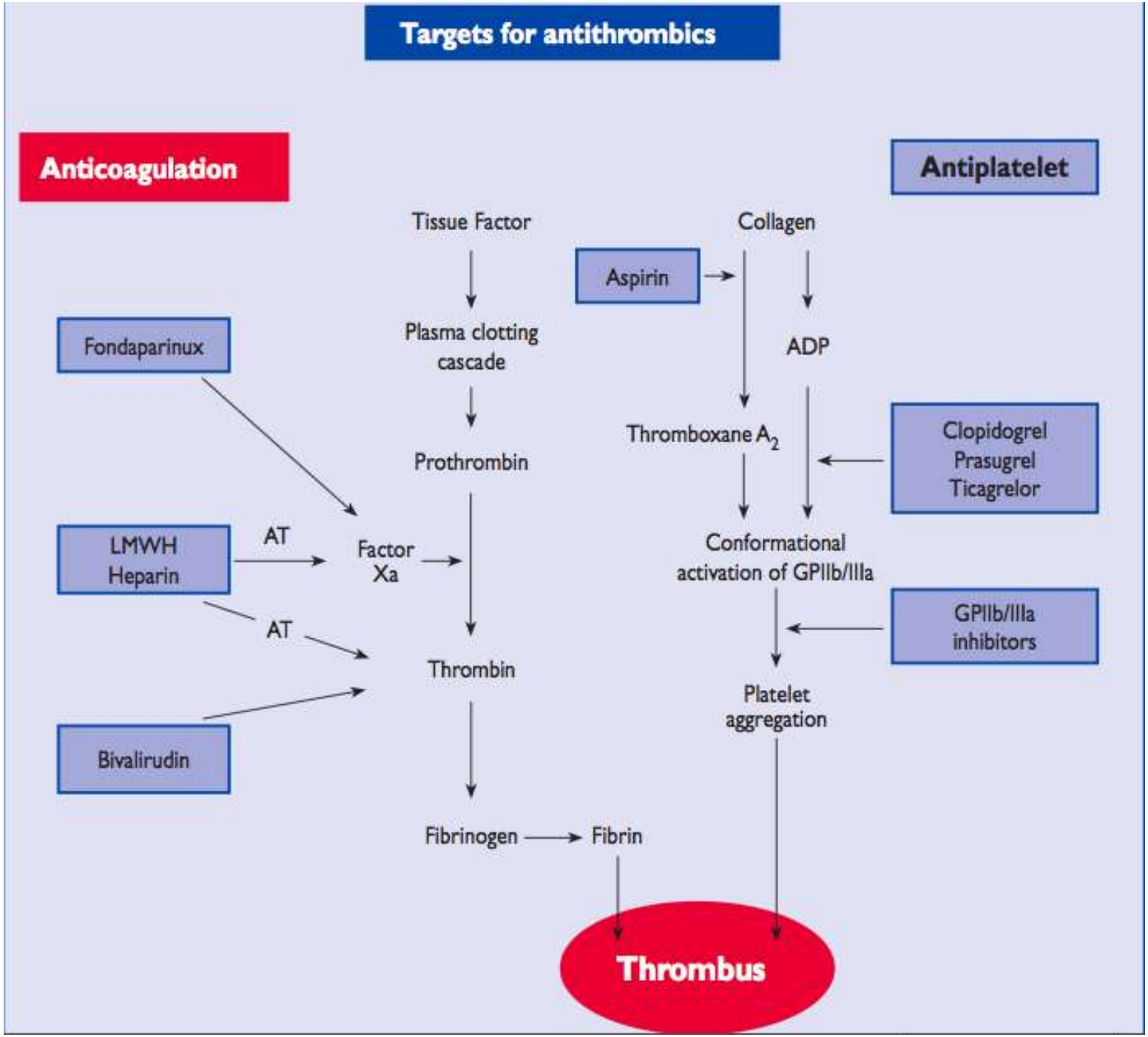
V Curso "José Gabay"
para Intervencionistas em Treinamento

Anticoagulant and antithrombotic therapy in the PCI of NSTE-ACS

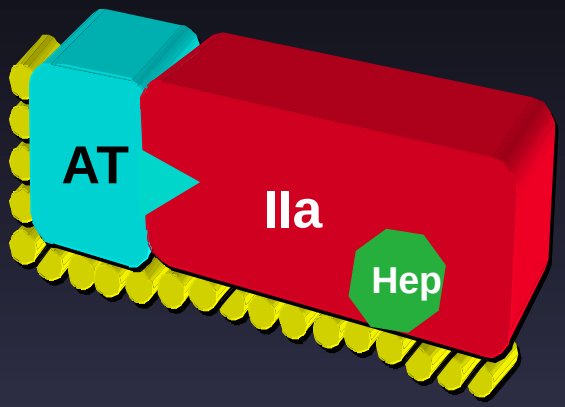
Jamil Abdalla Saad
SOLACI'S PRESIDENT 2013/15
Belo Horizonte – MG / BRAZIL

Anticoagulant and antithrombotic therapy in the PCI of NSTE-ACS

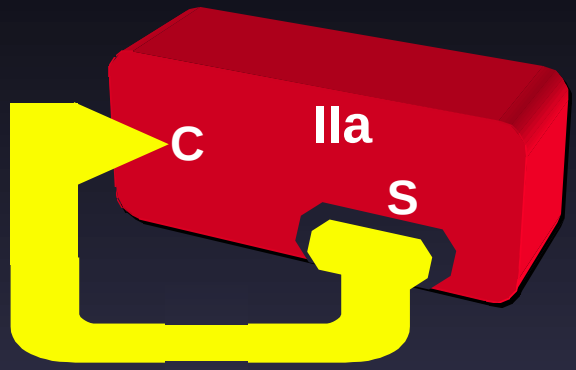
1. Drugs available – Mechanism of action
2. Drugs association
3. RCT
4. Guidelines
5. Conclusions


Targets for antithrombics
Anticoagulation
Antiplatelet
Tissue Factor
Collagen
Aspirin
Plasma clotting cascade
ADP
Fondaparinux
Thromboxane A_2
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

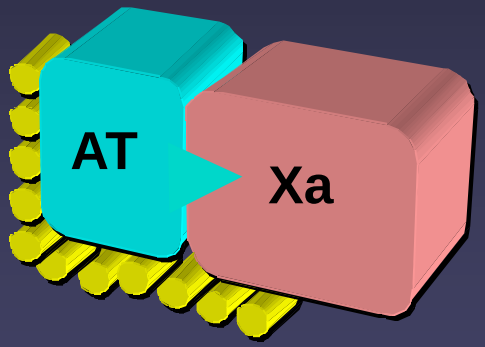
Four Anticoagulant Choices



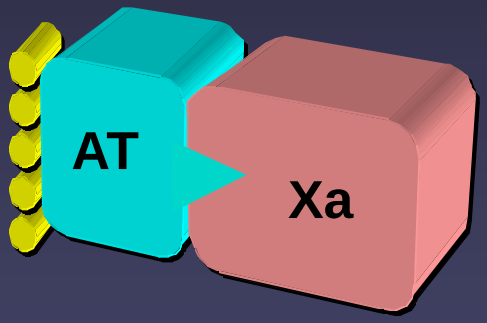
UFH



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.

$P2Y_{12}$ 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

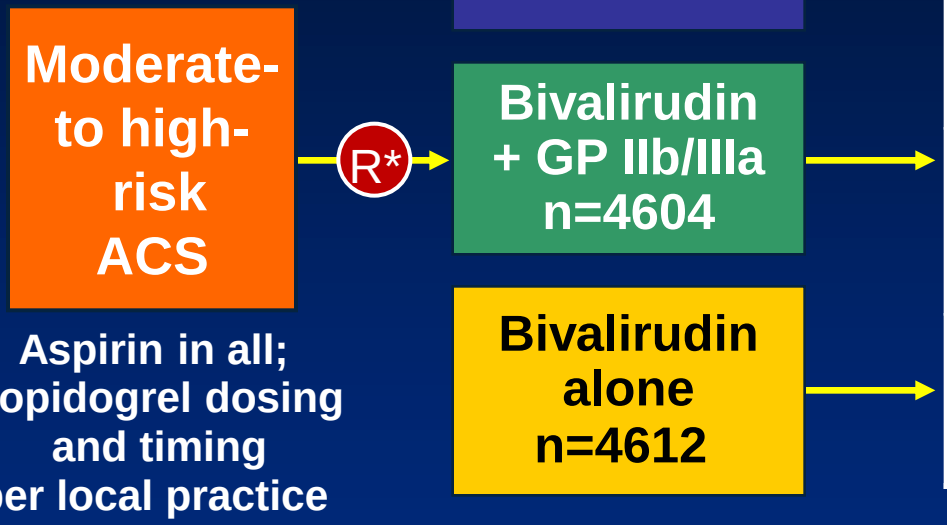
- Fondaparinux is a synthetic analog of the pentasaccharide sequence in heparin
- **The efficacy and safety of subcutaneous fondaparinux** 2.5 mg daily was **compared with routine treatment with enoxaparin** 1 mg/kg body weight for 8 days or until hospital discharge in the **OASIS-5** trial and was found 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)

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%

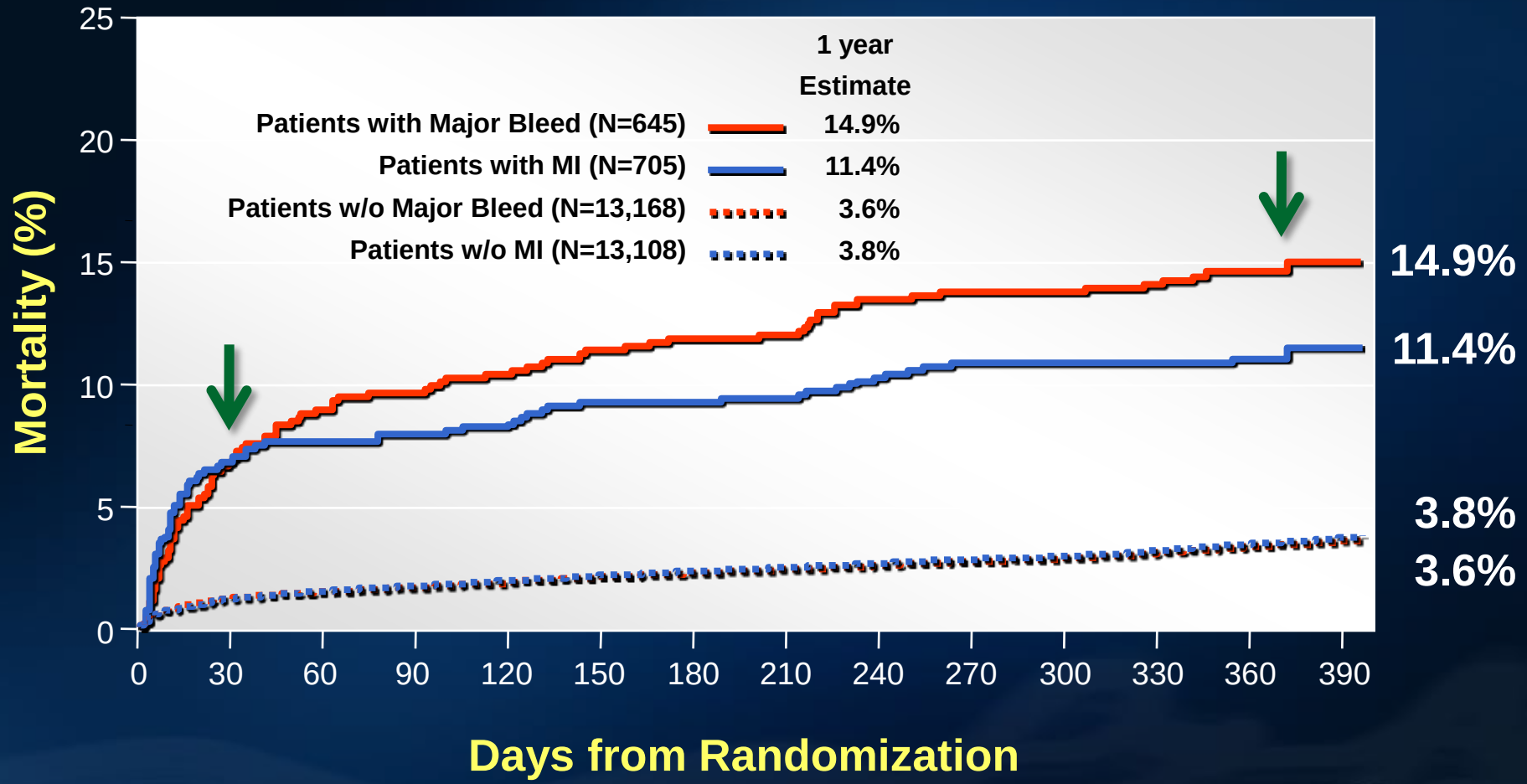
End points: death, MI, and unplanned revascularization for ischemia (30 days and 1 year); major bleeding (30 days); composite of the above (30 days)

*Stratified by preangiography thienopyridine use or administration.

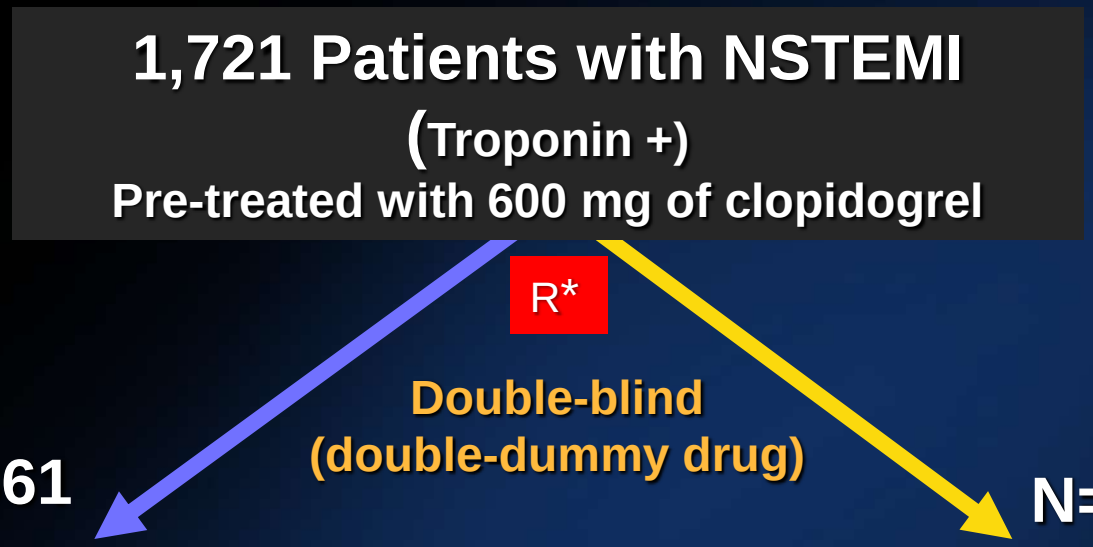
Stone GW, et al. *N Engl J Med*. 2006;355(21):2203-2216.

ACUITY (N=13,819)

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



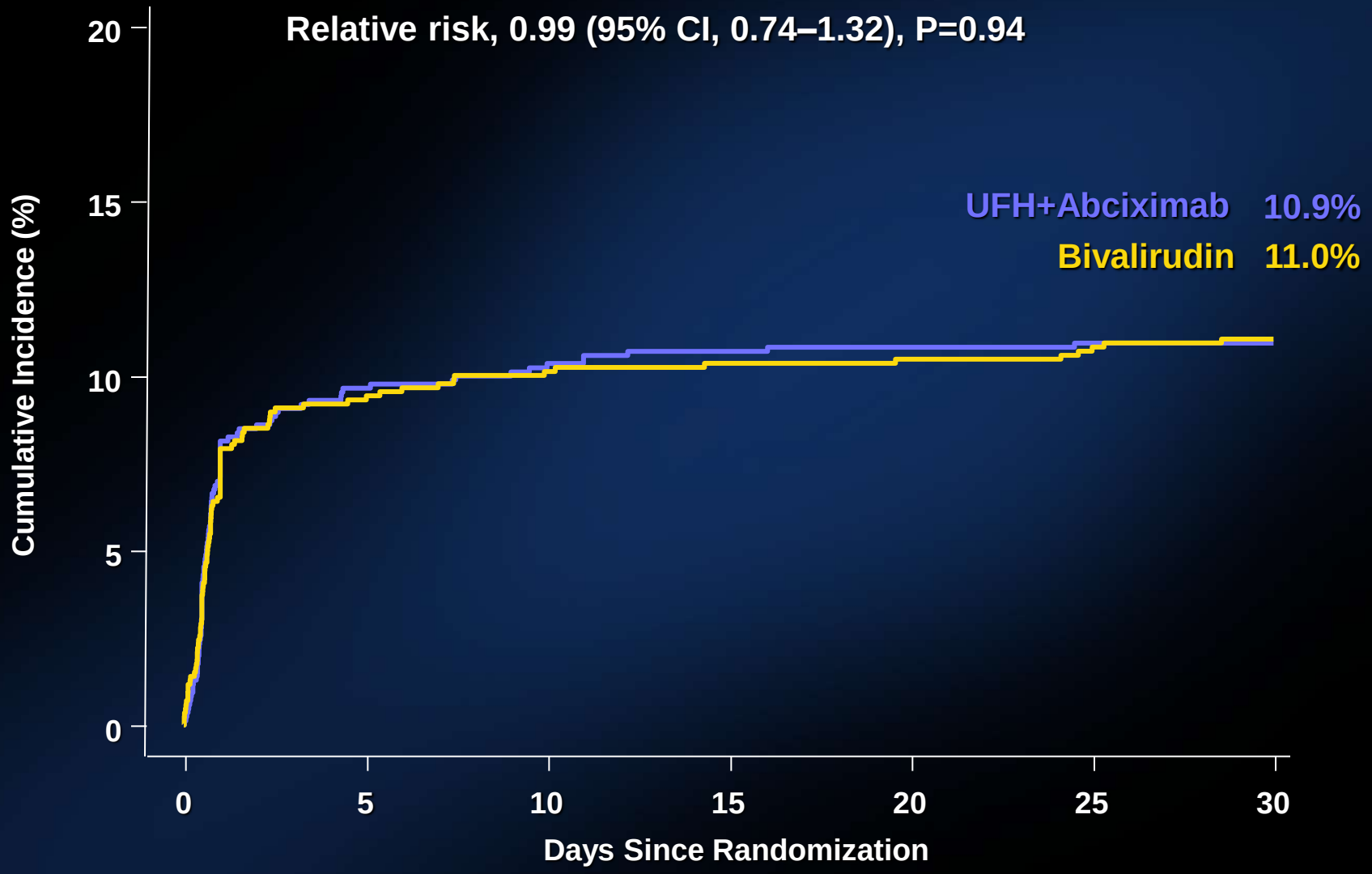
ISAR REACT 4 Design



Slide by C. Michael Gibson, M.S., M.D.

Kastrati et al. N Engl J Med 2011; 365:1980-89.

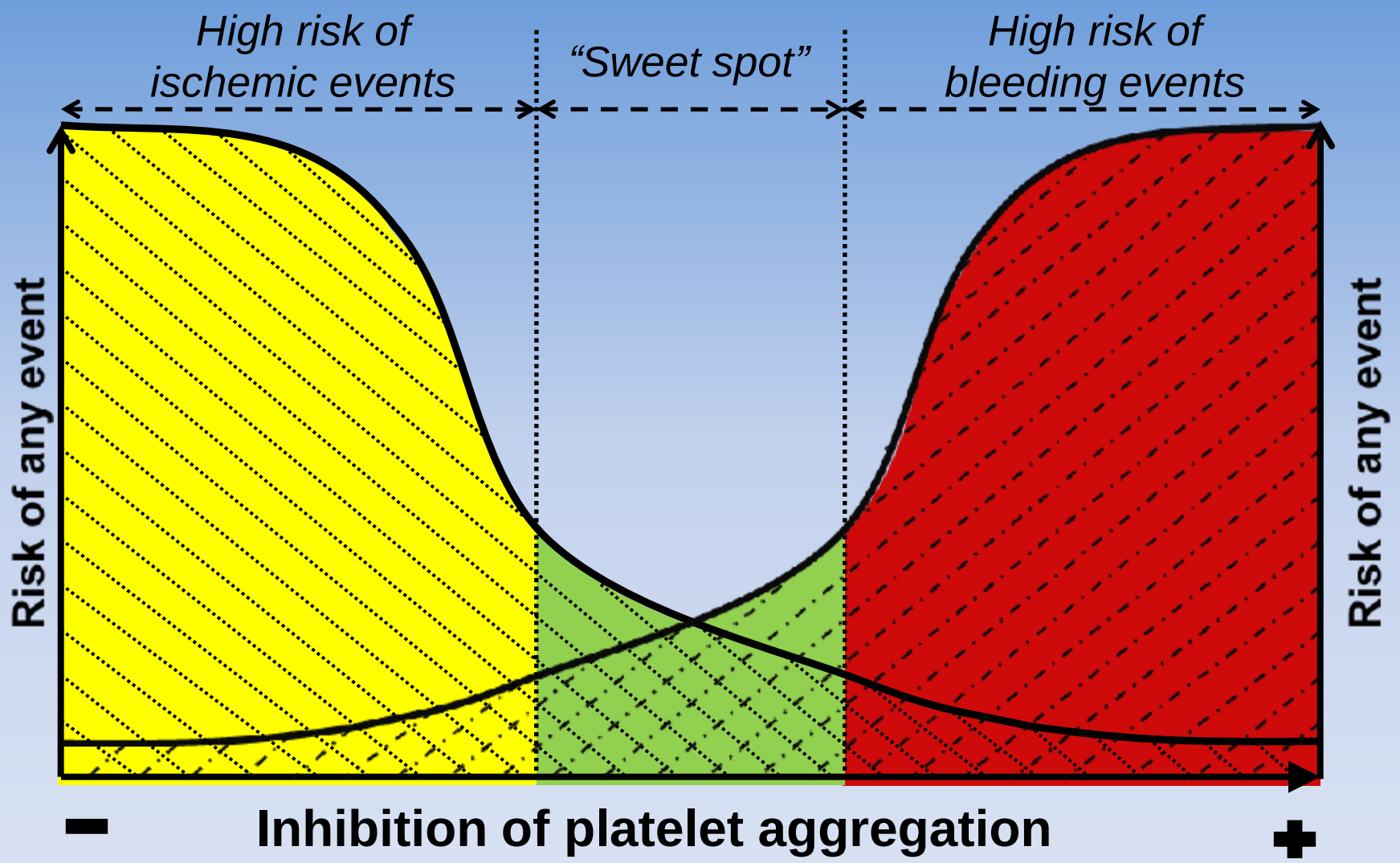
ISAR React 4: Primary Endpoint
Death, Large MI, uTVR, Major Bleeding



Slide by C. Michael Gibson, M.S., M.D.

Kastrati et al. N Engl J Med 2011; 365:1980-89.

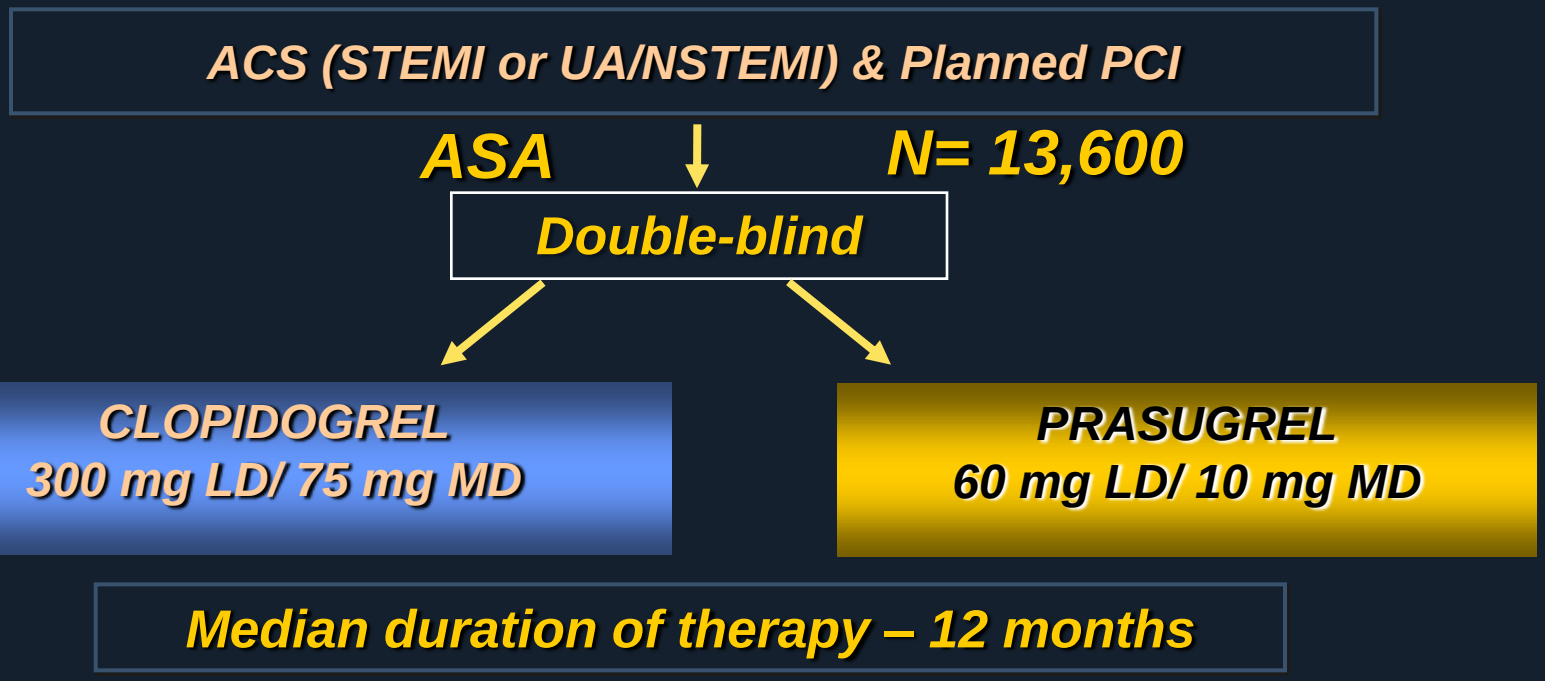
Balancing Safety and Efficacy



From Mehran R. TCT md

Ferreiro & Angiolillo. Thromb Haemost 2010 (in press)

TRITON-Study Design



1º endpoint: CV death, MI, Stroke

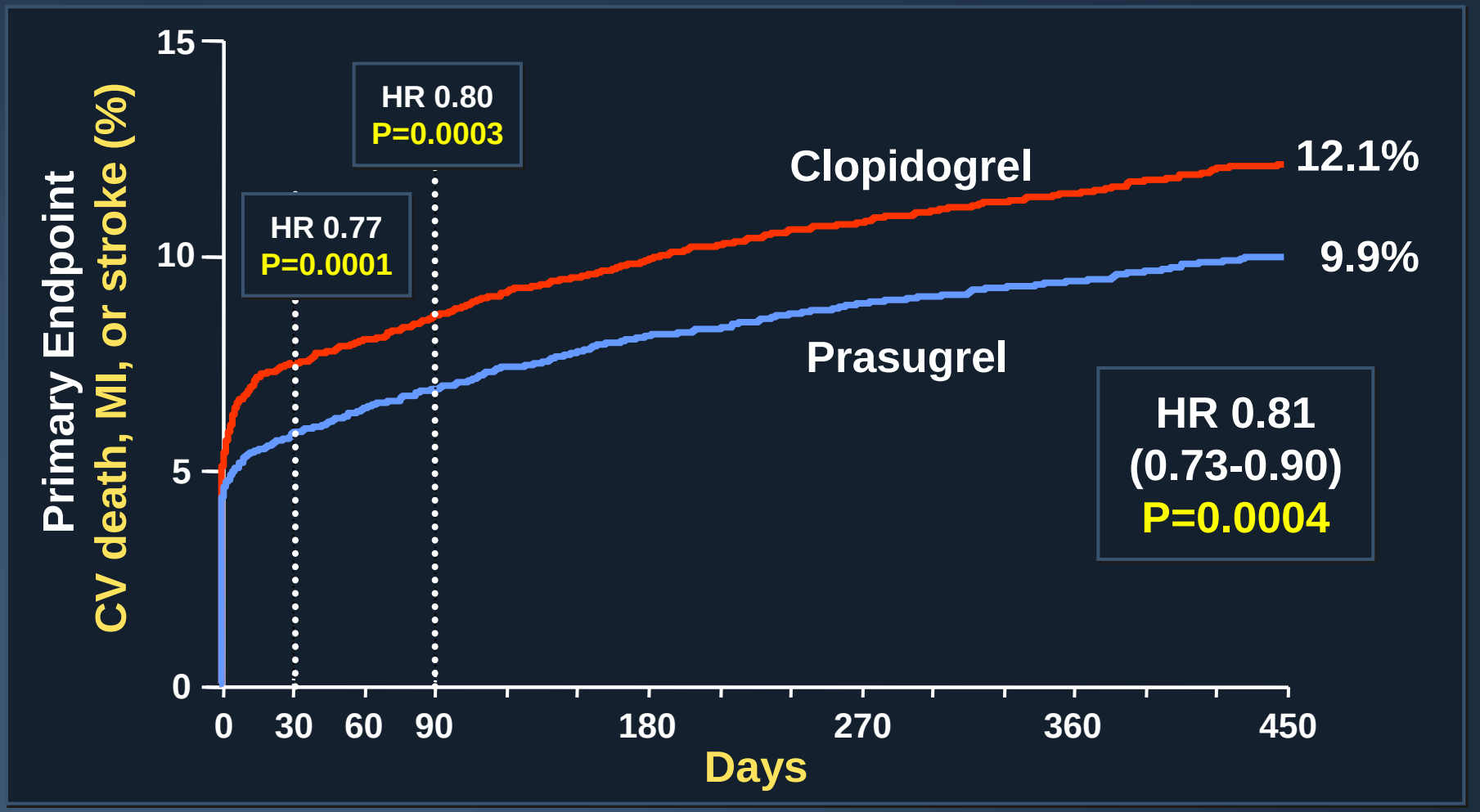
2º endpoints: CV death, MI, Stroke, Rehosp-Rec Isch, CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)

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)

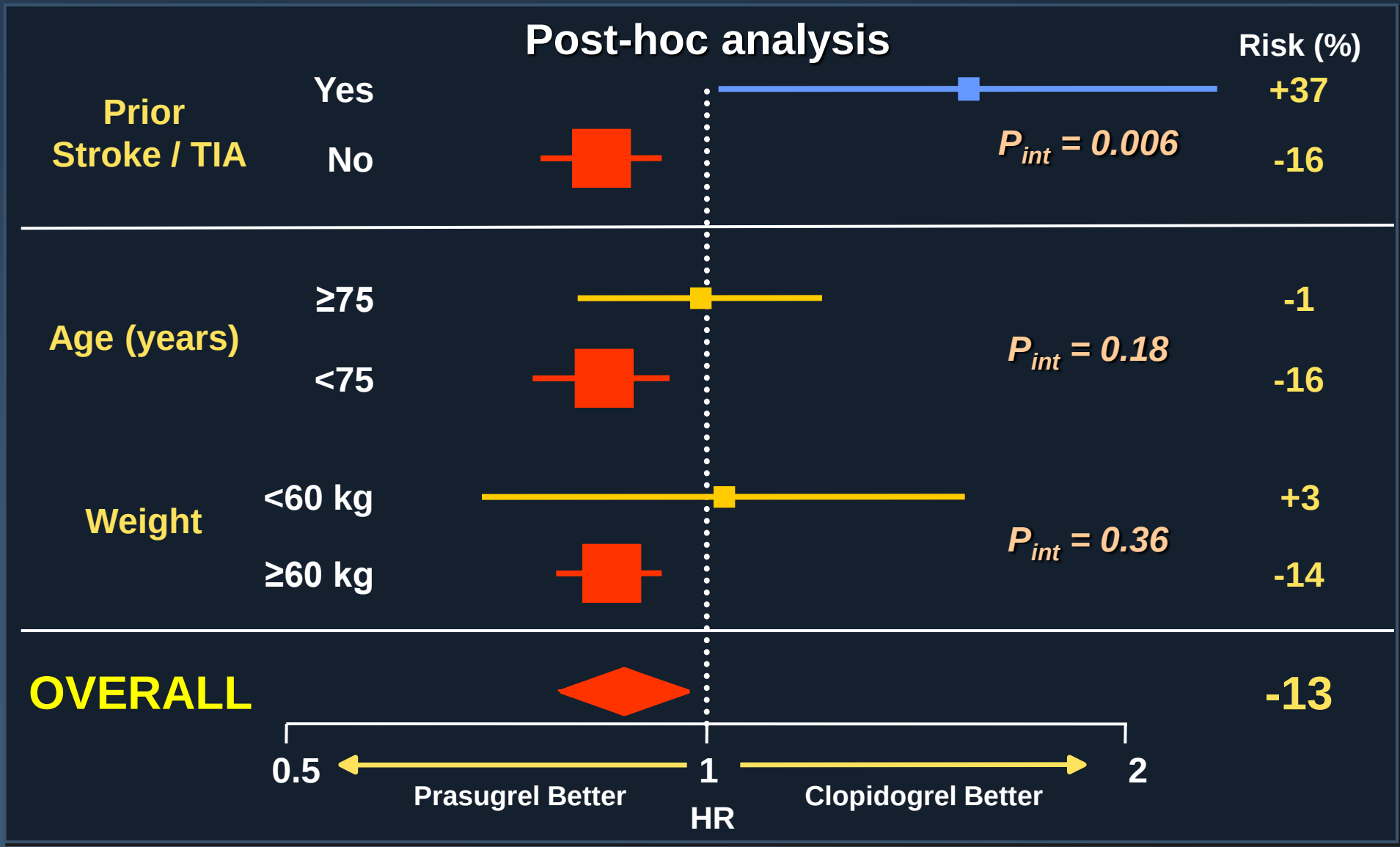


Wiviott SD et al. NEJM 2007;357:2001-15

TRITON TIMI-38

Net Clinical Benefit

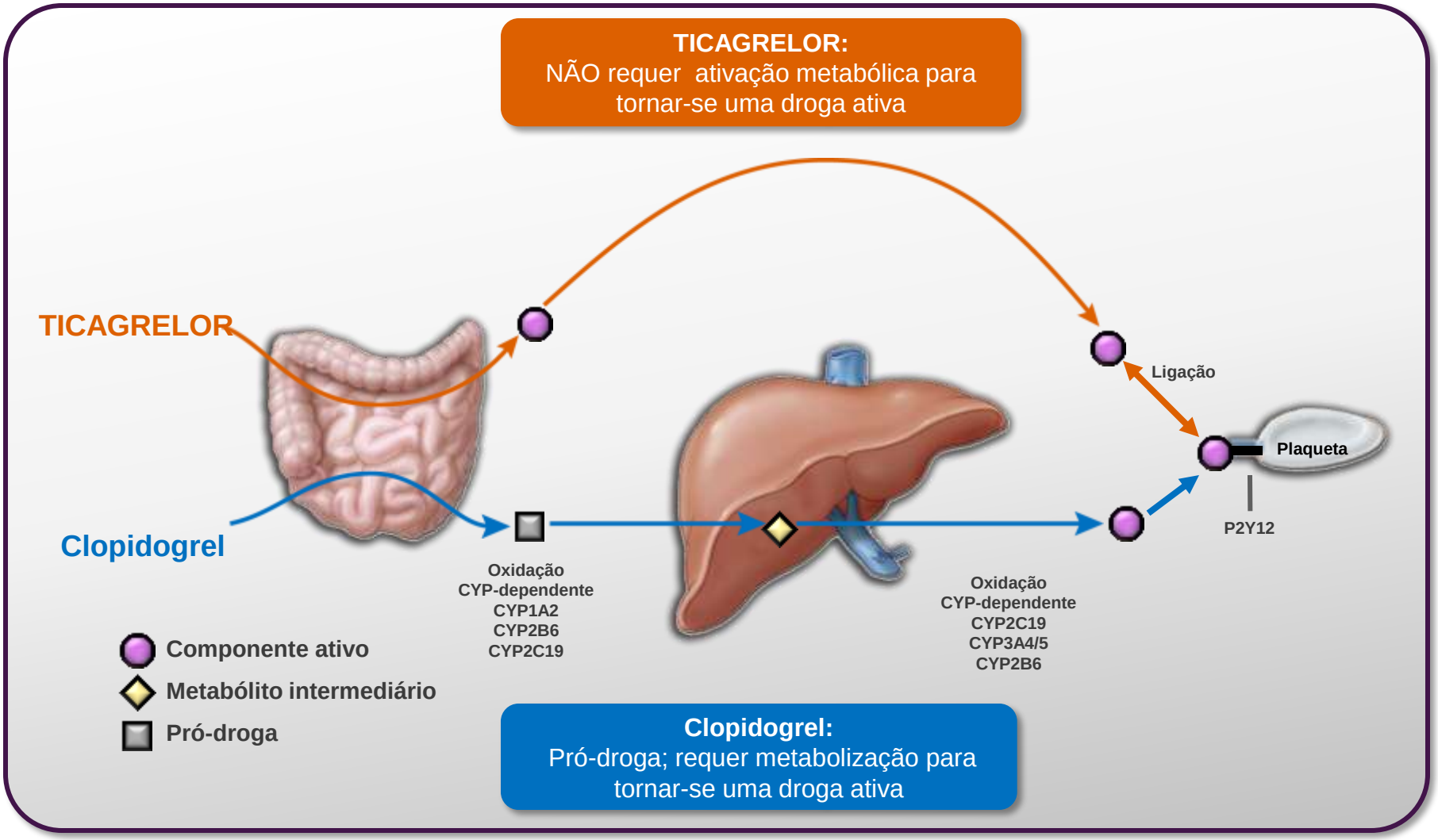
CV Death / MI / CVA / TIMI Major Bleeding



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

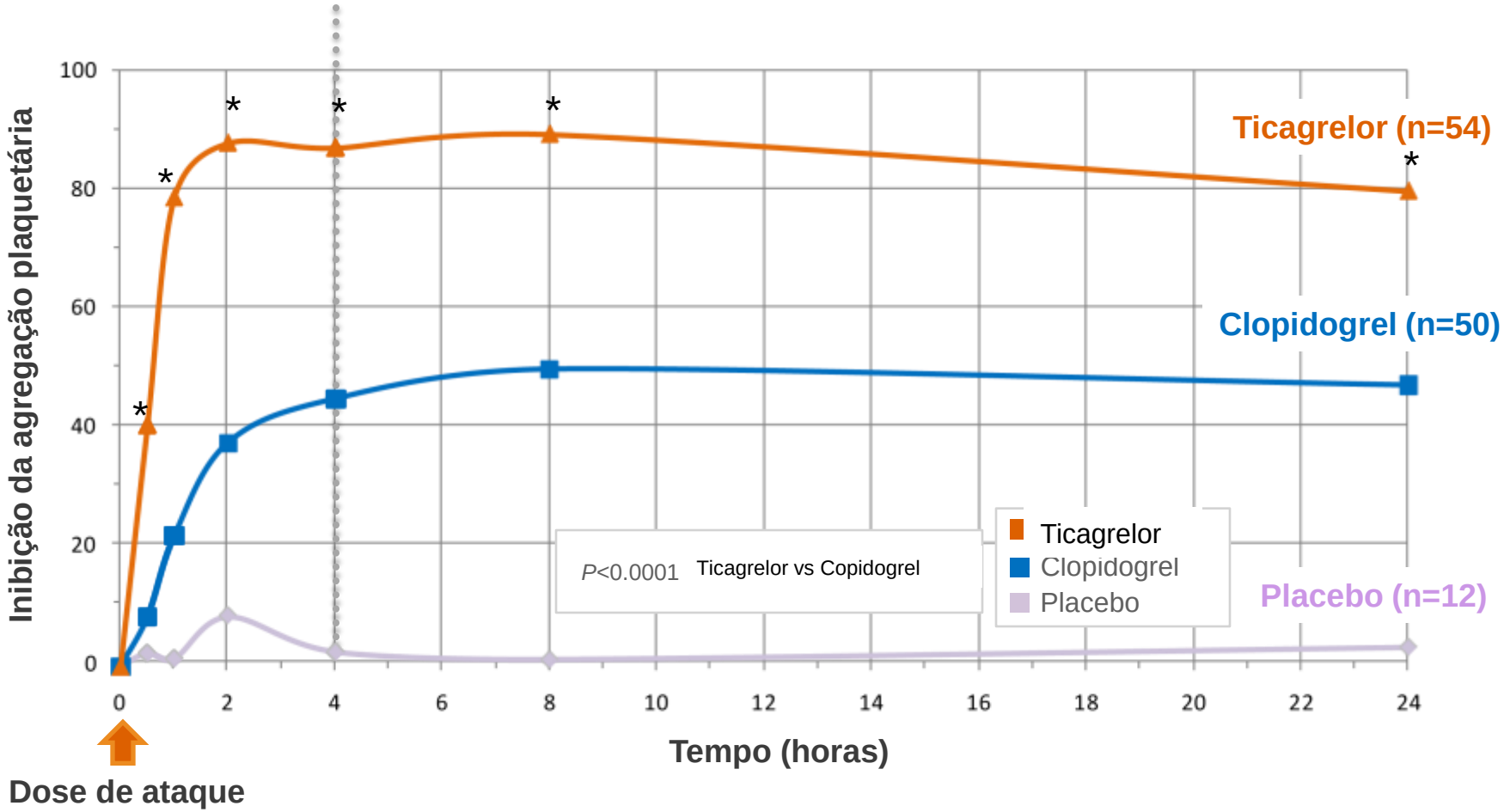

PLATO
TM

Ticagrelor :
Não requer metabolização hepática para ativação



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

Inibição da agregação plaquetária: Inicio de ação

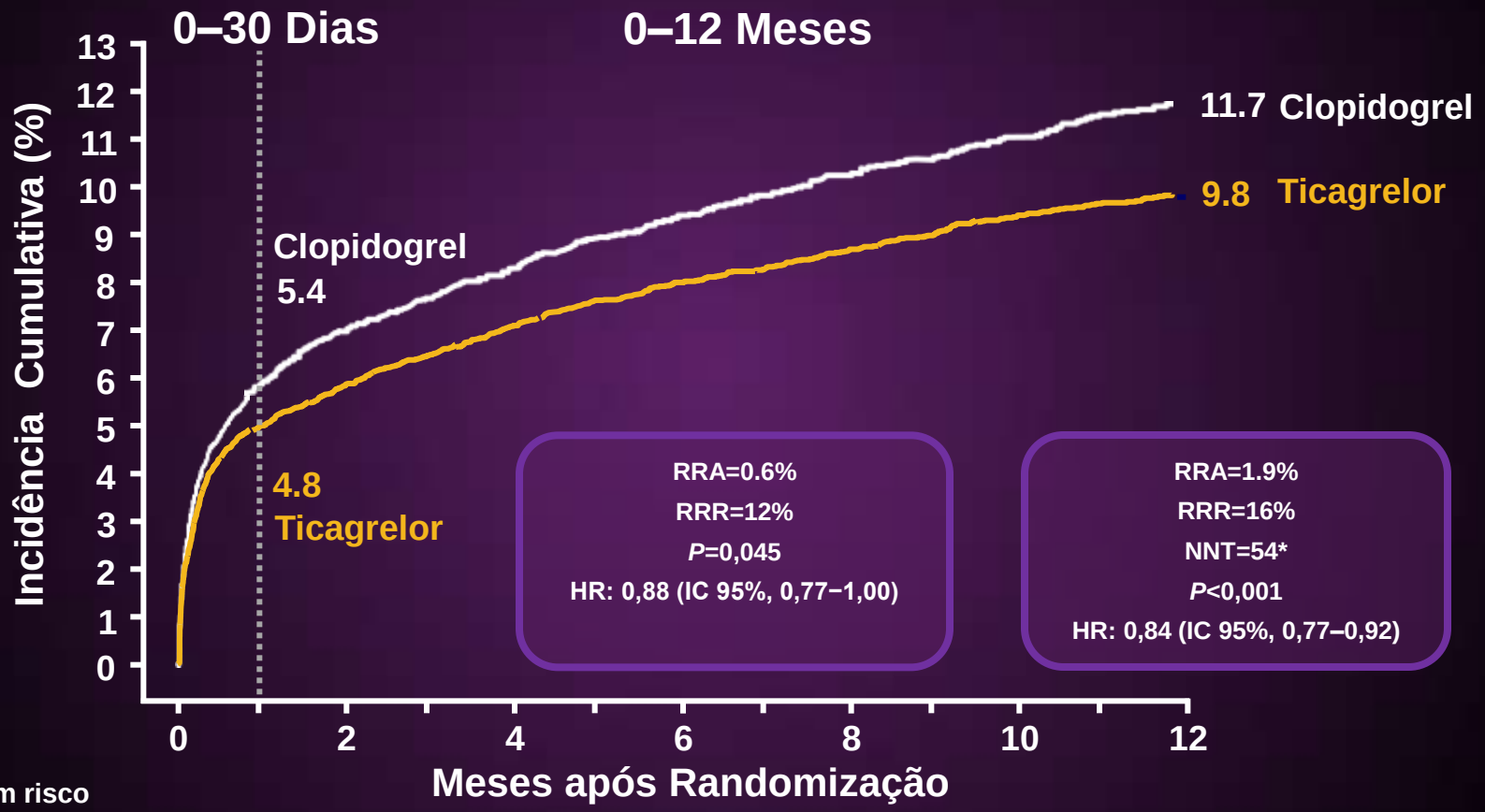


Ticagrelor 180-mg dose de ataque em pacientes com DAC estável
Clopidogrel 600-mg dose de ataque em pacientes com DAC estável

*P<0.0001 Ticagrelor vs Clopidogrel

Adaptado de Gurbel PA, et al. *Circulation.* 2009;120:2577–2585.

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

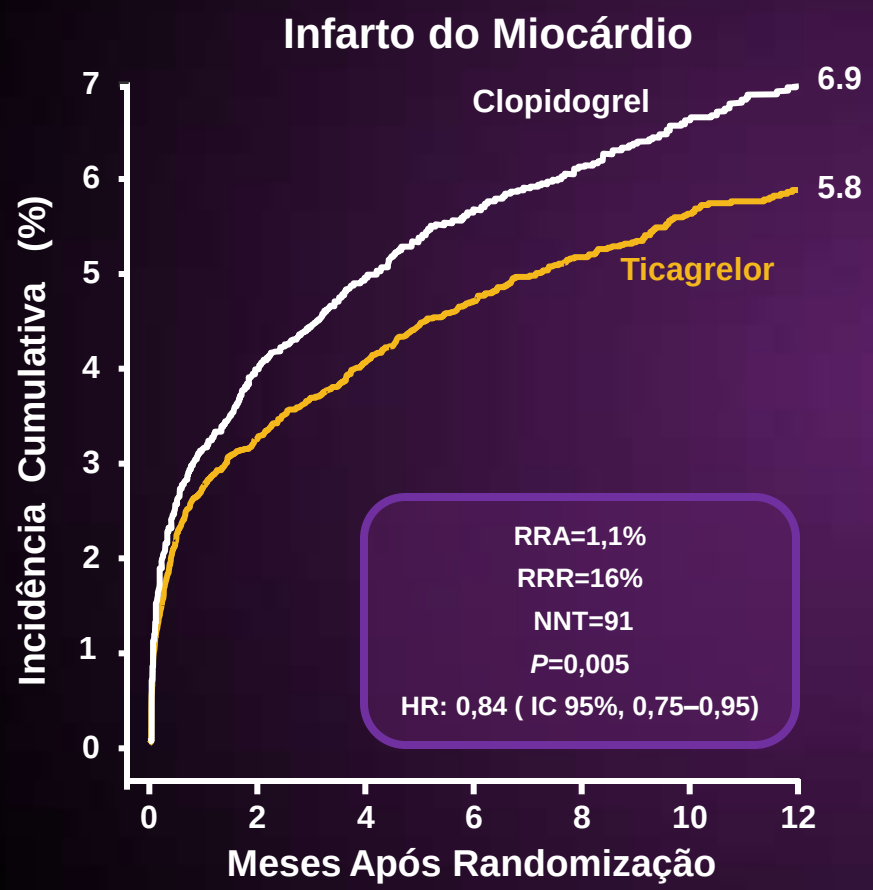


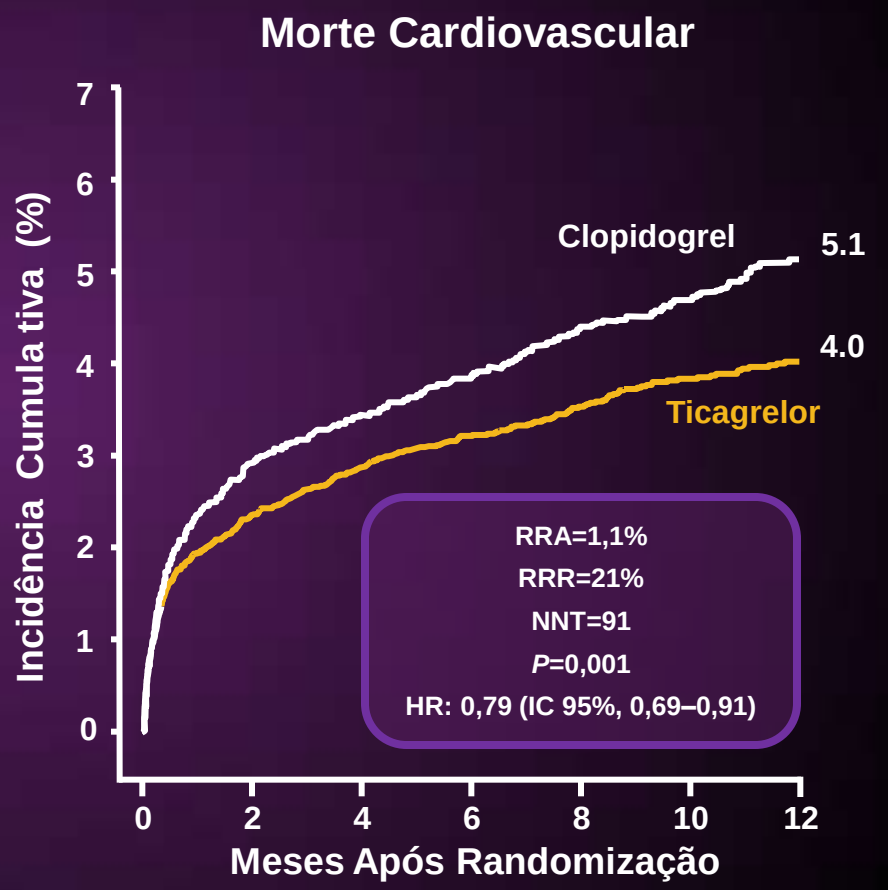
No. em risco							
Ticagrelor	9.333	8.628	8.460	8.219	6.743	5.161	4.147
Clopidogrel	9.291	8.521	8.362	8.124	6.650	5.096	4.047

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



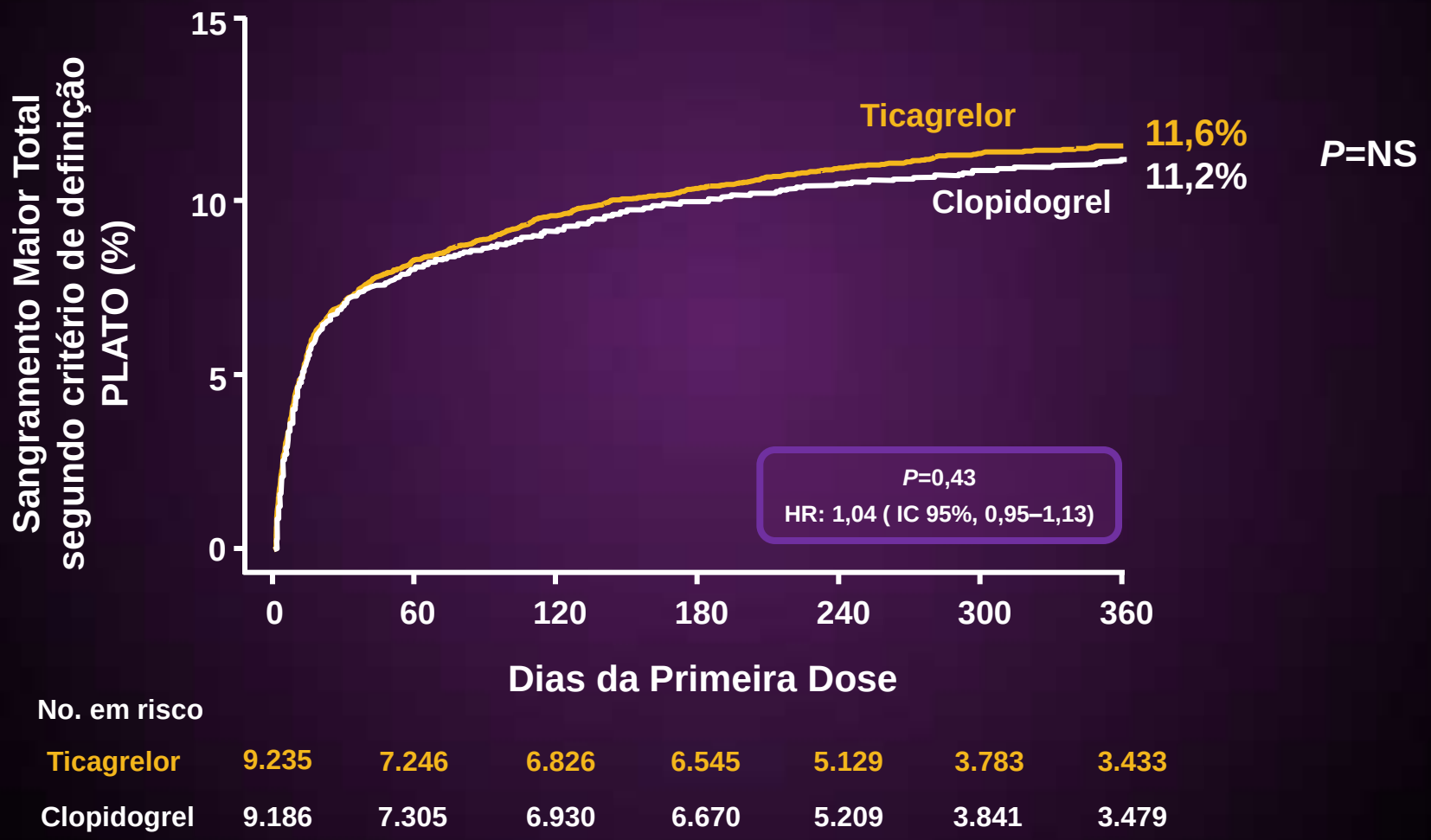


Taxa de AVC para ticagrelor não foi diferente de clopidogrel (1,3% vs 1,1%), *P*=0,225

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.

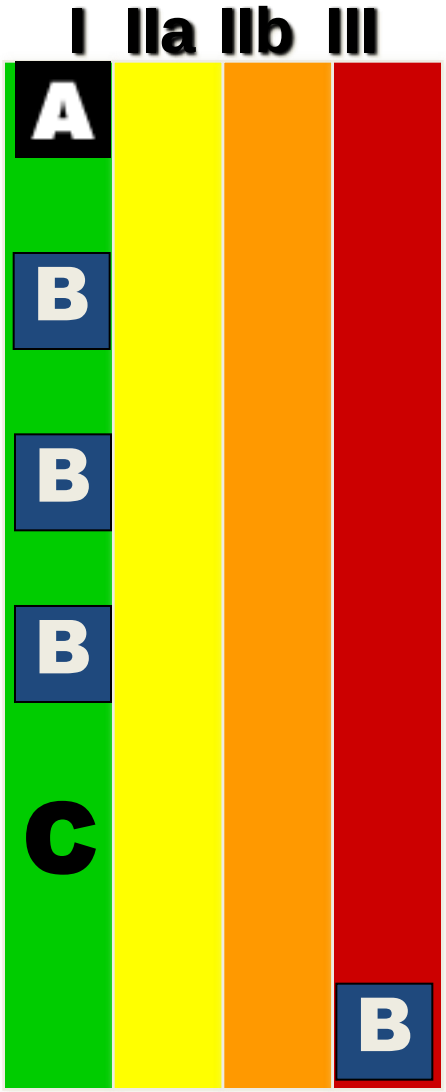
PLATO: Desfecho Primário de Segurança



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)

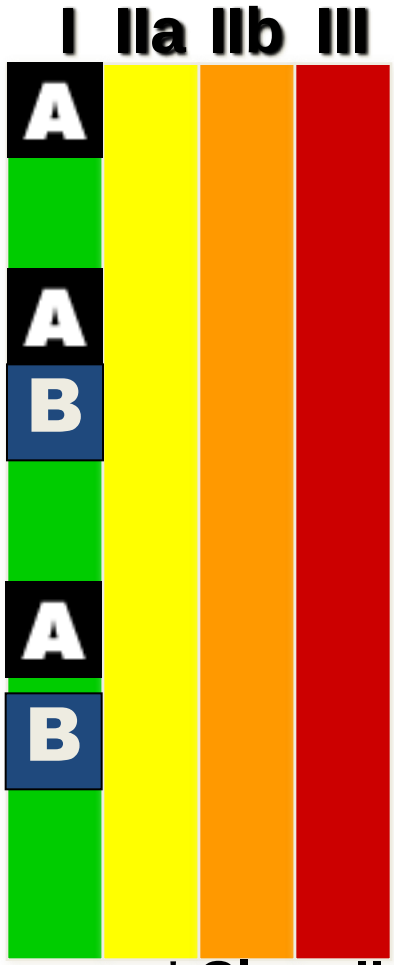
Enoxaparin (if Fdpx not available)

Bivalirudin+ GPIIb/IIIa prov.(Emerg + ⇑Bleeding)

UFH* (if only available)

Heparins crossover

ACC-AHA Guidelines 2007 + 2011 –Anticoagulant



Anticoagulant therapy added ASAP

For an invasive strategy-

Enoxaparin or UFH

Bivalirudin

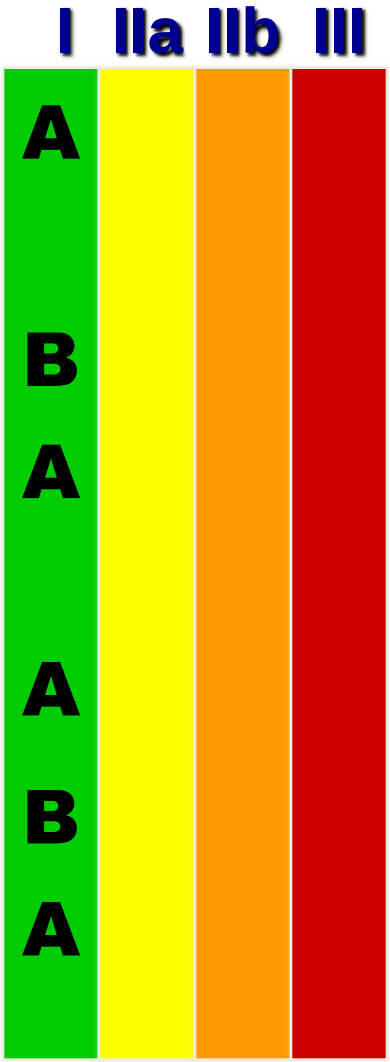
For a conservative strategy-

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)

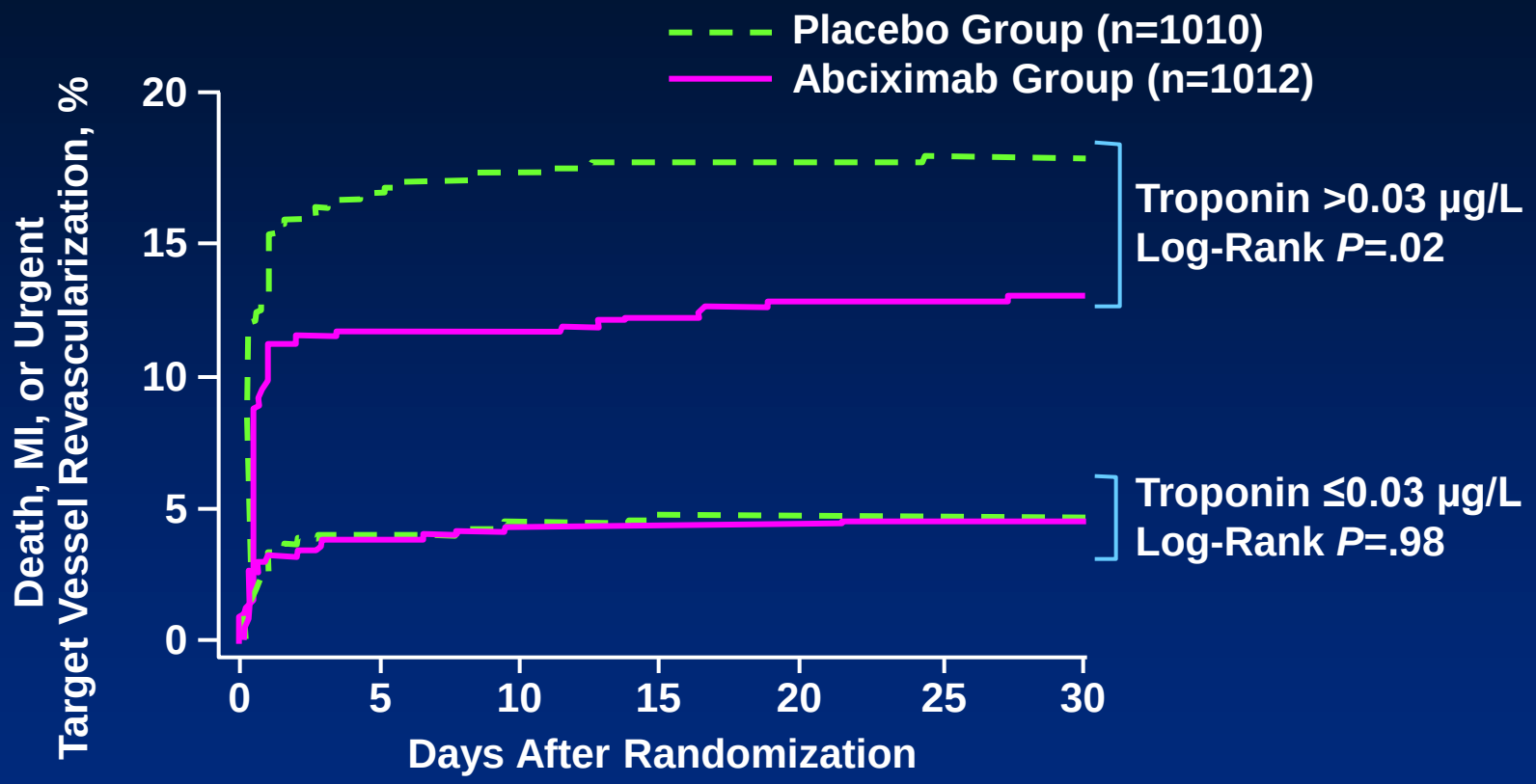
During PCI

Clopidogrel

Prasugrel

GP IIb/IIIa inhibitor (ISAR REACT 2 Tn+)

ISAR-REACT 2: High-Risk ACS Patients Undergoing PCI, Pretreated With ASA, Clopidogrel 600 mg, and UFH

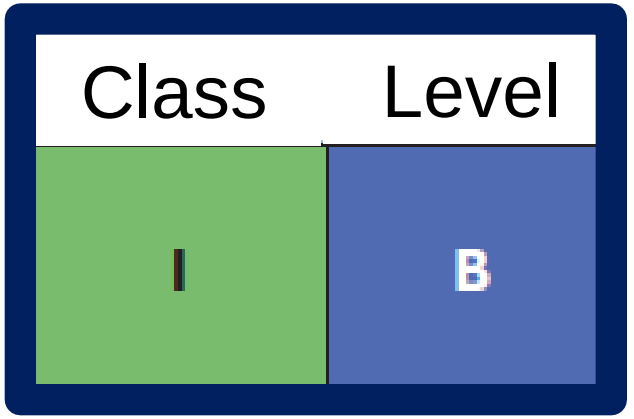


ISAR-REACT 2, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2.

Adapted with permission from Kastrati A, et al. *JAMA*. 2006;295(13):1531-1538.

Prasugrel

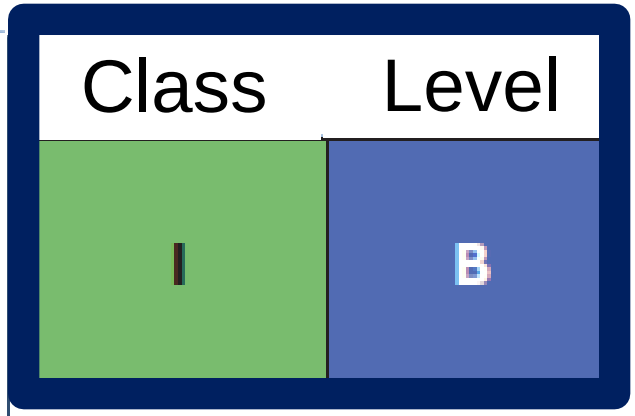
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of lifethreatening bleeding or other contraindications



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

The NEW ENGLAND JOURNAL of MEDICINE

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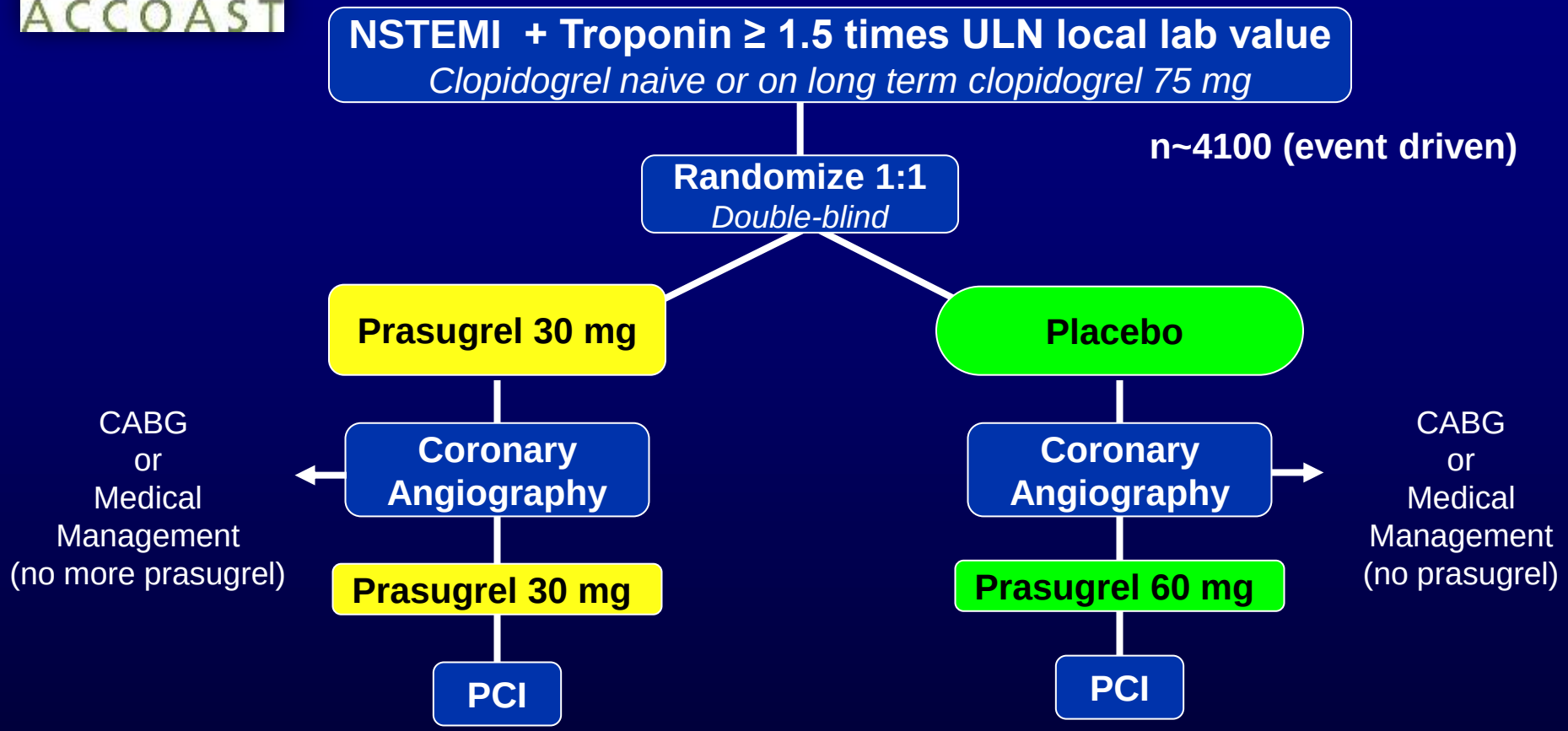
Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes

Gilles Montalescot, M.D., Ph.D., Leonardo Bolognese, M.D., Dariusz Dudek, M.D., Ph.D., Patrick Goldstein, M.D., Christian Hamm, M.D., Jean-Francois Tanguay, M.D., Jurrien M. ten Berg, M.D., Ph.D., Debra L. Miller, R.N., Timothy M. Costigan, Ph.D., Jochen Goedicke, M.D., Johanne Silvain, M.D., Ph.D., Paolo Angioli, M.D., Jacek Legutko, M.D., Ph.D., Margit Niethammer, M.D., Zuzana Motovska, M.D., Ph.D., Joseph A. Jakubowski, Ph.D., Guillaume Cayla, M.D., Ph.D., Luigi Oltrona Visconti, M.D., Eric Vicaut, M.D., Ph.D., and Petr Widimsky, M.D., D.Sc., for the ACCOAST Investigators*

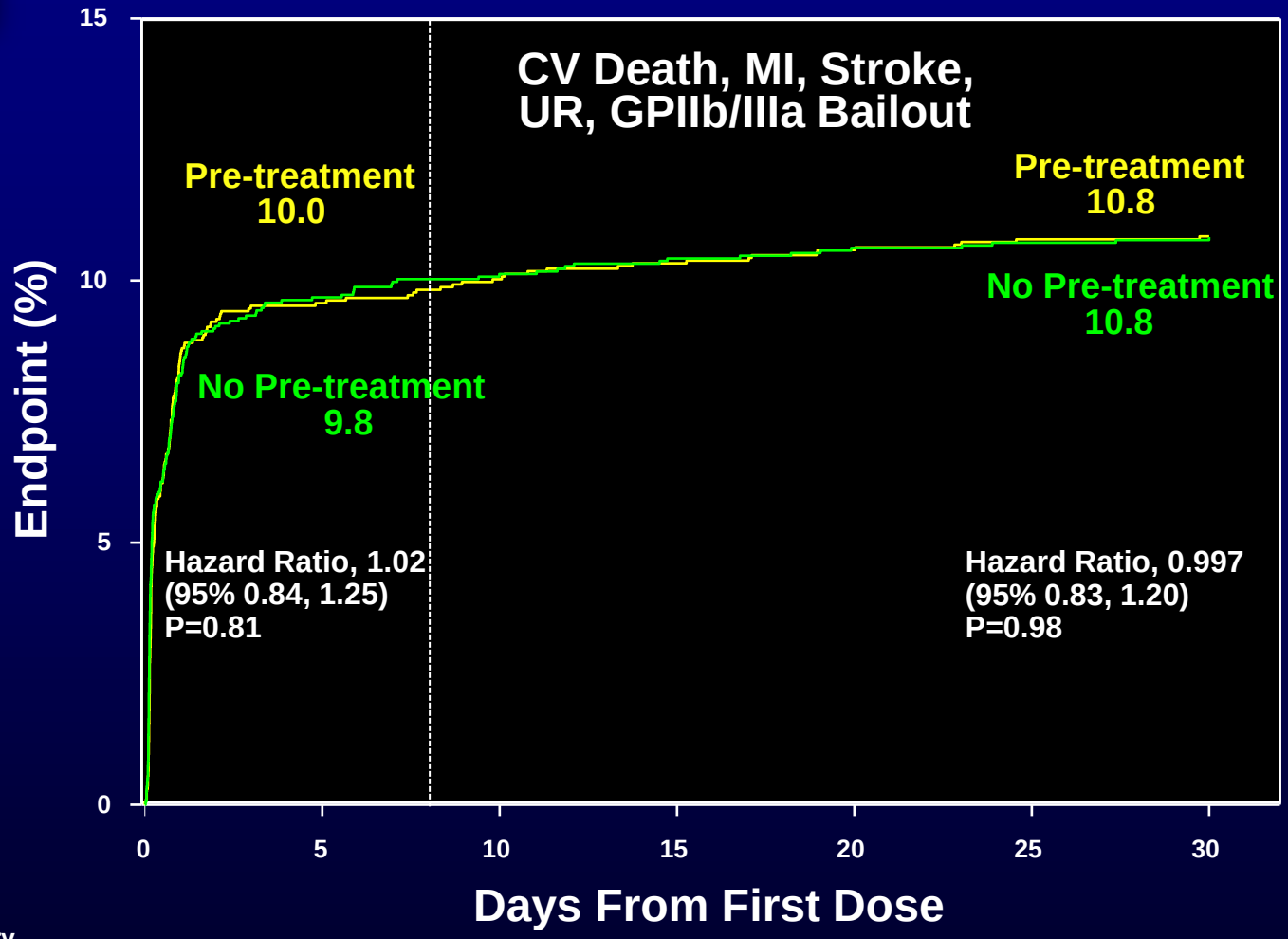
ACCOAST design



1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa inh. Bailout, at 7 days

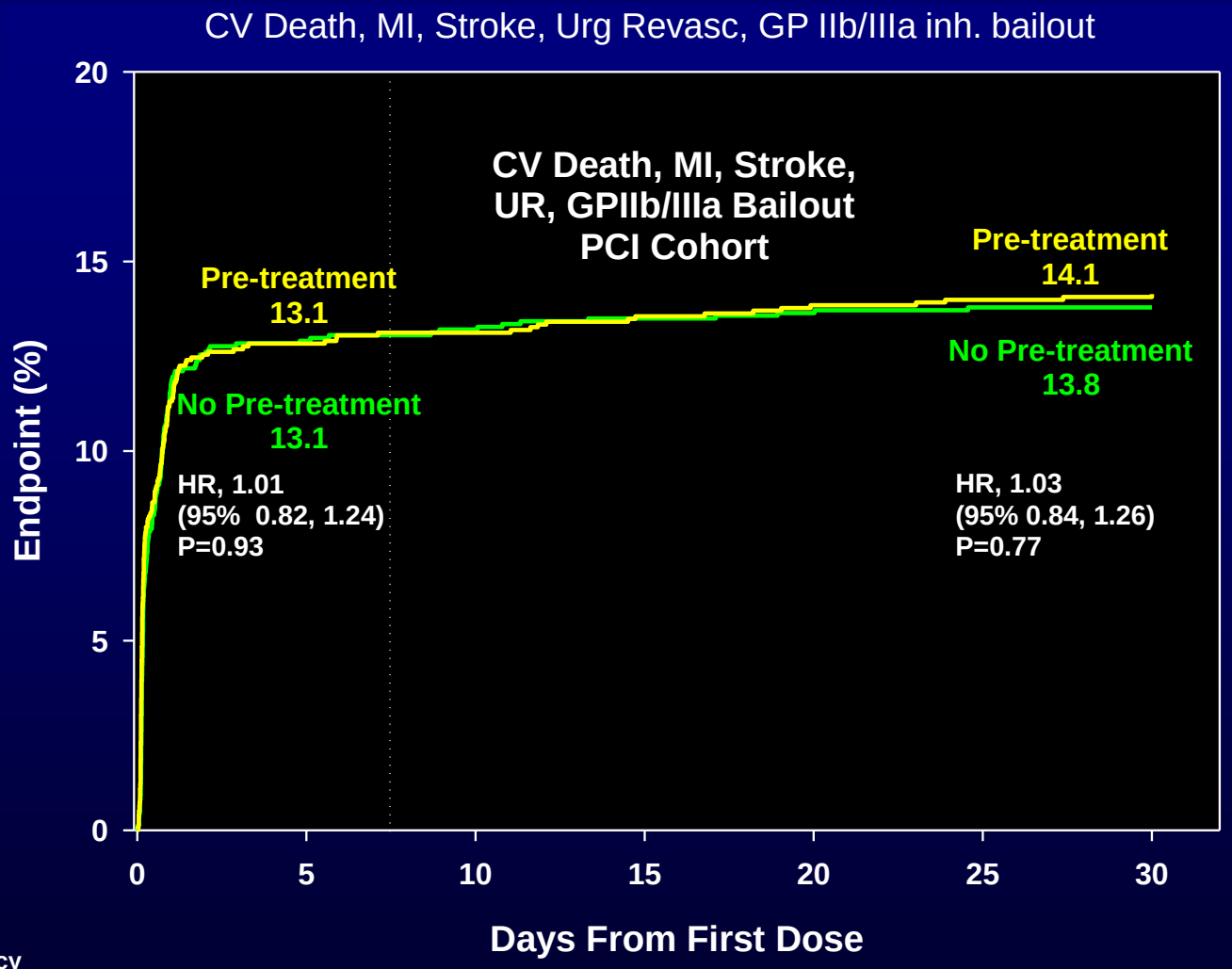
Montalescot G et al. *Am Heart J* 2011;161:650-656

1° Efficacy End Point @ 7 + 30 days (All Patients)



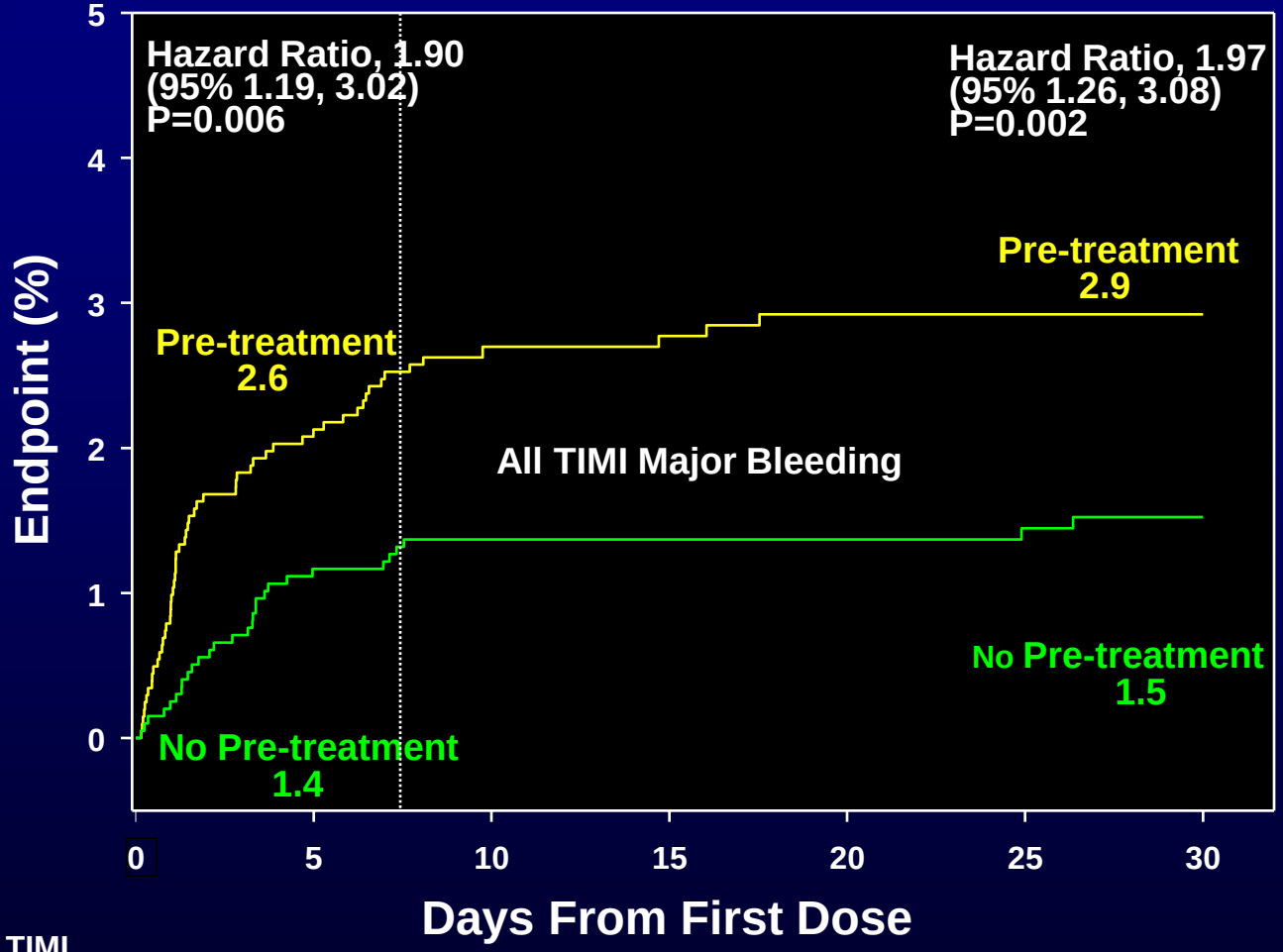
No. at Risk, Primary Efficacy End Point:							
No pre-treatment	1996	1788	1775	1769	1762	1752	1621
Pre-treatment	2037	1821	1809	1802	1797	1791	1616

1° Efficacy Endpoint (PCI Patients)



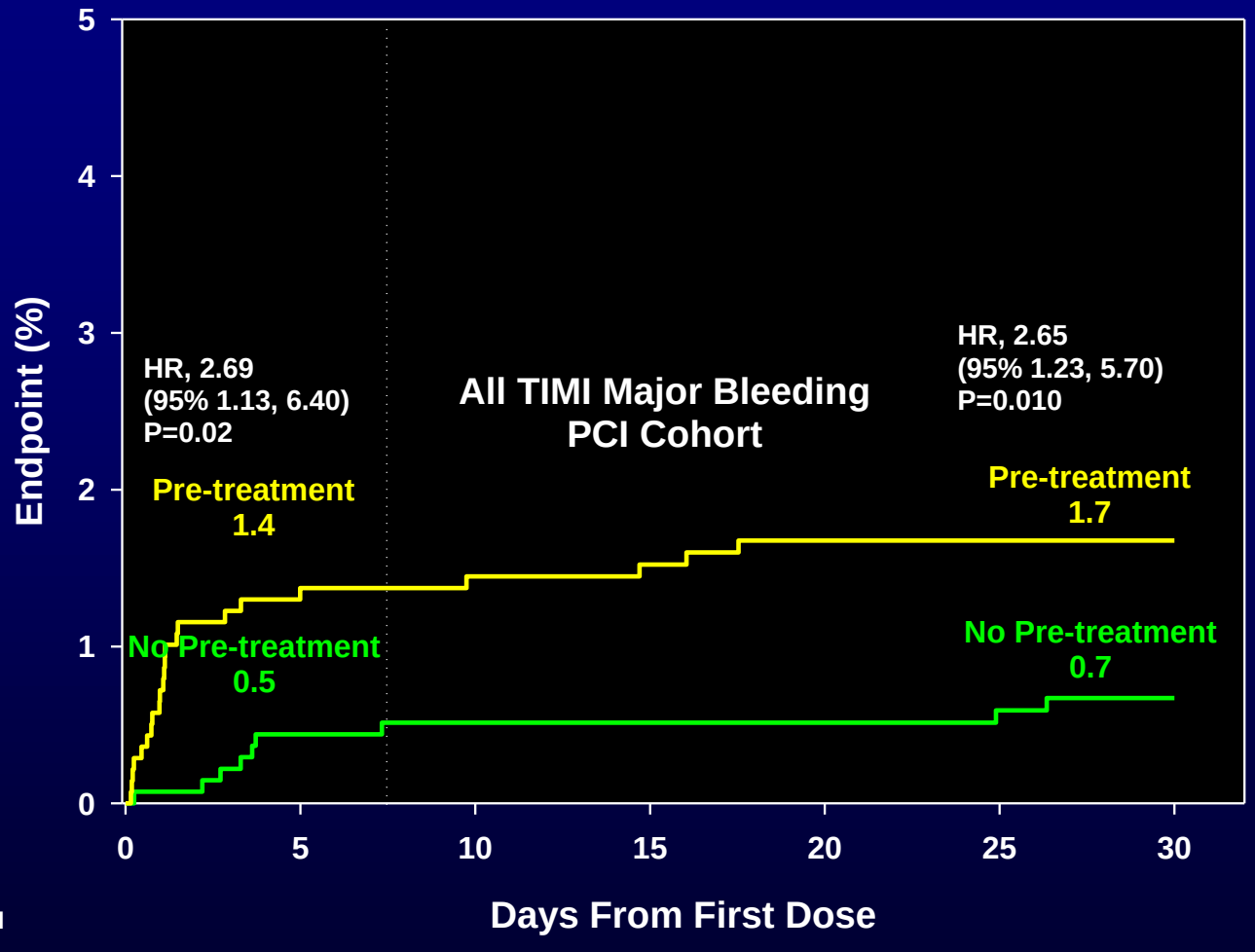
No. at Risk, Efficacy End Point:							
No pre-treatment	1372	1191	1187	1183	1179	1177	1177
Pre-treatment	1389	1206	1202	1194	1189	1186	1172

All TIMI (CABG or non-CABG) Major Bleeding (All Treated patients)



No. at Risk, All TIMI Major Bleeding:							
No pre-treatment	1996	1947	1328	1297	1288	1284	1263
Pre-treatment	2037	1972	1339	1310	1299	1297	1280

All TIMI (CABG or Non-CABG) Major Bleeding (PCI Patients)



No. at Risk, All TIMI Major Bleeding:							
No pre-treatment	1372	1356	1302	1280	1272	1268	1249
Pre-treatment	1389	1364	1314	1293	1282	1280	1269

Conclusions

- In NSTE-ACS patients managed invasively within 48 hours of admission, pre-treatment with prasugrel does not reduce major ischemic events through 30 days but increases major bleeding complications.
- The results are consistent among patients undergoing PCI supporting treatment with prasugrel once the coronary anatomy has been defined.
- No subgroup appears to have a favorable risk/benefit ratio of pre-treatment.
- Reappraisal of routine pre-treatment strategies in NSTE-ACS is needed.

ORIGINAL ARTICLE

Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization

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TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Median Time to Enrollment = 4.5 Days

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel[1]** 300 mg LD + 75 mg MD
- **Prasugrel[1]** 30 mg LD + 5 or 10 mg MD

Medical Management Decision ≤ 10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

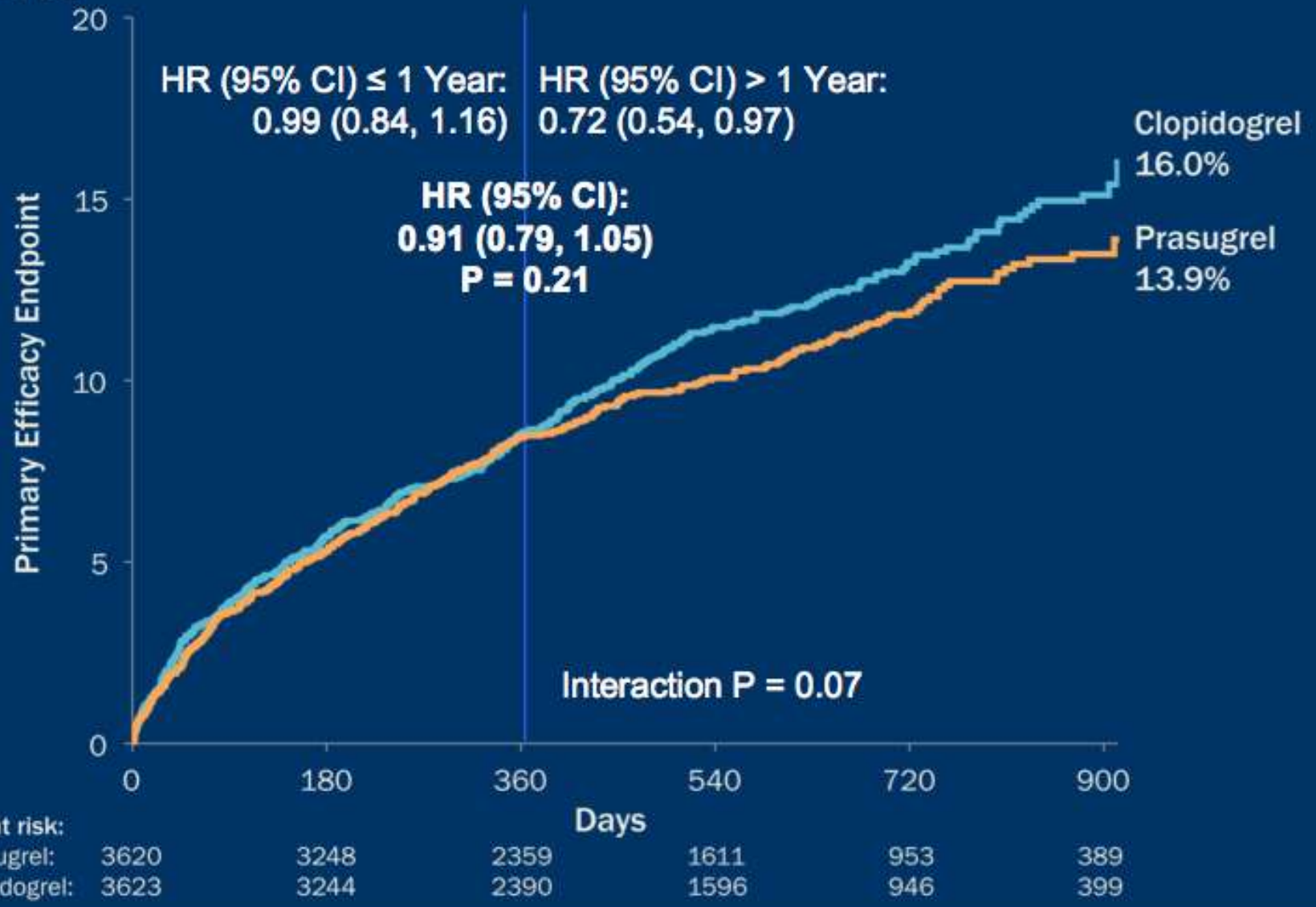
- **Clopidogrel[1]** 75 mg MD
- **Prasugrel[1]** 5 or 10 mg MD

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

Primary Efficacy Endpoint to 30 Months
(Age < 75 years)



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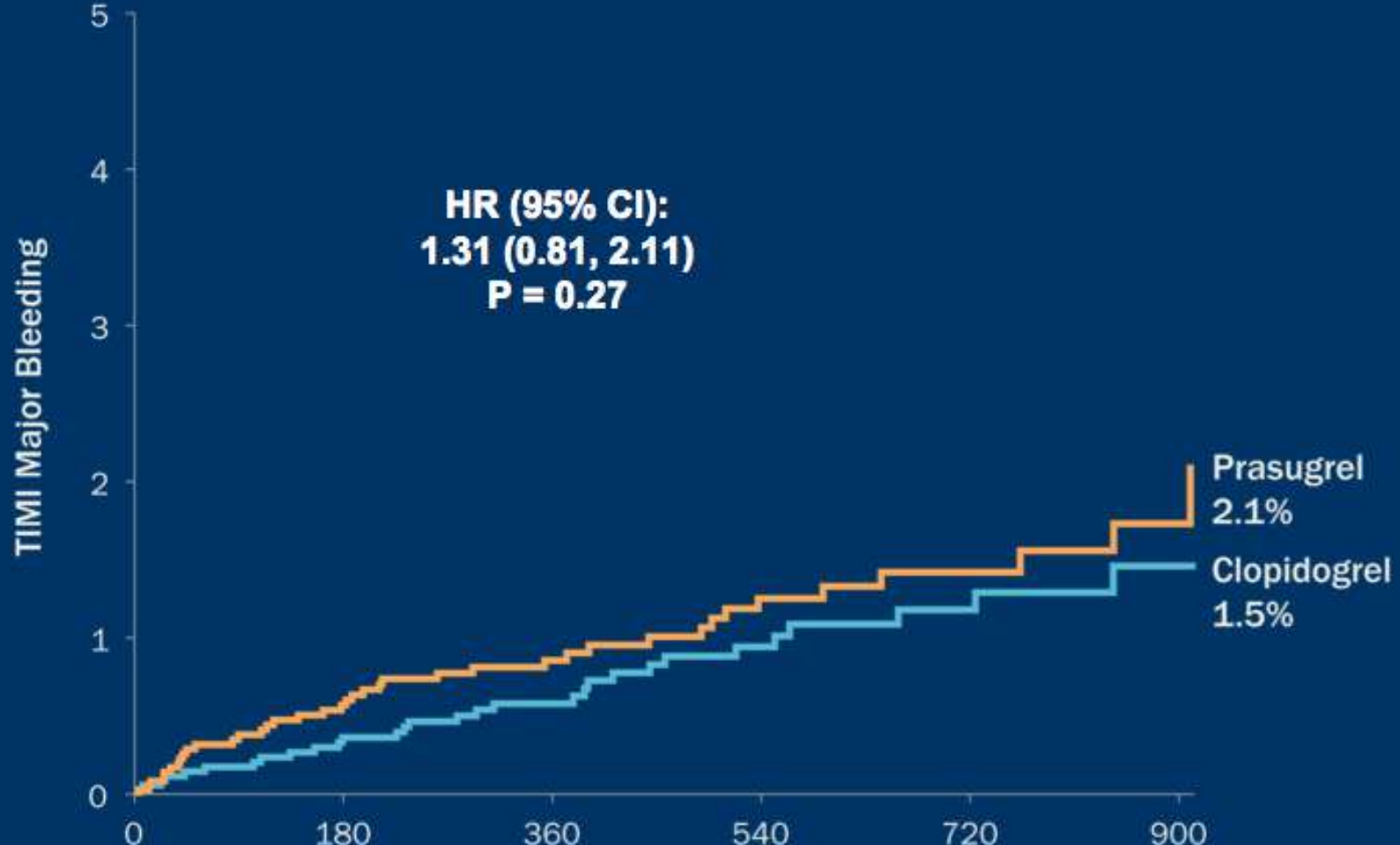
TIMI Major Bleeding to 30 Months

(Age < 75 years)



No. at risk:						
Prasugrel:	3590	3072	2244	1499	885	427
Clopidogrel:	3590	3116	2303	1552	925	425

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Conclusions

- In the largest trial to date of ACS patients managed medically without revascularization, prasugrel was not statistically different from clopidogrel during 2.5 years of follow-up among patients < 75 years of age
- Further analyses of the primary endpoint yielded several important findings favoring prasugrel treatment
  - Trend for a time-dependent benefit after 1 year
  - Fewer total recurrent ischemic events, particularly after 1 year
- No statistical differences in major, life-threatening, or fatal bleeding with prasugrel vs. clopidogrel

Disponibilização das drogas antitrombóticas

Países Latino-americanos

	Bivalirudin	Fondaparinux	Prasugrel	Ticagrelor
Argentina	+	+	+	+
Brasil	-	+	+	+
Chile	+	+	-	+
Colombia	-	+	+	+
Uruguai	+	+	-	-
Venezuela	+	+	+	+

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.