Nuevos antiagregantes en el SCACEST (infarto ST alto)

Nuevas oportunidades para mejores resultados

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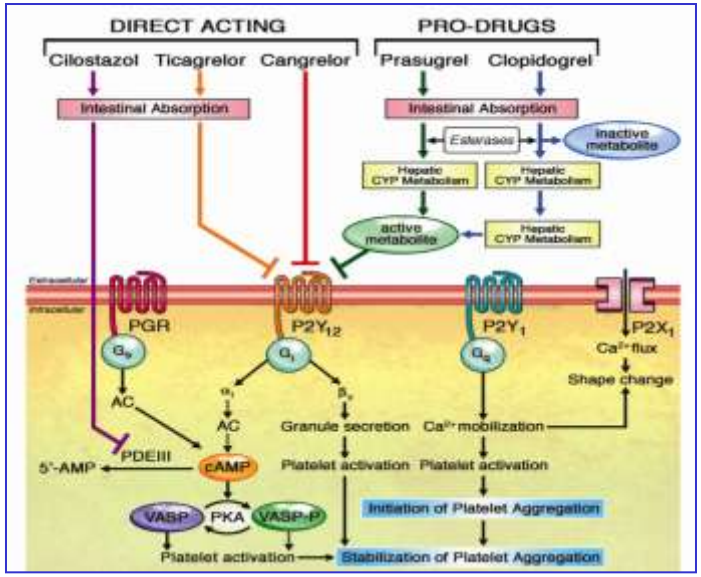
Santander



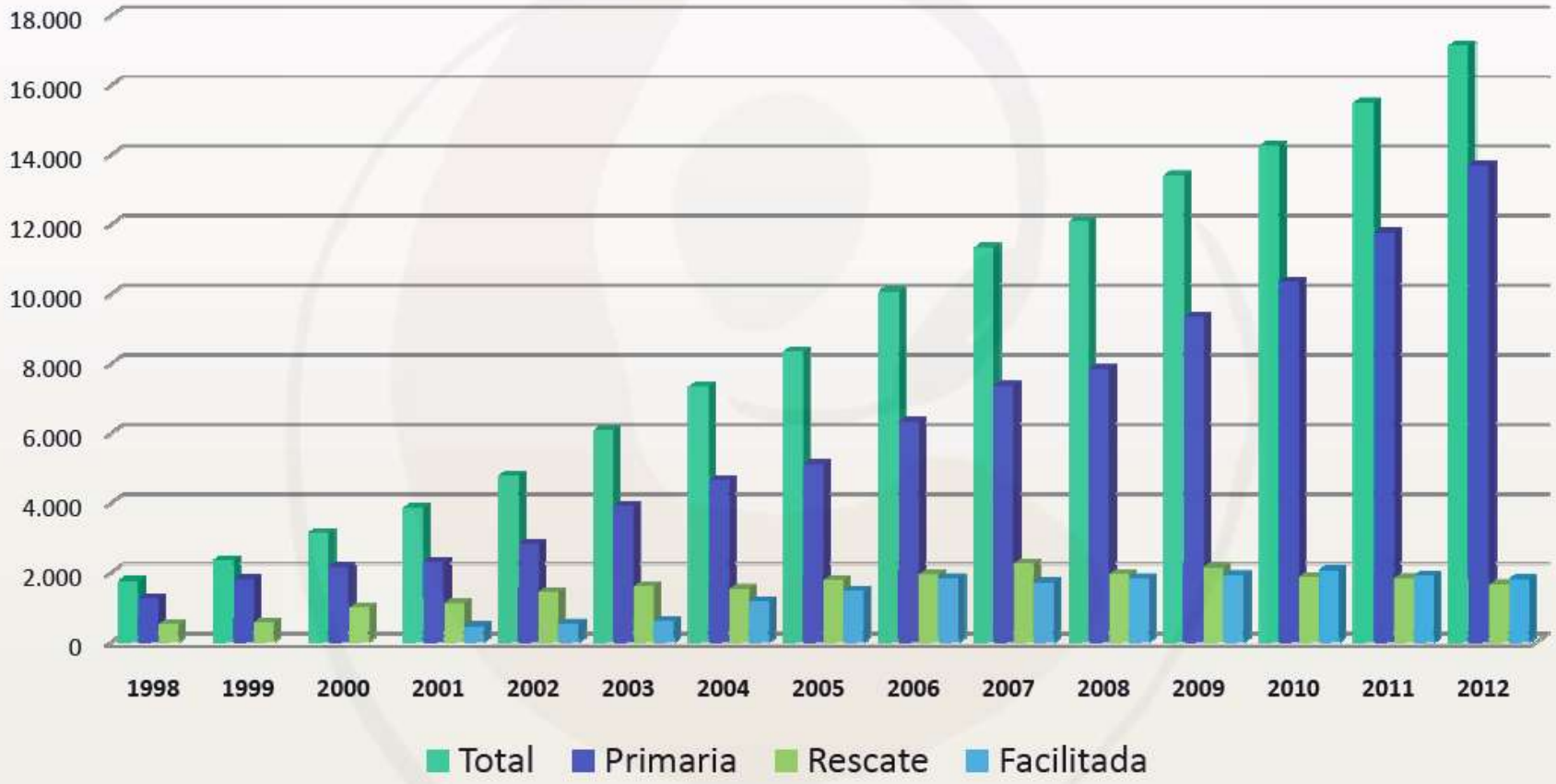
Cardiología
VALDECILLA SANTANDER

Intervencionismo en el IAM

Evolución histórica ⇧ 10,55%

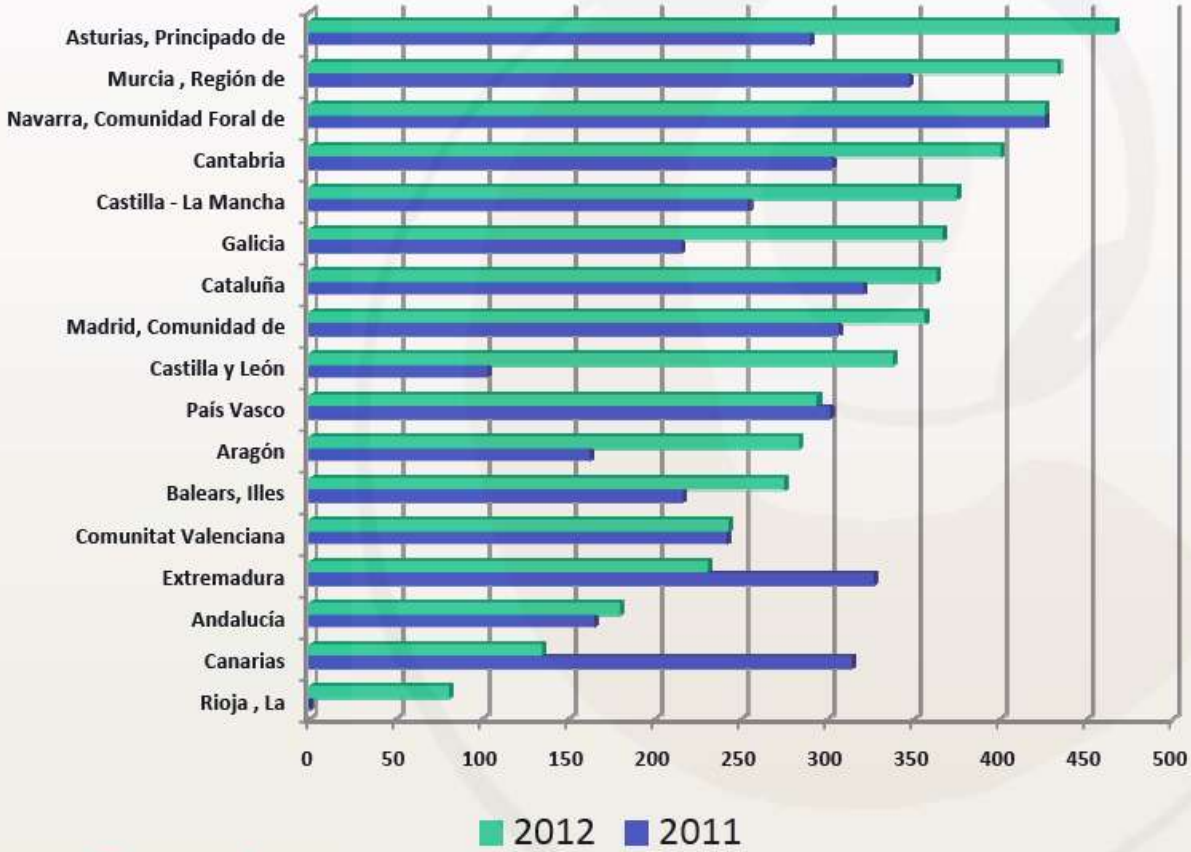
ICP en IAM

Evolución Histórica



ICP 1ª por millón de habitantes

Media de España 298 (256 en 2011)



	2011	2012
Asturias	290	467
Murcia , Región de	347	433
Navarra,	426	426
Cantabria	302	400
Castilla - La Mancha	254	374
Galicia	215	367
Cataluña	320	363
Madrid	306	356
Castilla y León	103	338
País Vasco	301	294
Aragón	162	283
Balears, Illes	216	275
Valencia	241	243
Extremadura	327	230
Andalucía	165	179
Canarias	314	135
Rioja	0	81
	256	298

Evolucion en la reperfusion del IAMEST
(Cantabria)

	Reperfusion	Trombolíticos	ICP1ª
2006	**71%**	**55%**	**45%**
2011	80%	35%	65%
2012	86%	15%	85%
-2013-	**92%**	**3%**	**97%**

Beneficio de antiagregacion dual
Clopidogrel + AAS
en infarto tratado con **trombolisis**
y en el **no reperfundido**

COMMIT/CCS-2

(ClOpidogrel & Metoprolol in Myocardial Infarction Trial)

Designed, conducted, analysed and interpreted independently by COMMIT/CCS-2 collaboration

Sources of funding (US$ 3M):

- SanofiAventis/BMS
- AstraZeneca
- British Heart Foundation
- UK Medical Research Council

45.582 pacientes
Mitad de los pacientes sin trombolisis

commit

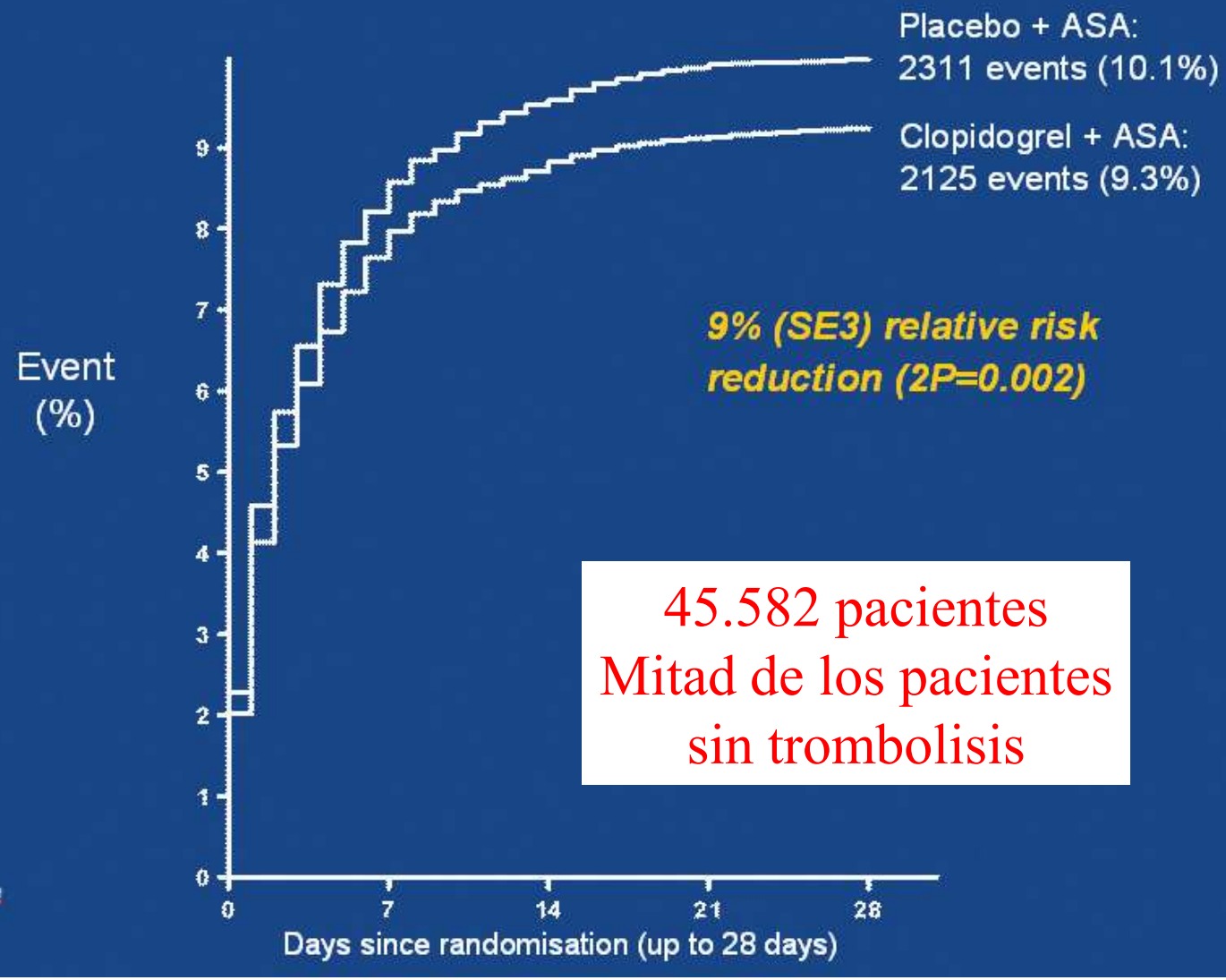
COMMIT: Study design

TREATMENT:	Clopidogrel 75 mg daily vs placebo (aspirin 162mg daily in both groups)
INCLUSION:	Suspected acute MI (ST change or LBBB) within 24 h of symptom onset
EXCLUSION:	Primary PCI or high-risk of bleeding
1° OUTCOMES:	Death & death, re-MI or stroke up to 4 weeks in hospital (or prior discharge)

Mean treatment and follow-up: 16 days

commit CCS-2

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke



9% (SE3) relative risk reduction (2P=0.002)

45.582 pacientes
Mitad de los pacientes sin trombolisis

commit CCS2

From ISIS-2 to COMMIT: Effects of aspirin and clopidogrel on Death, Re-MI or Stroke

ISIS-2:	*Placebo*	14%	
		↓	~40 per 1000
	ASA	10%	
COMMIT:	*ASA*	10%	
		↓	~10 per 1000
	ASA + Clop.	9%	

ASA + Clopidogrel vs nil: ~50 per 1000 treated

commit CCS-2

CLARITY

TIMI 28

CLopidogrel as Adjunctive Reperfusion TherapY – Thrombolysis In Myocardial Infarction (TIMI) 28

CLARITY TIMI 28

Study Design

Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 yrs with STEMI < 12 hours

↓

Fibrinolytic, ASA, Heparin

randomize

↙ ↘

Clopidogrel 300 mg + 75 mg qd | **Placebo**

↘ ↙

Coronary Angiogram (2-8 days)

↓

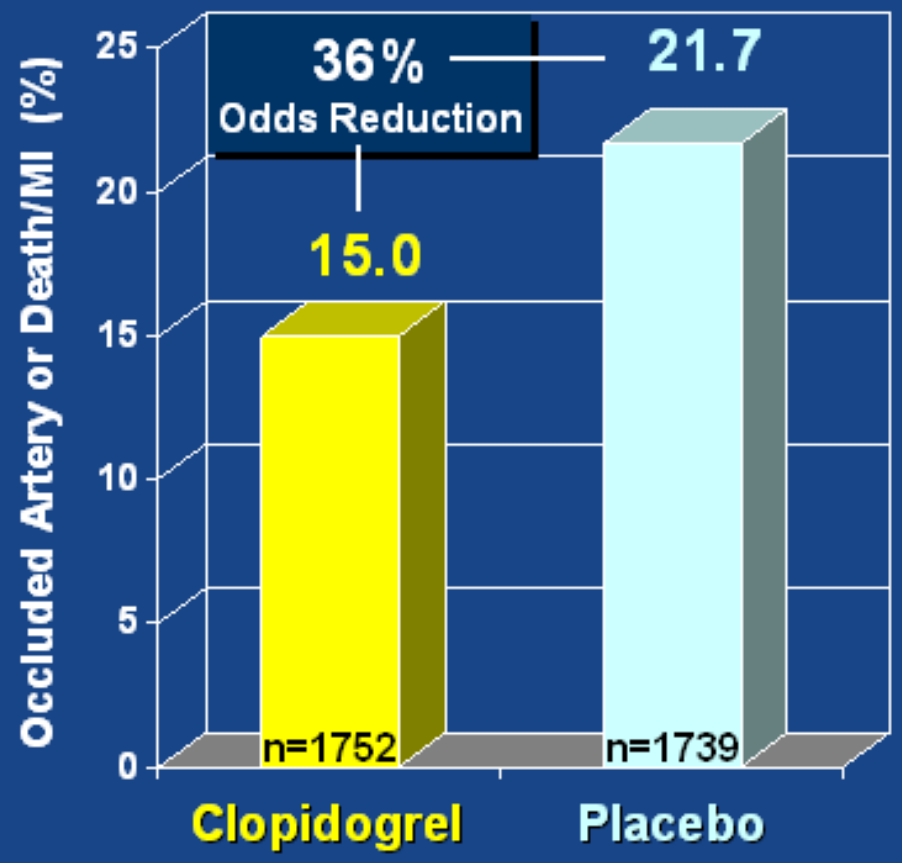
30-day clinical follow-up

Study Drug

Open-label clopidogrel per MD in both groups

Primary endpoint: *Occluded artery (TIMI Flow Grade 0/1) or D/MI by time of angio*

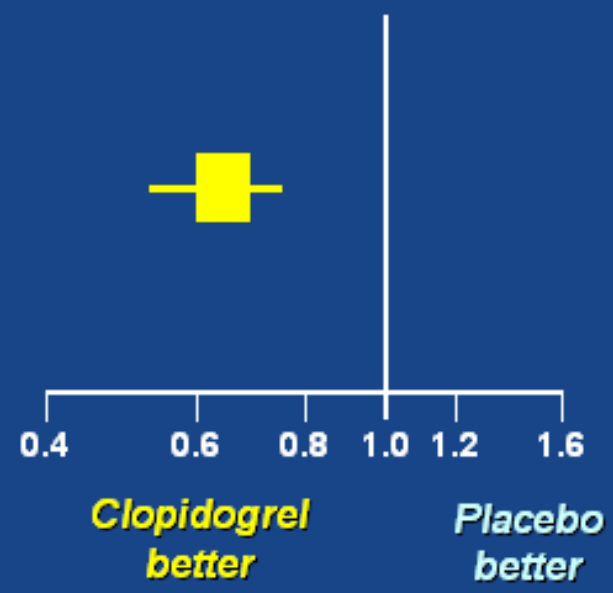
Primary Endpoint: Occluded Artery (or D/MI thru Angio/HD)



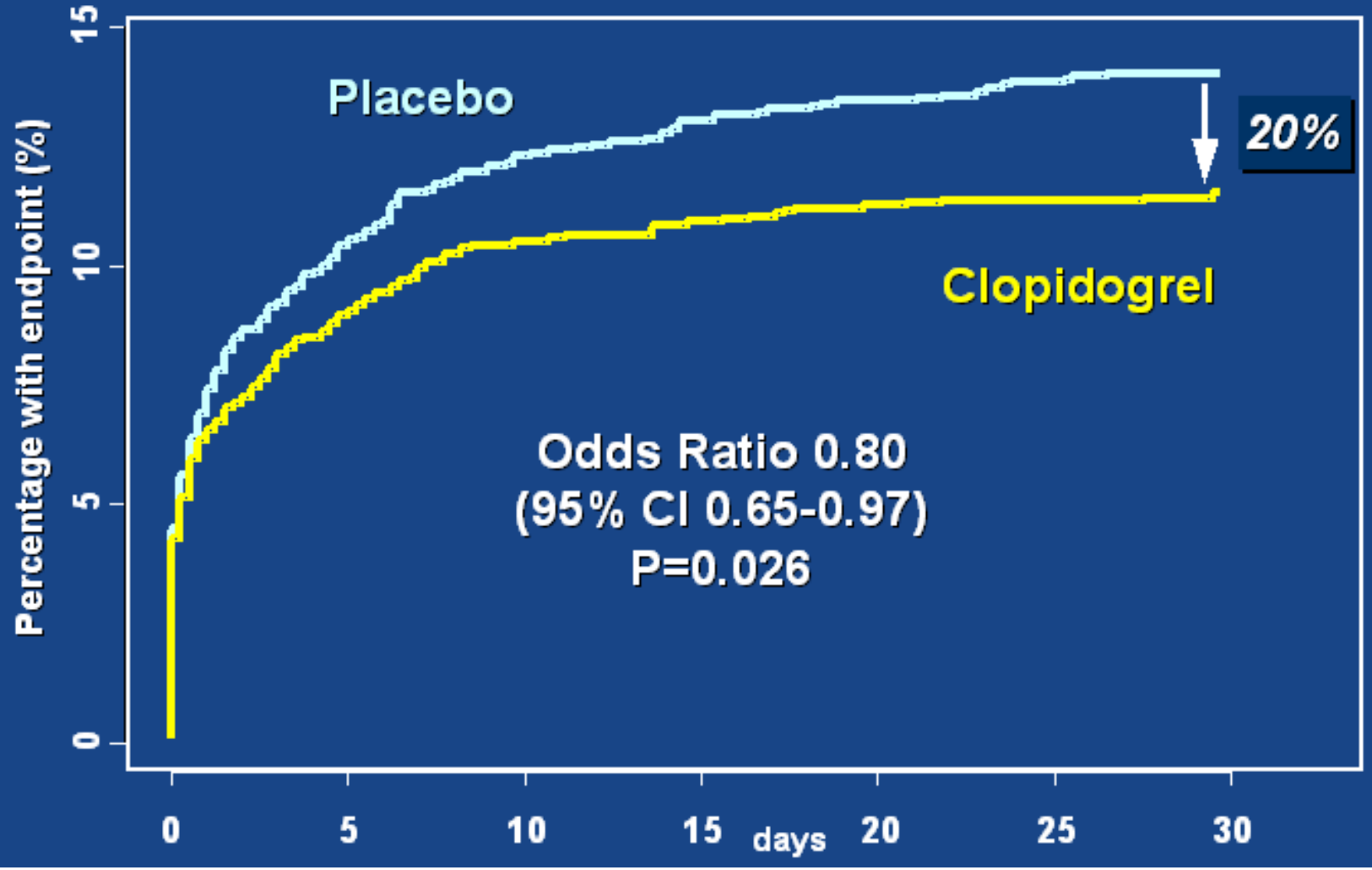
Odds Ratio 0.64

(95% CI 0.53-0.76)

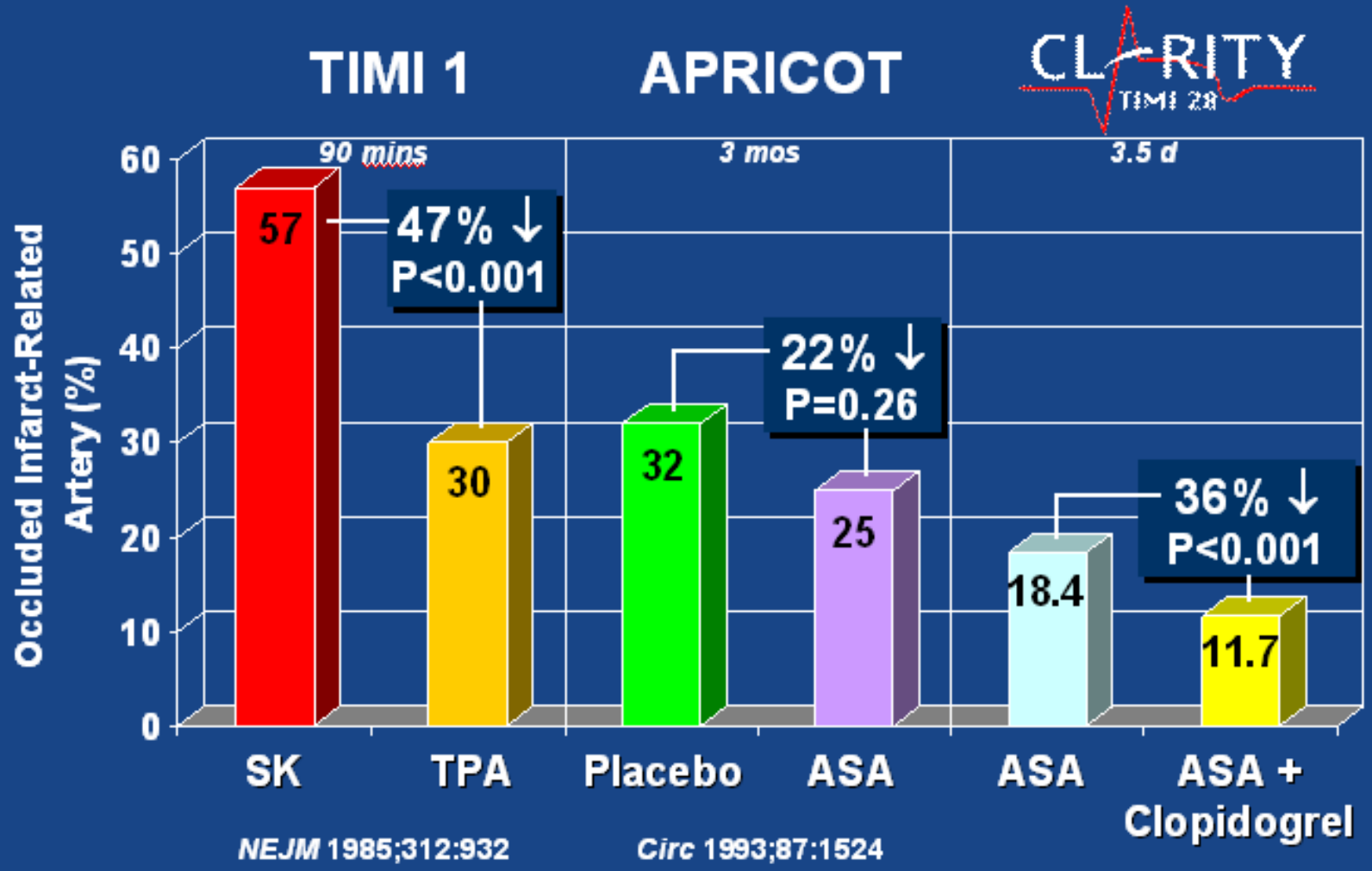
P=0.00000036



CV Death, MI, RI → Urg Revasc

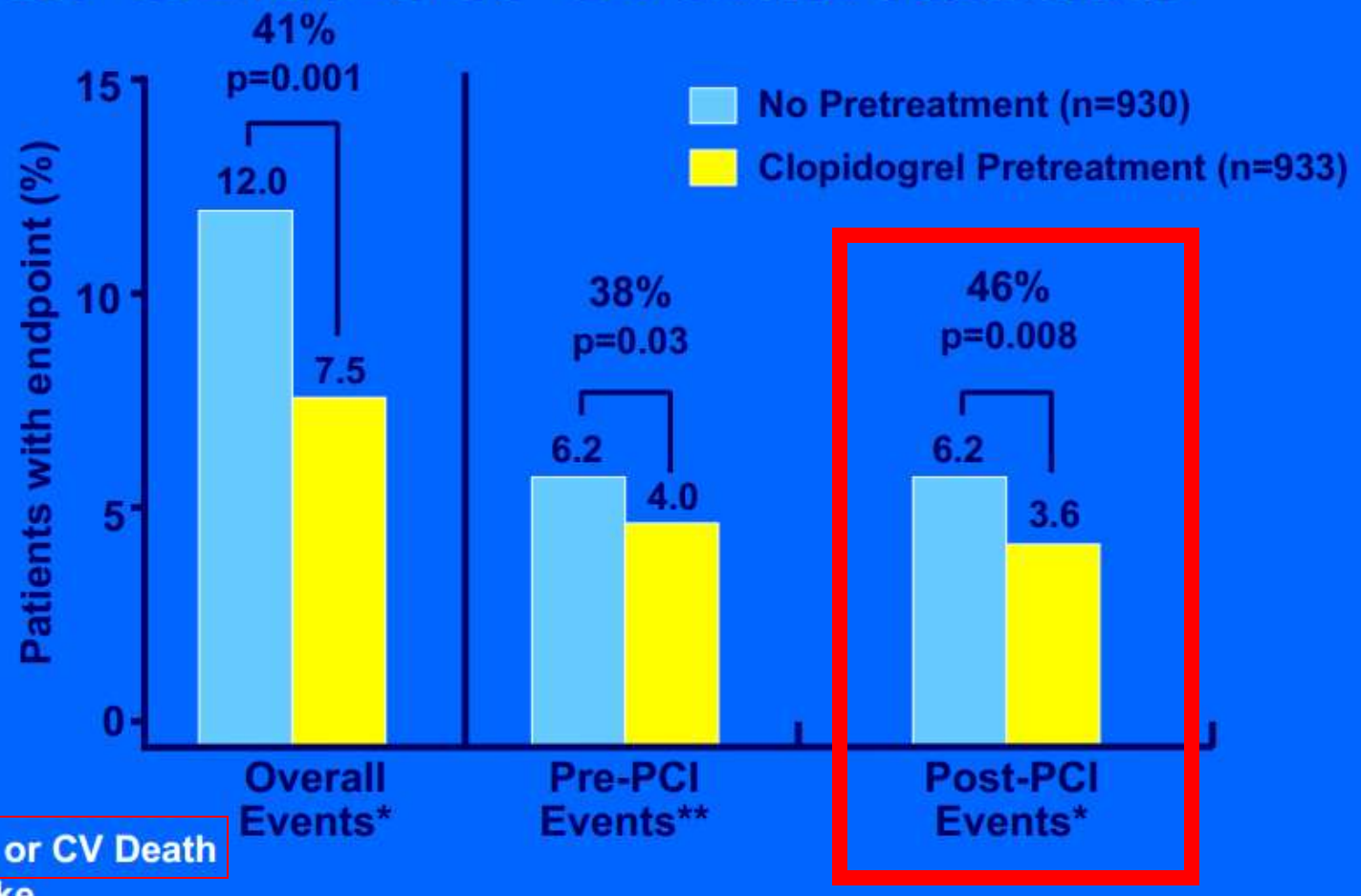


Evolution of Pharmacologic Reperfusion



Beneficio de antiagregacion dual **Clopidogrel + AAS** en infarto tratado con **ICP 1ª**

PCI-CLARITY: Overall Results



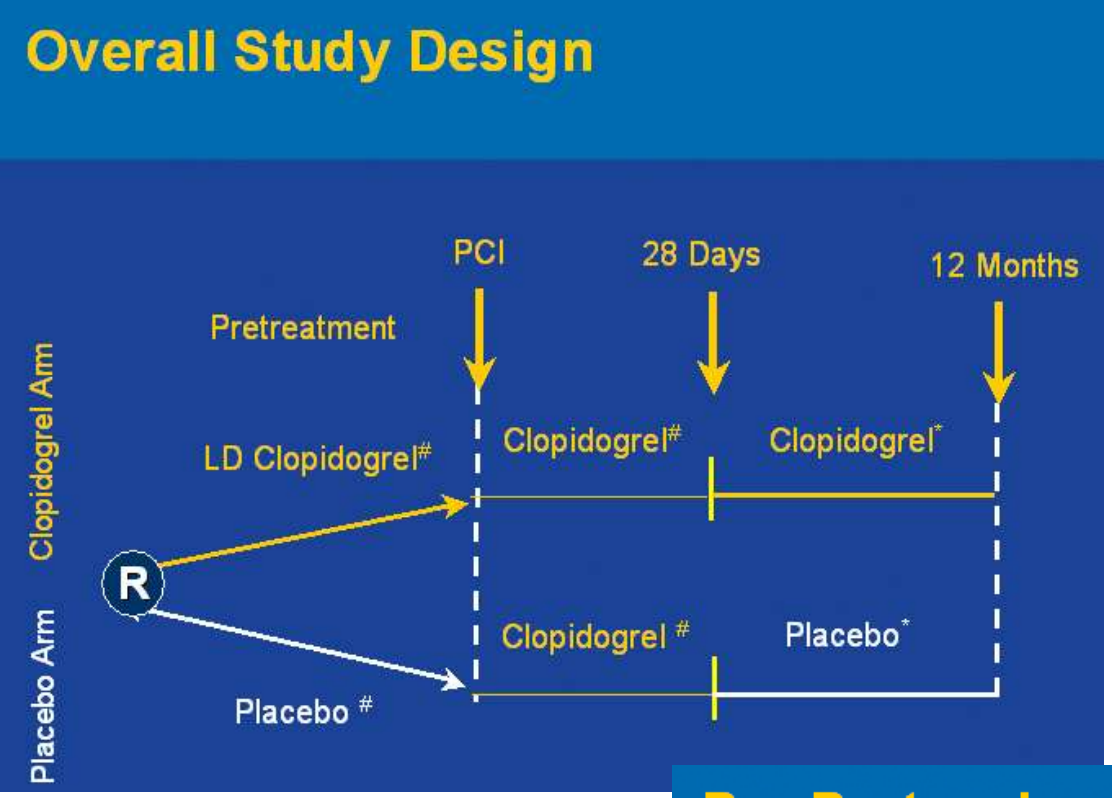
*MI, Stroke, or CV Death

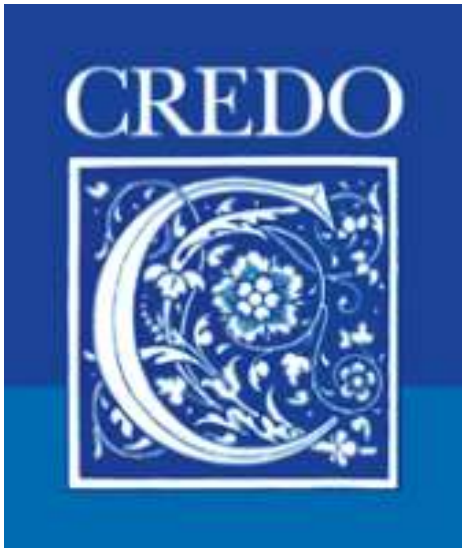
**MI or Stroke

Overall events includes events from randomization through 30 days. Percent reduction based on odds ratio for event rates. Odds ratios adjusted for propensity score for likelihood of PCI, type of lytic, initial type of heparin, and infarct location.

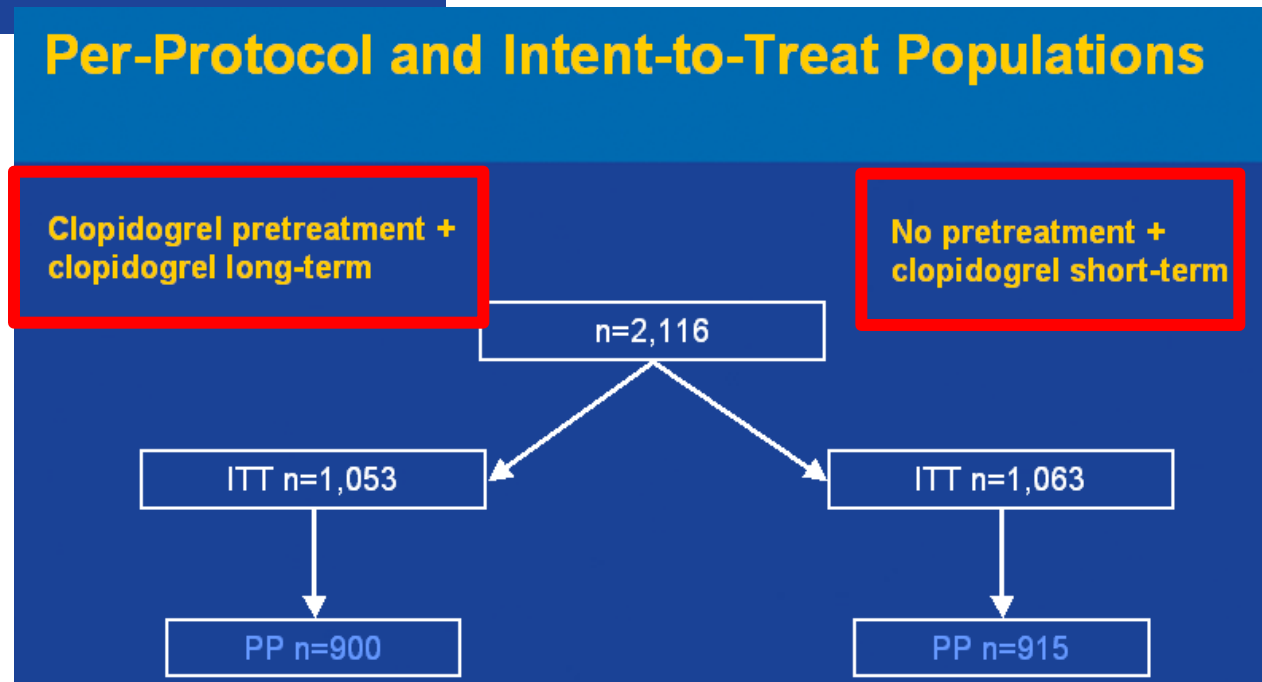
M Sabatine, et al. JAMA. 2005;294:1224-1232.

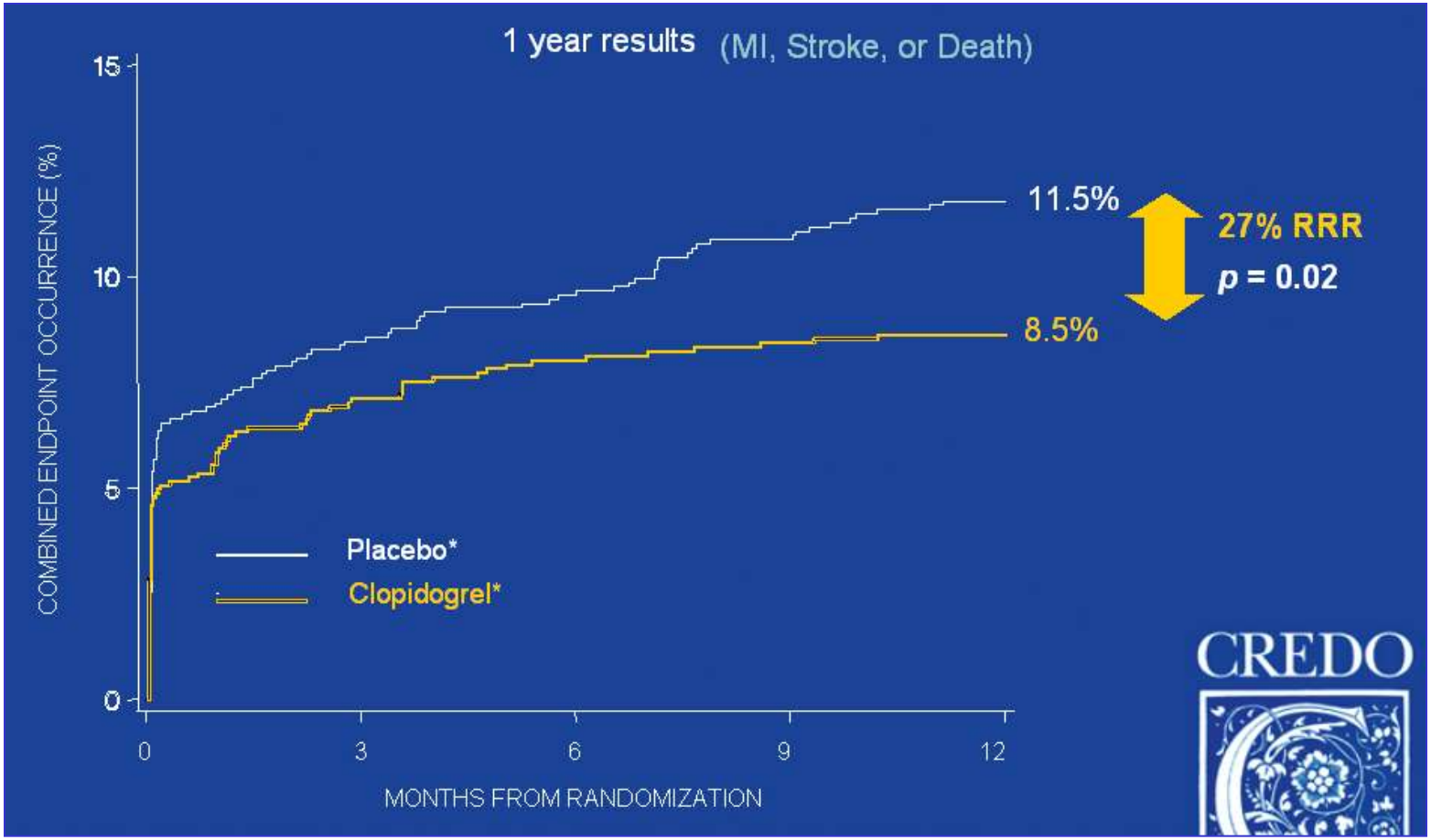
AAS + Clopidogrel,
¿ por **cuanto tiempo** despues del infarto ?





Estudio SCASEST





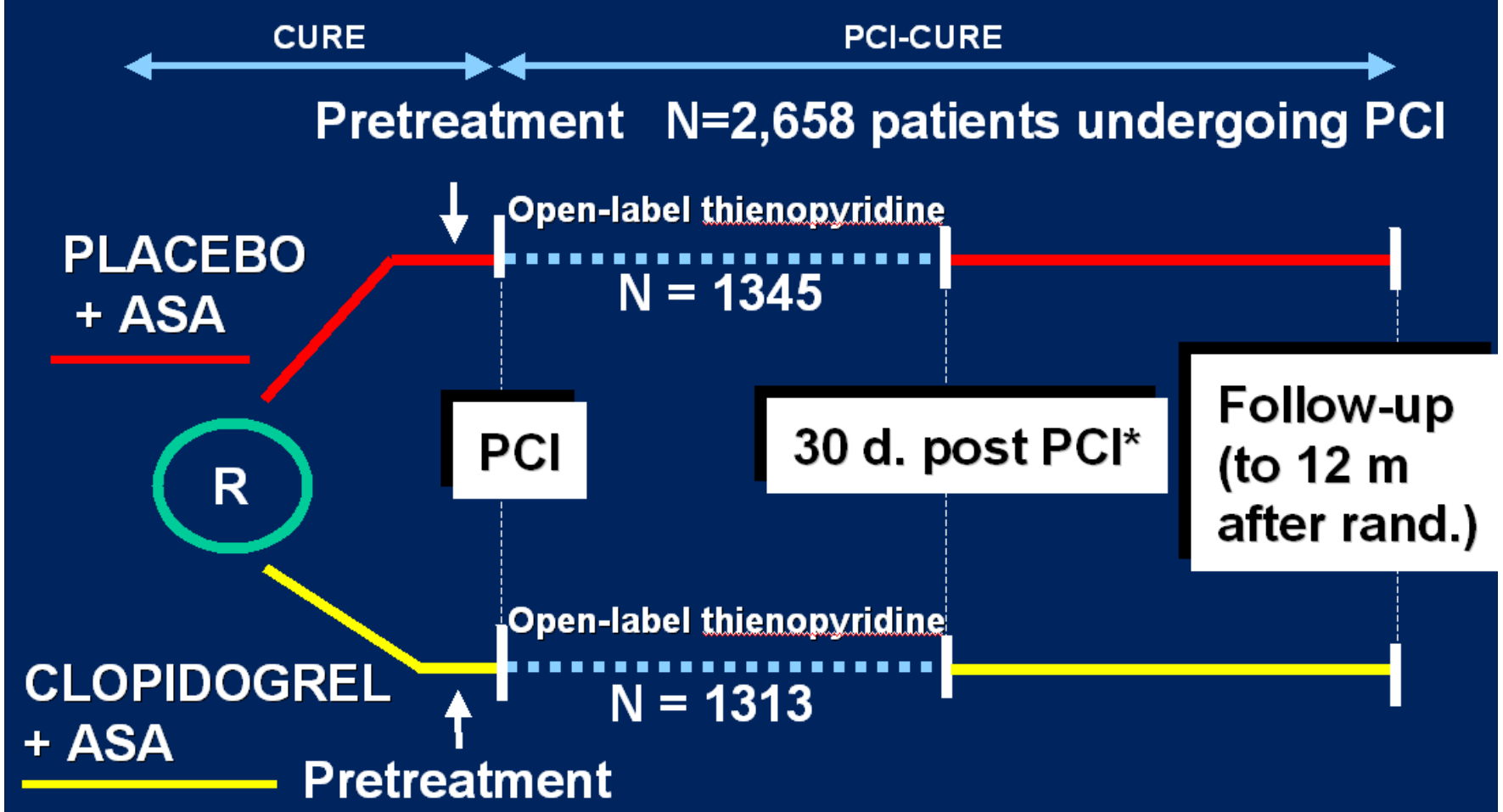
Safety Outcomes: Major Bleeding Events 1 Year Results

Major Bleeding	Clopidogrel* (n=1,053)	Placebo* (n=1,063)	P-value
Any	93 (8.8%)	71 (6.7%)	0.07

PCI-CURE

Estudio en SCASEST

PCI-CURE: Study Design

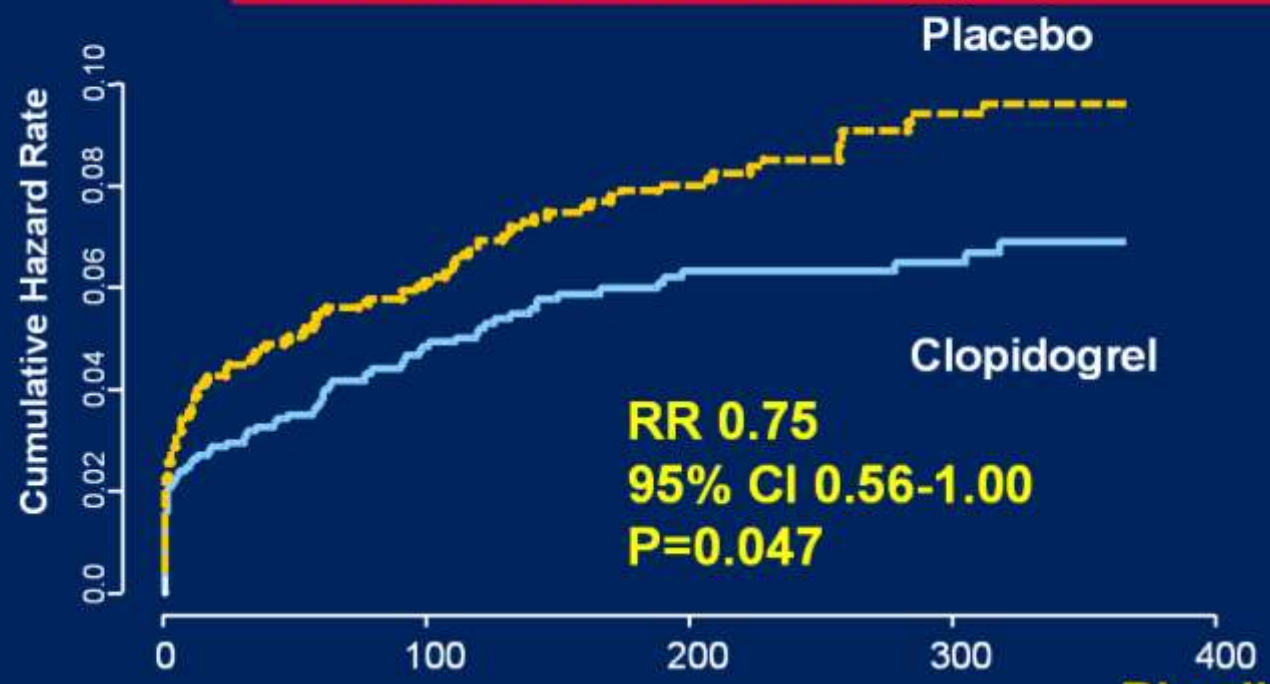


*1º Outcome: CV Death, MI, Urg Revasc.

Mehta SR et al. *Lancet* 2001:358:527-33

PCI-CURE

CV Death, MI:
From PCI to End of Followup



Bleeding Outcomes

	Placebo N=1362	Clopidogrel N=1362	RR	P
From PCI to 30 days				
Major	1.4%	1.6%	1.13	0.69
Life threatening	0.7%	0.7%	0.92	0.86
Minor	0.7%	1.0%	1.33	0.49
From PCI to follow-up				
Major	2.5%	2.7%	1.12	0.64
Life threatening	1.3%	1.2%	0.91	0.78
Minor	2.1%	3.5%	1.68	0.03

Beneficio de antiagregacion con **precarga oral de Clopidogrel 600** mgrs y dosis mas alta en fase aguda

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 then 150 mg/d × 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)

Angio 24,769 (99%)

- **PCI 17,232 (70%)**
- **No PCI 7,855 (30%)**
  - **No Sig. CAD 3,616**
  - **CABG 1,809**
  - **CAD 2,430**

Compliance:

Clop in 1st 7d (median)	**7d**	**7 d**	**2 d**	**7d**

Efficacy Outcomes: CV Death, MI or stroke at day 30
Stent Thrombosis at day 30

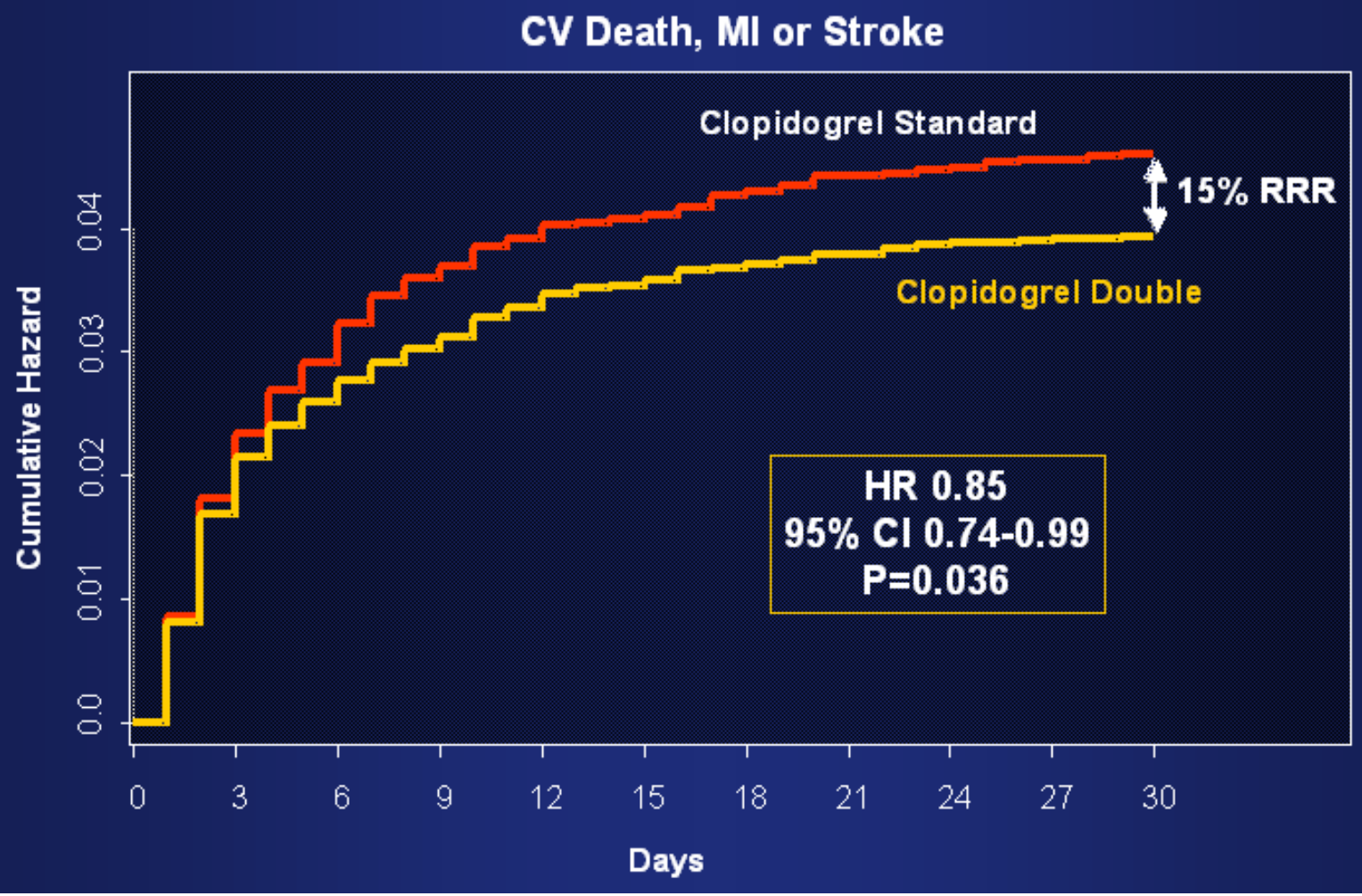
Safety Outcomes: Bleeding (CURRENT defined Major/Severe and TIMI Major)

Key Subgroup: PCI v No PCI

Complete Followup 99.8%

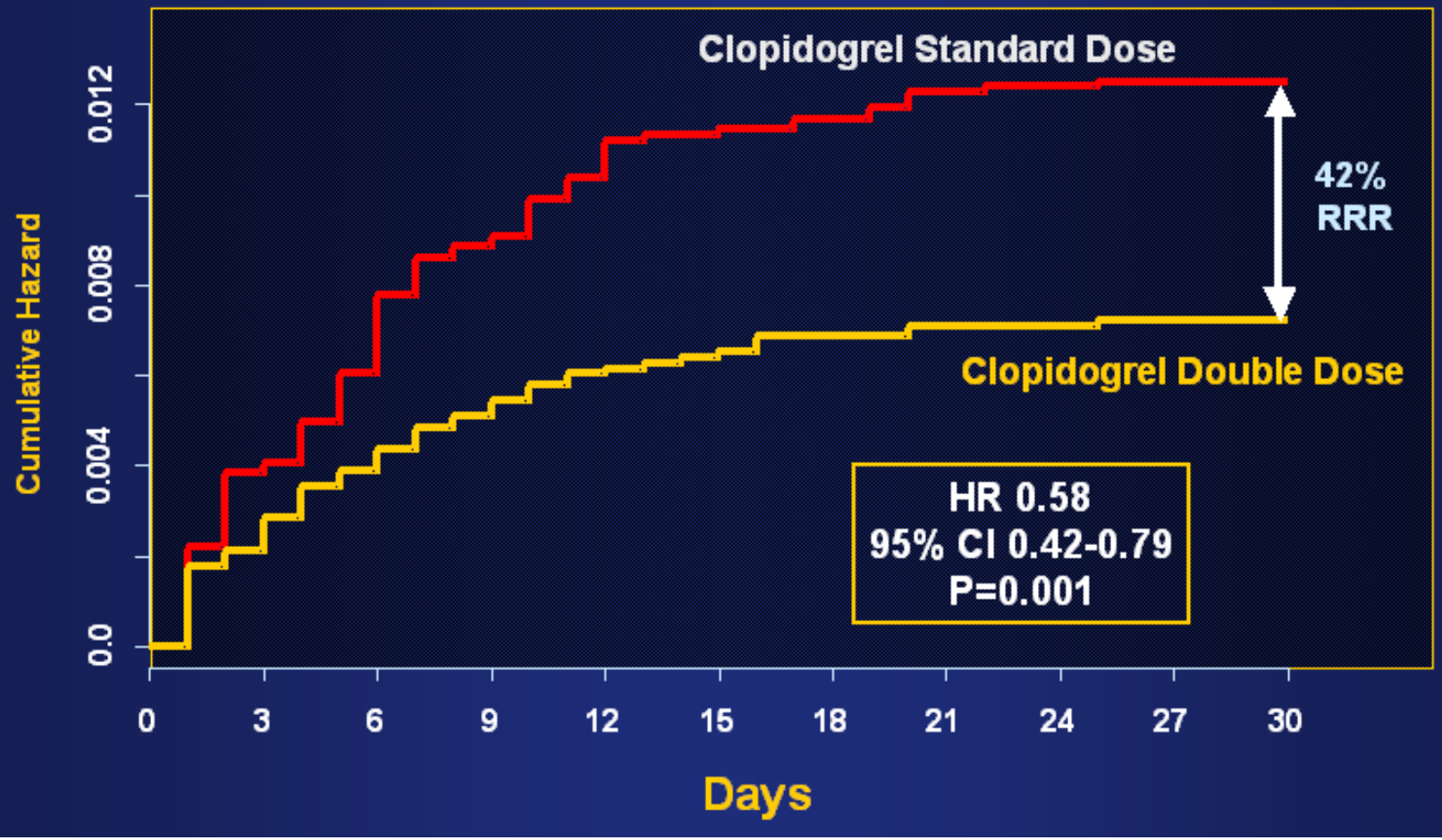
CURRENT

Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients



CURRENT

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



CURRENT

Clopidogrel Double vs Standard Dose Bleeding Overall Population

	Clopidogrel Standard N=12579	Clopidogrel Double N=12508	Hazard Ratio	95% CI	P
TIMI Major[1]	0.95	1.04	1.09	0.85-1.40	0.50
CURRENT Major[2]	2.0	2.5	1.25	1.05-1.47	0.01
CURRENT Severe[3]	1.5	1.9	1.23	1.02-1.49	0.03

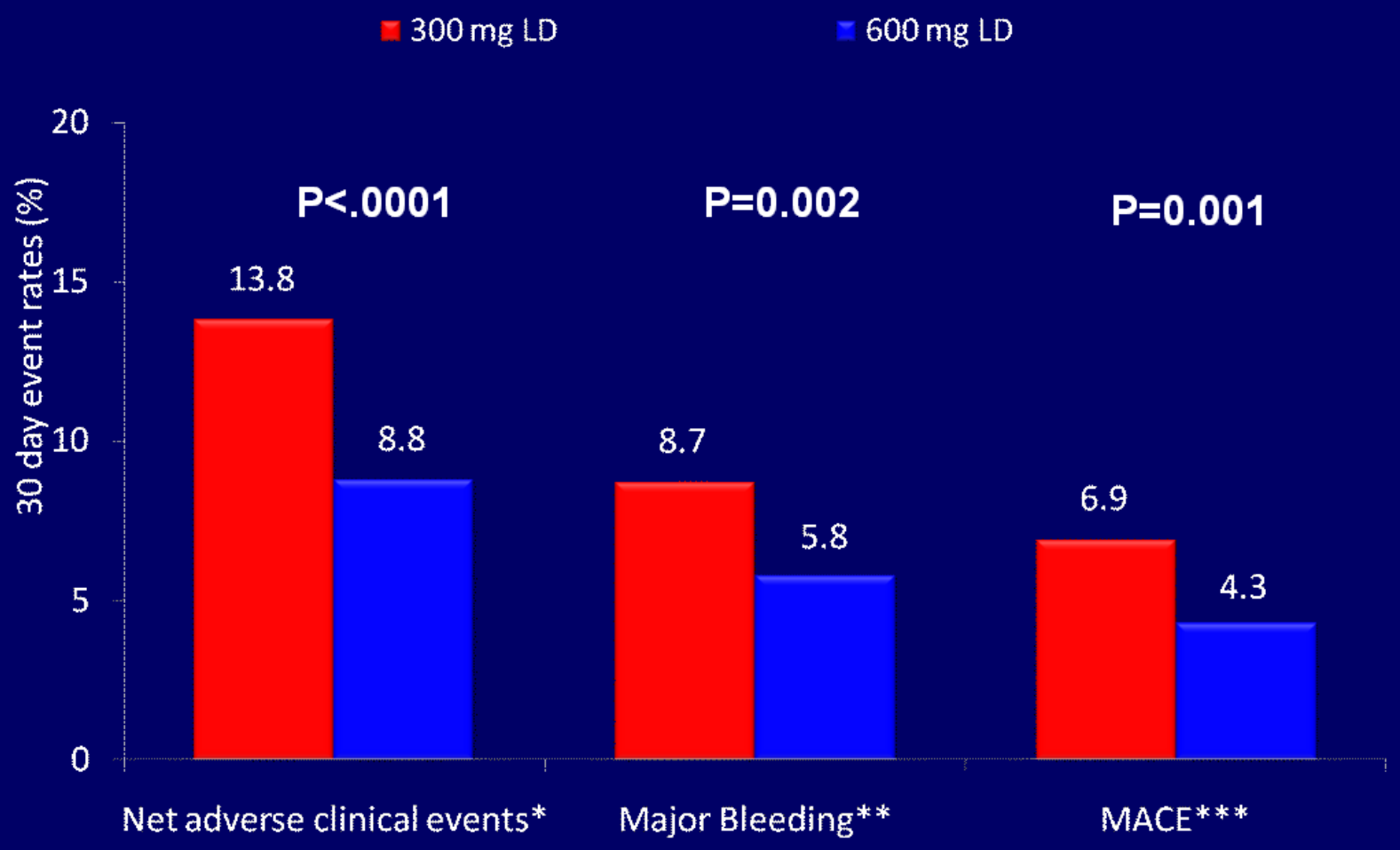
[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units

HORIZONS AMI

Impact of clopidogrel loading dose on the safety and effectiveness of bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction: The HORIZONS AMI trial

George Dangas, Giulio Guagliumi, Bernhard Witzenbichler, Deepak Bhatt, Frederick Feit, Magnus Ohman, S. Chiu Wong, Helen Parise, Roxana Mehran, Gregg W. Stone

Overall: Primary Outcomes (ITT)

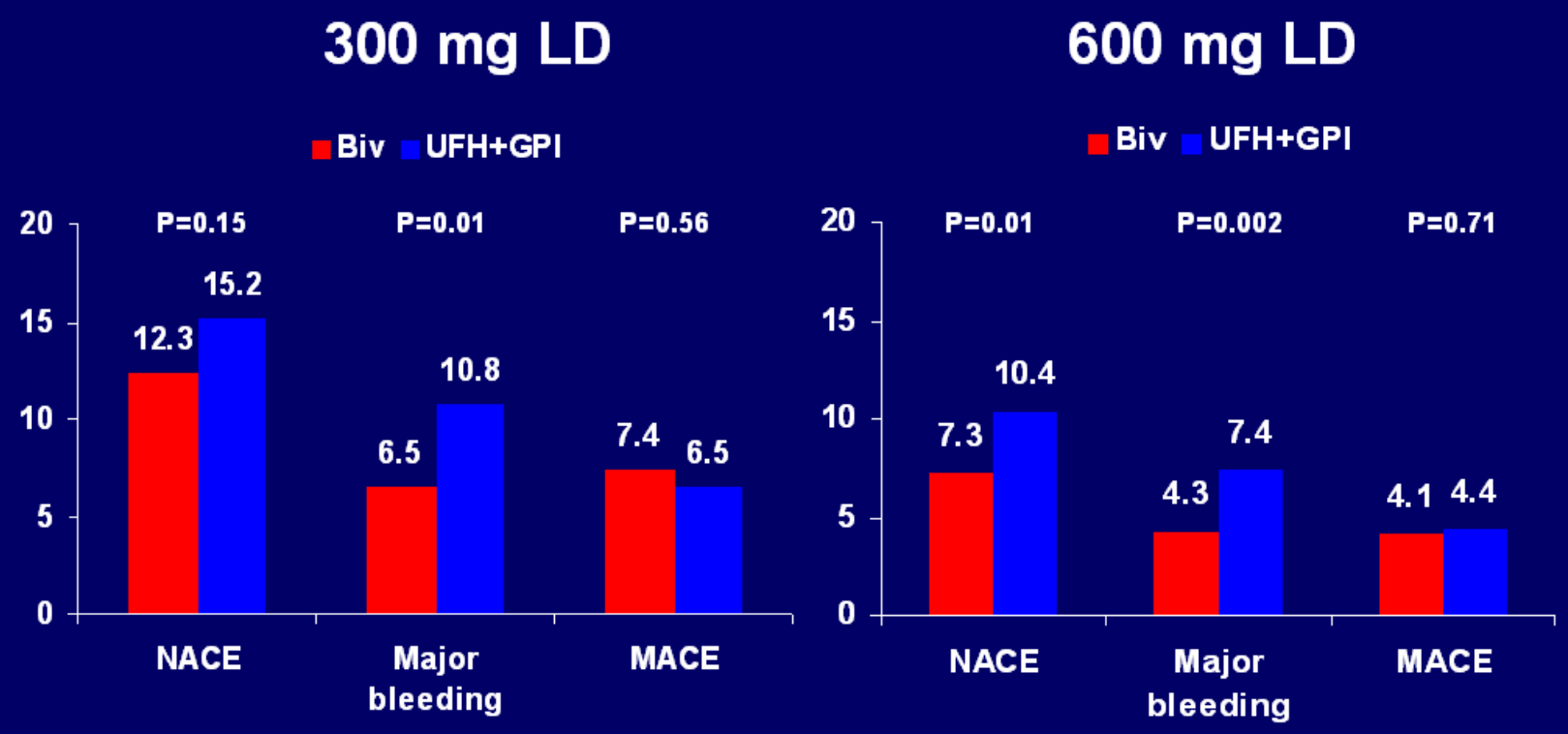


*NACE = MACE or major bleeding
**Not related to CABG
***MACE = All cause death, reinfarction, ischemic TVR or stroke

Dangas et al, SCAI-ACCi2 2008

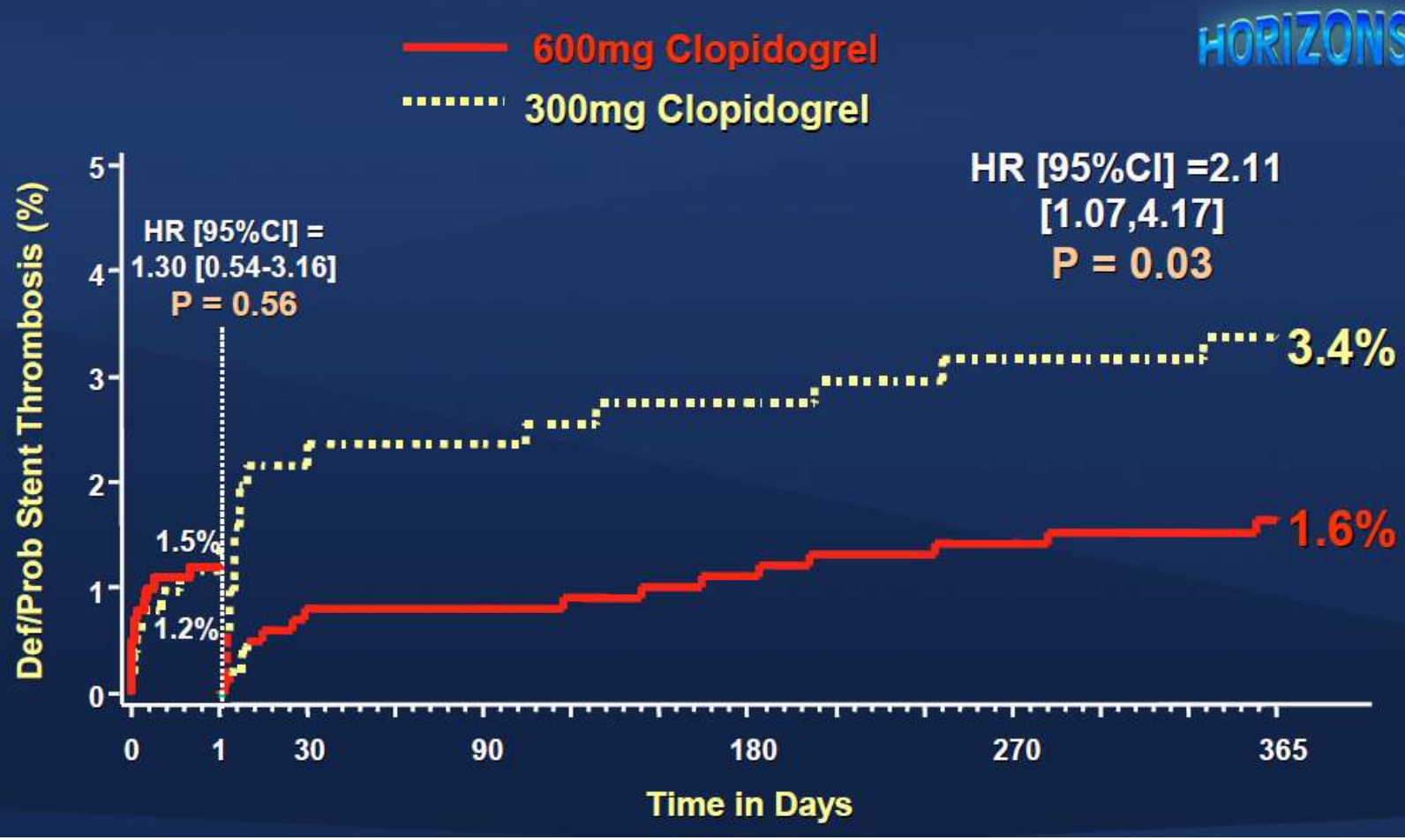
Primary Outcomes (ITT)

- The impact of Biv was independent of the dose of clopidogrel loading. Interaction P values for the above 3 endpoints = 0.48 (NACE) 0.41 (Major bleeding), and 0.75 (MACE).



Dangas et al, SCAI-ACCi2 2008

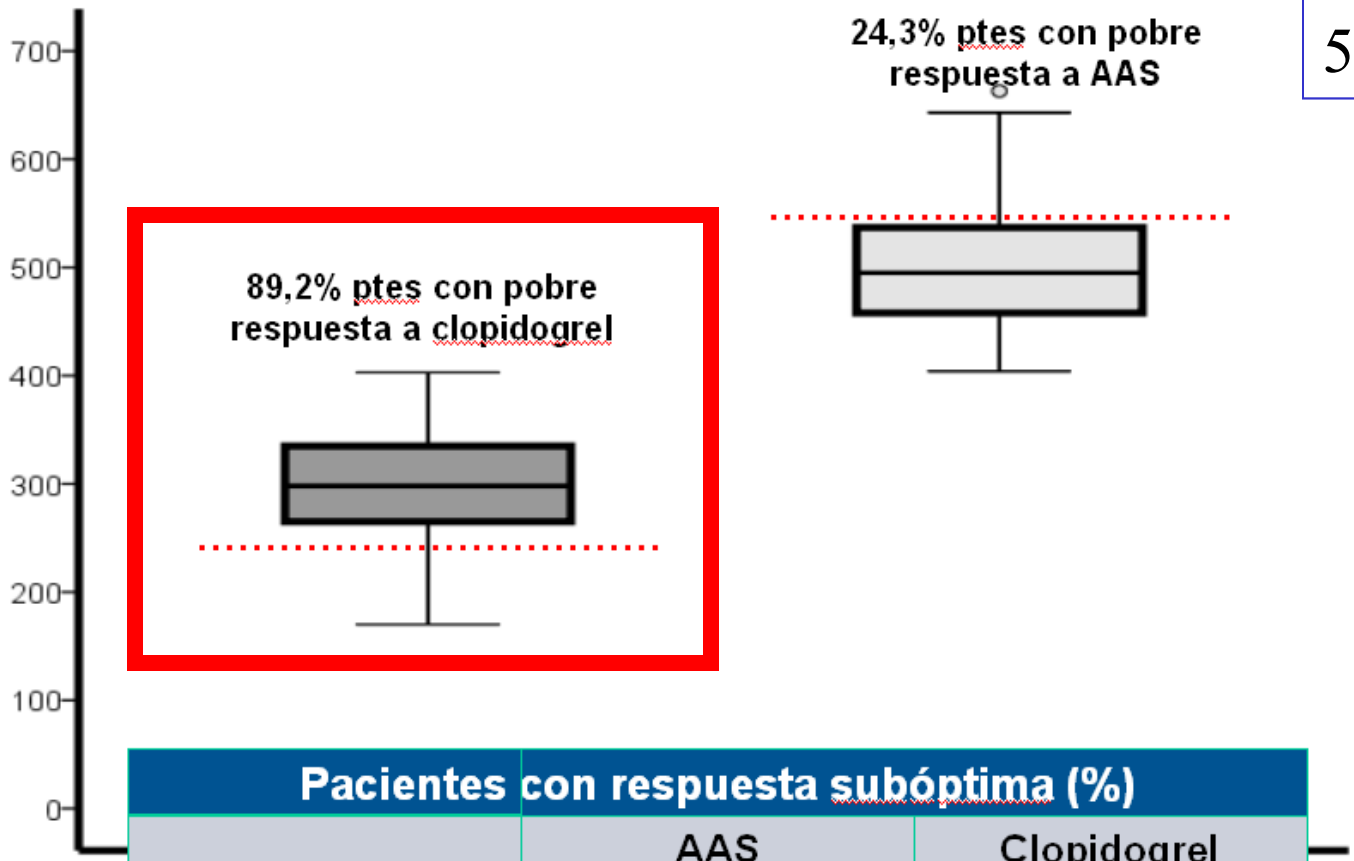
Impact of Clopidogrel Loading Dose on Stent Thrombosis in Bivalirudin Group



Pero,……

Pacientes en ICP primaria

50 pac
600 Clop
500 AAS



Pacientes con respuesta subóptima (%)		
	AAS	Clopidogrel
VerifyNow	24.3%	89.2%
LTA (AA/ADP)	38.9%	84.2%
MEA		95%

IDIBELL
Bellvitge Hospital

Ferreiro JL et al. Thromb Haemost. 2013 Apr 25;110(1).

	Permeabilidad inicial de la ARI
Pacientes con pobre respuesta a Clopidogrel	16%
	p=0.013
Pacientes con buena respuesta a Clopidogrel	66.7%

Ferreiro JL et al. Thromb Haemost. 2013 Apr 25;110(1).

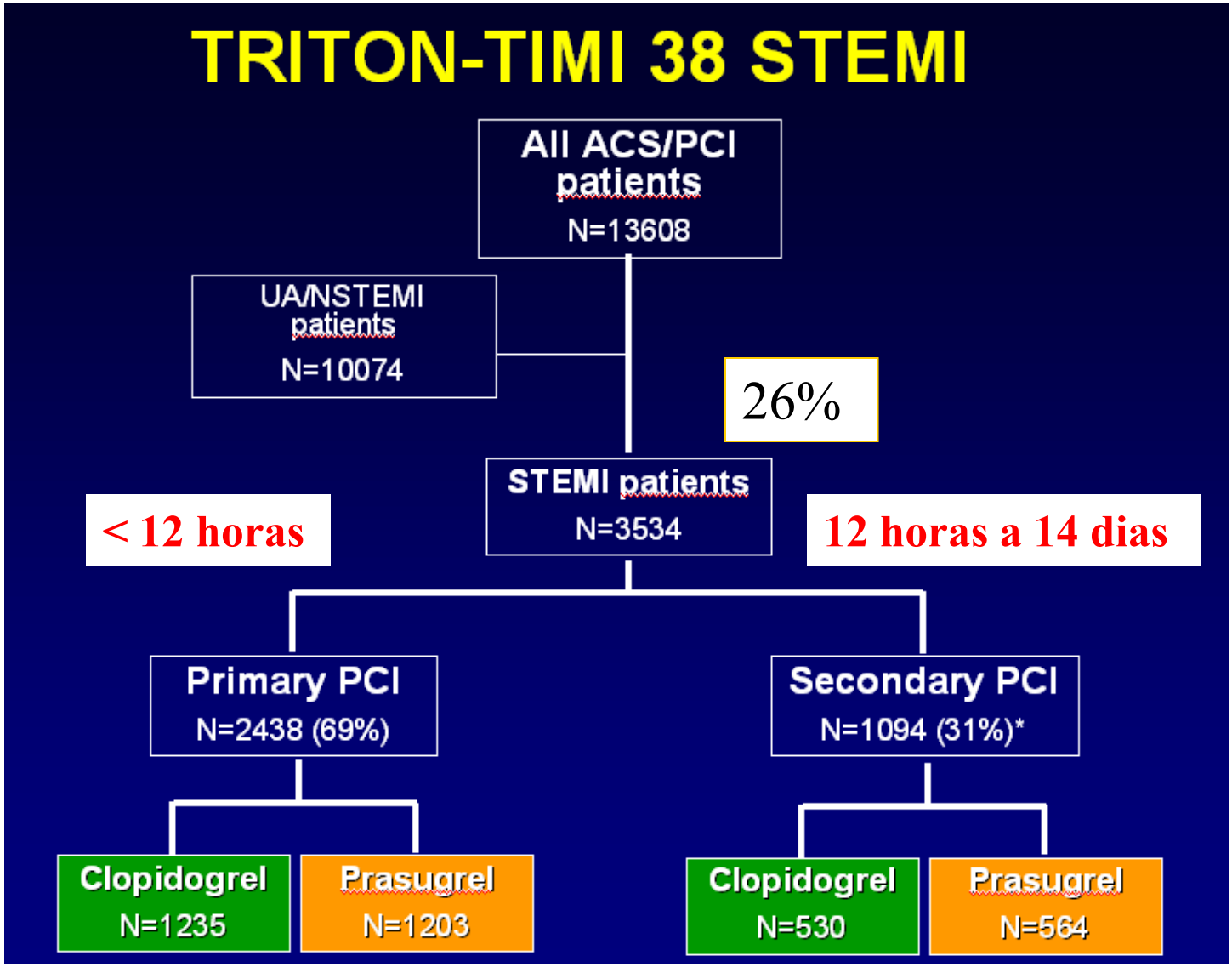
Evidencias que soportan la **superioridad** de la antiagregacion prolongada doble con aspirina mas **nuevos antiagregantes** en el IAMEST

Prasugrel

Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial

Gilles Montalescot, Stephen D Wiviott, Eugene Braunwald, Sabina A Murphy, C Michael Gibson, Carolyn H McCabe, Elliott M Antman, for the TRITON-TIMI 38 investigators

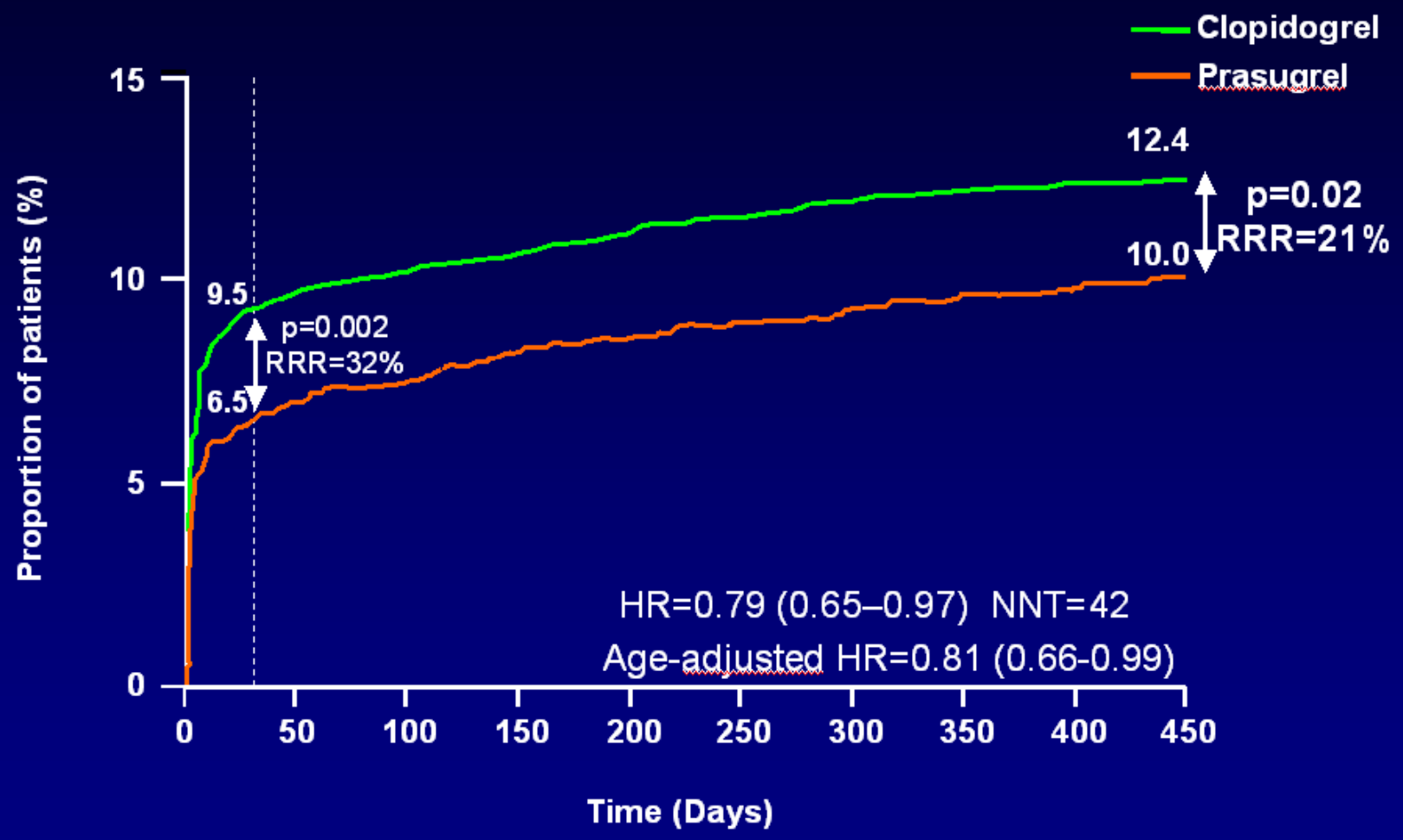
Lancet 2009; 373: 723–31



Carga oral pre ICP	**31%**	**19%**

TRITON TIMI-38 STEMI cohort

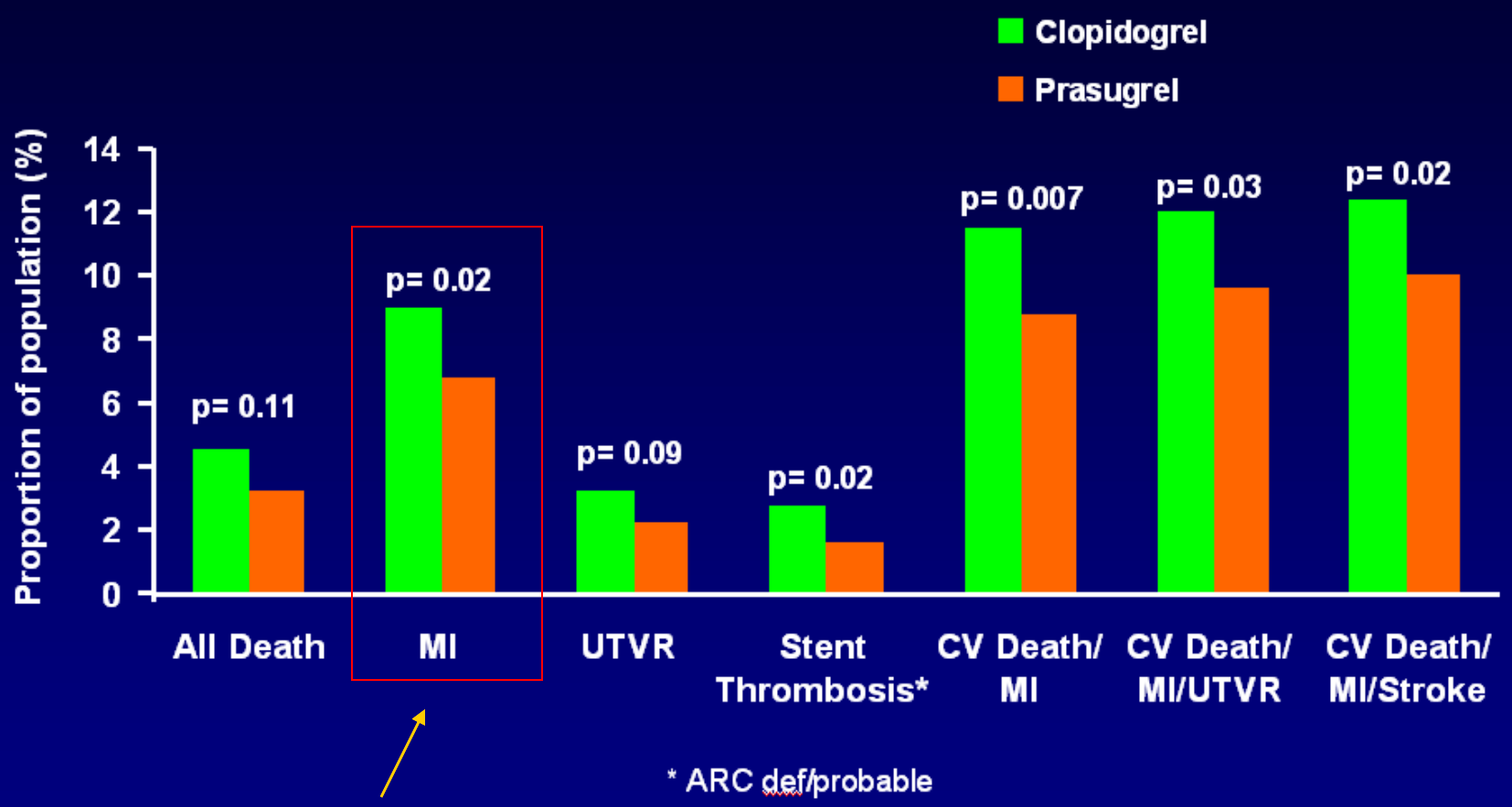
Primary EP (CV death, MI and stroke at 15 months)



Montalescot et al. ESC 2008

TRITON TIMI-38 STEMI cohort

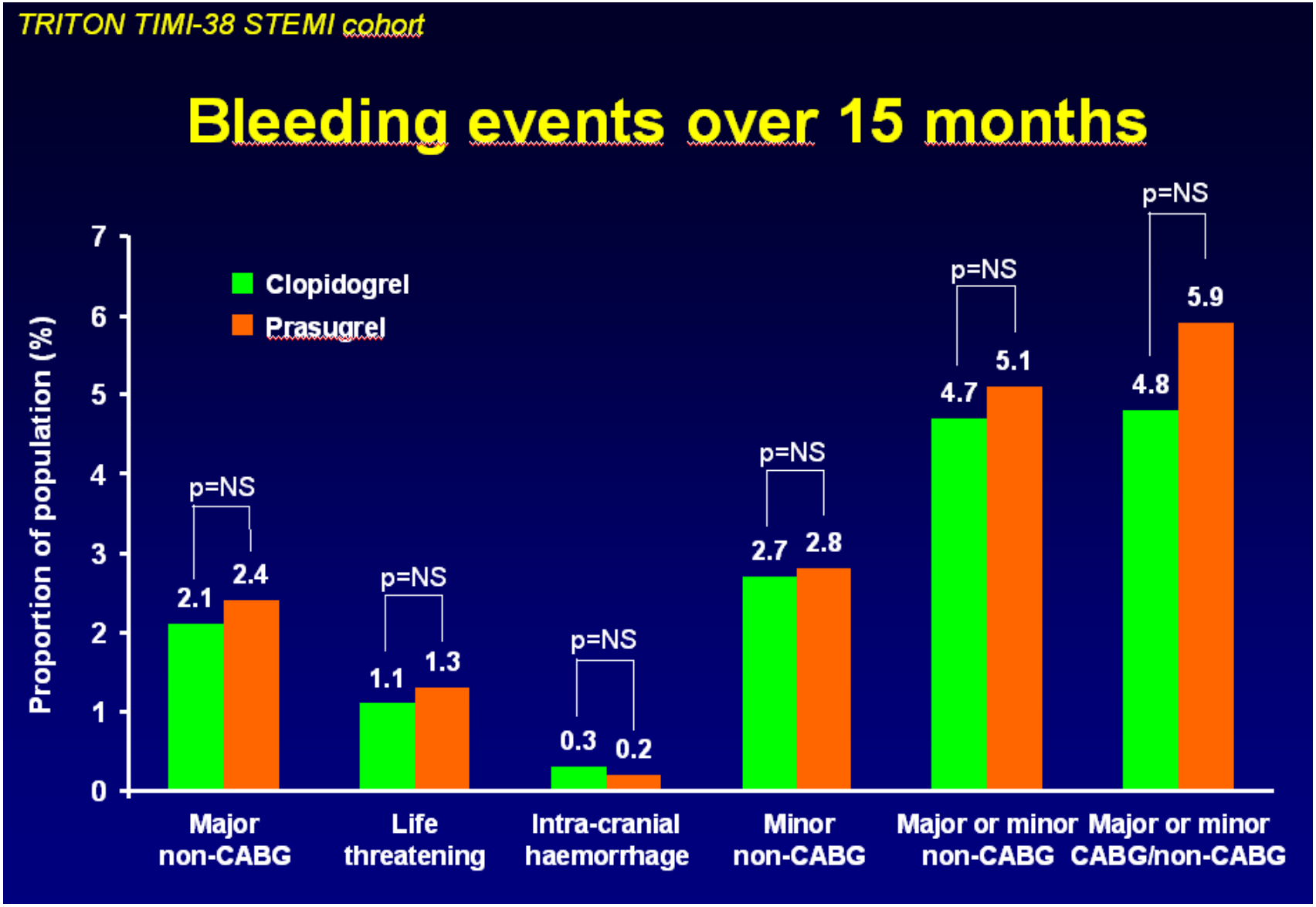
Efficacy endpoints at 15 months



* ARC def/probable

Incluyen peri-ICP

Montalescot et al. ESC 2008

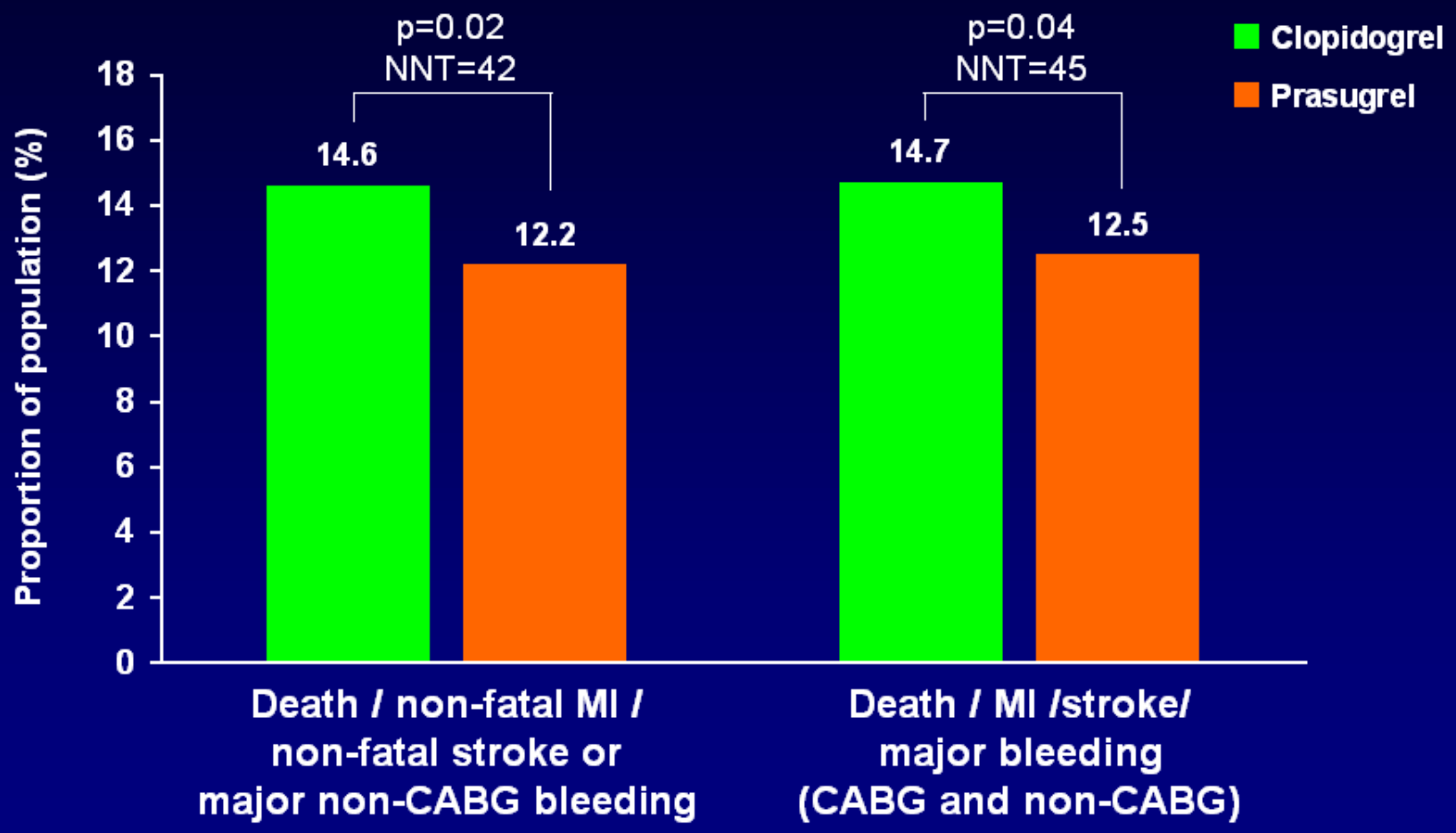


Poblacion de menor riesgo hemorragico que la TRITON- SCASEST

(2 años menos, menos mujeres, menos DM,....)

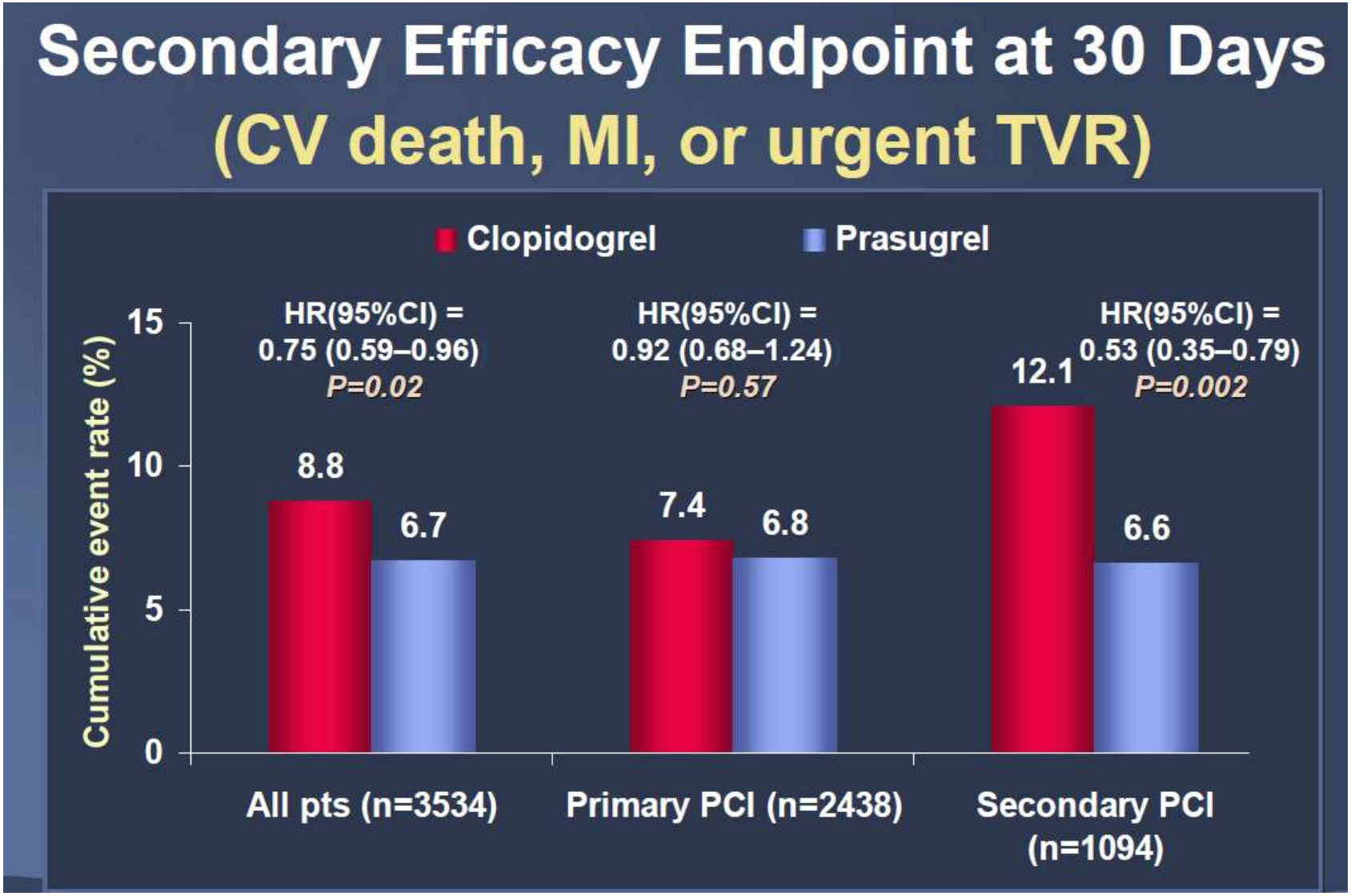
TRITON TIMI-38 STEMI cohort

Net clinical benefit at 15 months



Prasugrel en subgrupos

- Mas beneficio en **infartos anteriores**
  - (interaccion significativa)
- Mas beneficio en **ICP 2ª**
  - (no interaccion significativa)
- Mas beneficio con **inh IIb-IIIa** (usados en 62%)
  - (no interaccion significativa)
- Mas sangrado en **ICP 1ª**
  - (interaccion significativa)



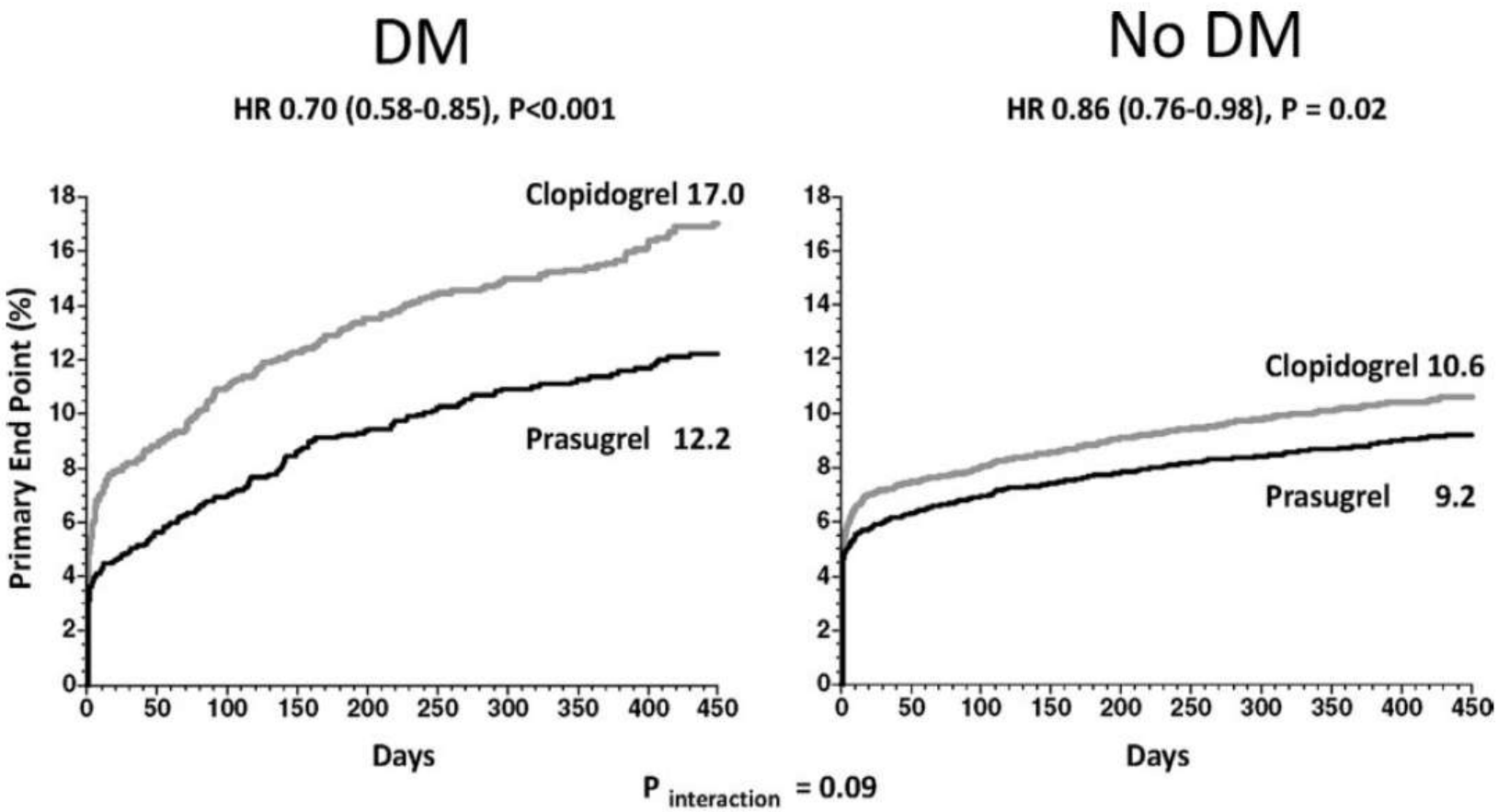
Beneficio de Prasugrel en ICP secundaria

(en los 14 días tras infarto, por isquemia)

Montalescot G et al.
Lancet 2009;373:723–31

	Clopidogrel	Prasugrel	Hazard ratio (95% CI)	p	Number needed to treat (95% CI)*
Efficacy endpoints					
Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)					
All STEMI cohort	216 (12·4%)	174 (10·0%)	0·79 (0·65–0·97)	0·0221	41 (24–266)
Primary PCI	142 (11·6%)	121 (10·2%)	0·87 (0·68–1·11)	0·2662	..
Secondary PCI	74 (14·1%)	53 (9·6%)	0·65 (0·46–0·92)	0·0154	21 (14–100)
Key secondary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal urgent target vessel revascularisation)					
All STEMI cohort	209 (12·0%)	168 (9·6%)	0·79 (0·65–0·97)	0·0250	42 (25–316)
Primary PCI	136 (11·2%)	118 (9·9%)	0·89 (0·70–1·14)	0·3571	..
Secondary PCI	73 (13·9%)	50 (9·0%)	0·62 (0·43–0·89)	0·0090	20 (13–71)
Cardiovascular death or myocardial infarction	201 (11·5%)	153 (8·8%)	0·75 (0·61–0·93)	0·0071	36 (23–124)
Cardiovascular death	58 (3·4%)	43 (2·4%)	0·74 (0·50–1·09)	0·1290	..
All-cause death	76 (4·3%)	58 (3·3%)	0·76 (0·54–1·07)	0·1127	..
Myocardial infarction	157 (9·0%)	119 (6·8%)	0·75 (0·59–0·95)	0·0163	45 (28–226)
Stroke	25 (1·5%)	26 (1·6%)	1·03 (0·60–1·79)	0·9110	..
Urgent target vessel revascularisation	54 (3·2%)	38 (2·2%)	0·70 (0·46–1·06)	0·0870	..
Stent thrombosis					
All STEMI cohort	45 (2·8%)	26 (1·6%)	0·58 (0·36–0·93)	0·0232	84 (55–537)
Primary PCI	30 (2·7%)	16 (1·5%)	0·55 (0·30–1·00)	0·0476	..
Secondary PCI	15 (3·1%)	10 (1·9%)	0·63 (0·28–1·39)	0·2458	..
Safety endpoints					
TIMI major bleeding unrelated to CABG surgery					
All STEMI cohort	34 (2·1%)	38 (2·4%)	1·11 (0·70–1·77)	0·6451	..
Primary PCI	22 (1·9%)	33 (3·1%)	1·54 (0·90–2·64)	0·1143	..
Secondary PCI	12 (2·5%)	5 (0·9%)	0·39 (0·14–1·11)	0·0671†	..
TIMI life-threatening bleeding	18 (1·1%)	20 (1·3%)	1·11 (0·59–2·10)	0·7500	..
Fatal TIMI major bleeding unrelated to CABG surgery	2 (0·13%)	7 (0·45%)	3·48 (0·72–16·75)	0·0973	..
TIMI major or minor bleeding unrelated to CABG surgery	77 (4·7%)	83 (5·1%)	1·07 (0·79–1·47)	0·6494	..
TIMI major bleeding after CABG surgery (4%)	2/73 (2·7%)	12/64 (18·8%)	8·19 (1·76–38·18)‡	0·0033	6 (2–51)
TIMI major or minor bleeding after CABG surgery	3/73 (4·1%)	14/64 (21·9%)	6·53 (1·78–23·94)‡	0·0032	6 (2–33)
TIMI major or minor bleeding, including CABG or non-CABG bleeds	80 (4·8%)	96 (5·9%)	1·20 (0·89–1·61)	0·2339	..

TRITON-TIMI 38 Diabéticos



Datos del estudio general

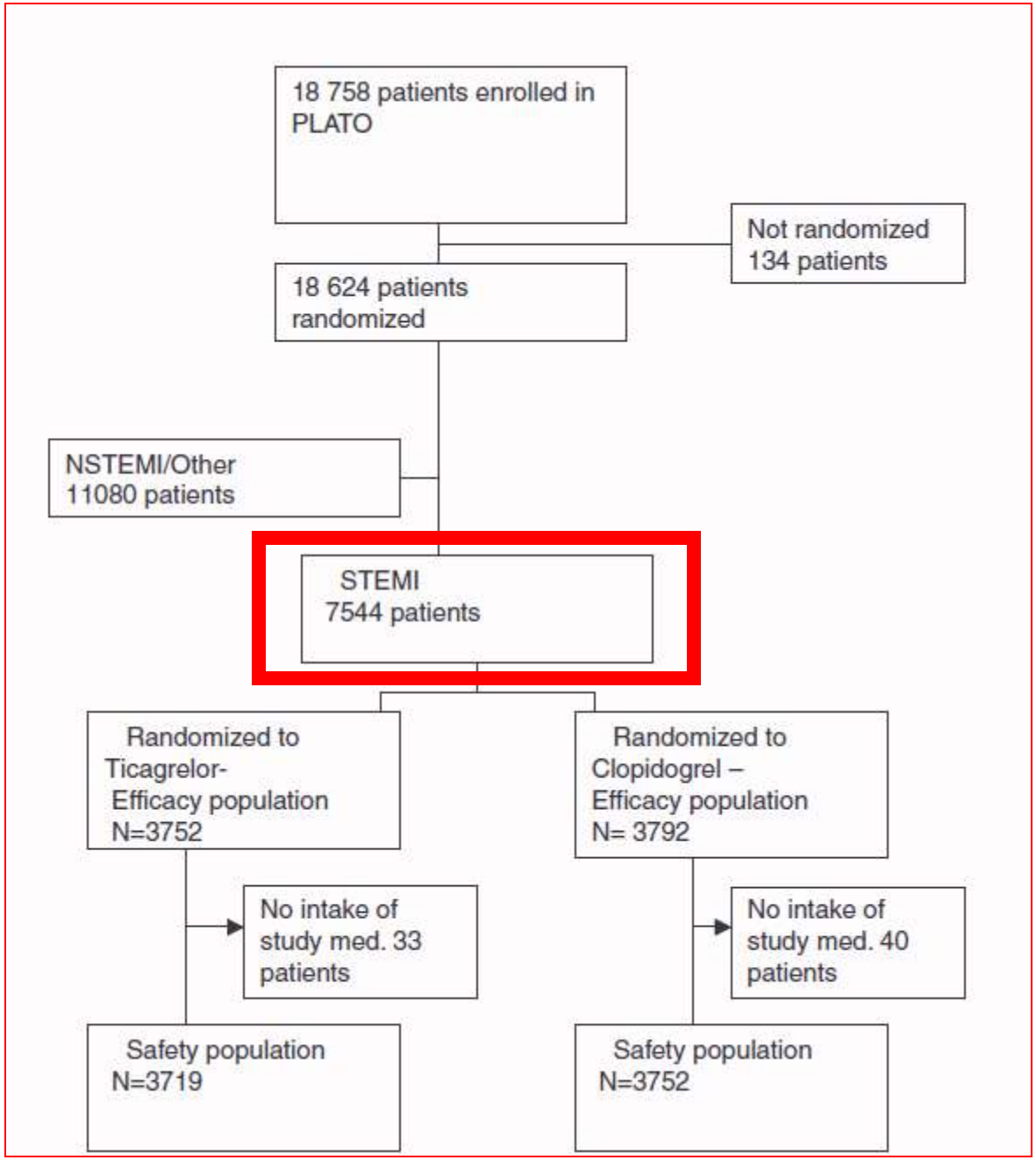
Ticagrelor

Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention

A Platelet Inhibition and Patient Outcomes (PLATO) Trial Subgroup Analysis

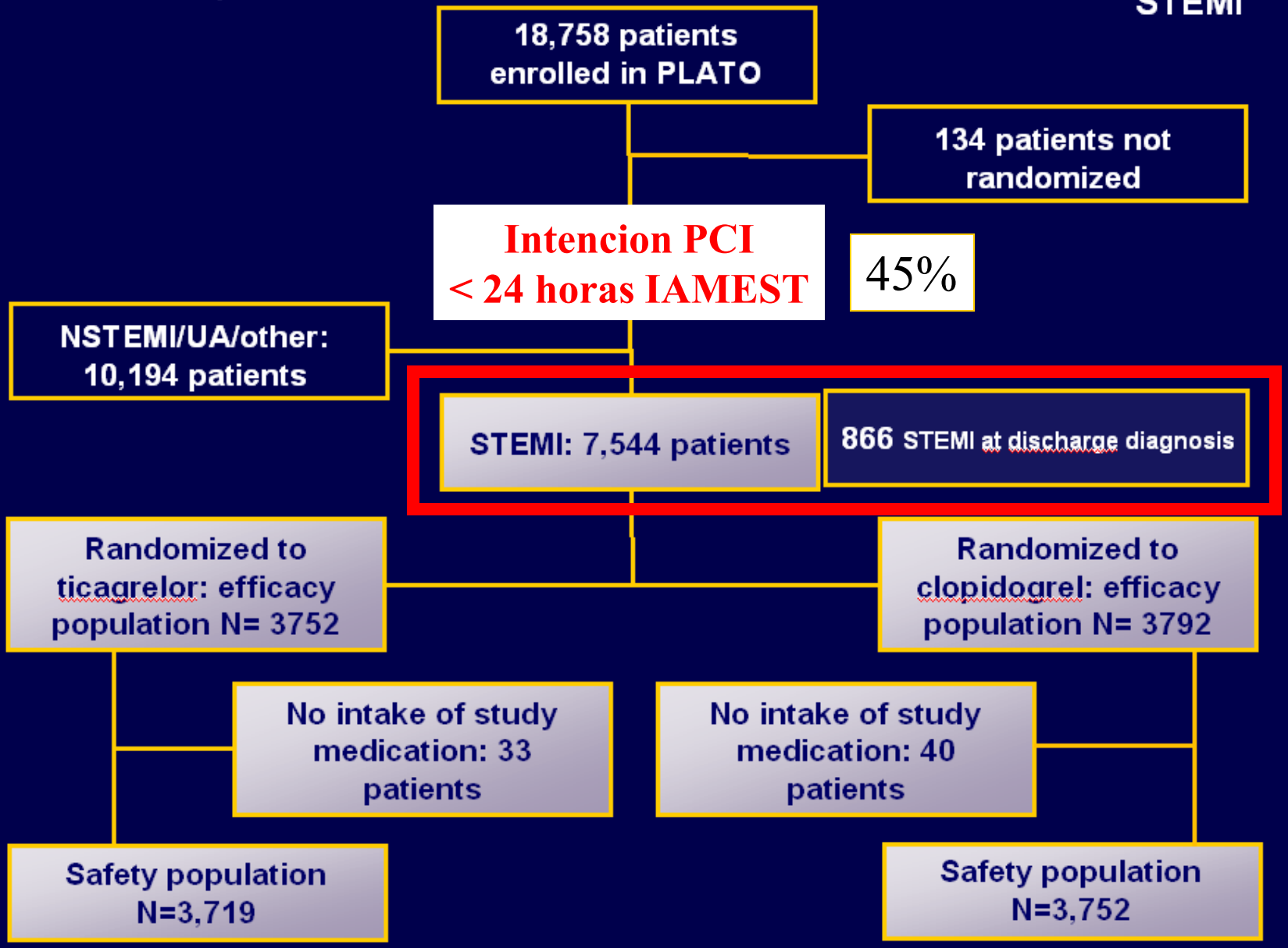
Philippe Gabriel Steg, MD; Stefan James, MD, PhD; Robert A. Harrington, MD; Diego Ardissino, MD; Richard C. Becker, MD; Christopher P. Cannon, MD; Håkan Emanuelsson, MD, PhD; Ariel Finkelstein, MD; Steen Husted, MD, DSc; Hugo Katus, MD; Jan Kilhamn, MD, PhD; Sylvia Olofsson, BSc; Robert F. Storey, MD, DM; W. Douglas Weaver, MD; Lars Wallentin, MD, PhD; for the PLATO Study Group

Circulation. 2010;122:2131-2141


18 758 patients enrolled in PLATO
Not randomized 134 patients
18 624 patients randomized
NSTEMI/Other 11080 patients
STEMI 7544 patients
Randomized to Ticagrelor- Efficacy population N=3752
Randomized to Clopidogrel – Efficacy population N= 3792
No intake of study med. 33 patients
No intake of study med. 40 patients
Safety population N=3719
Safety population N=3752

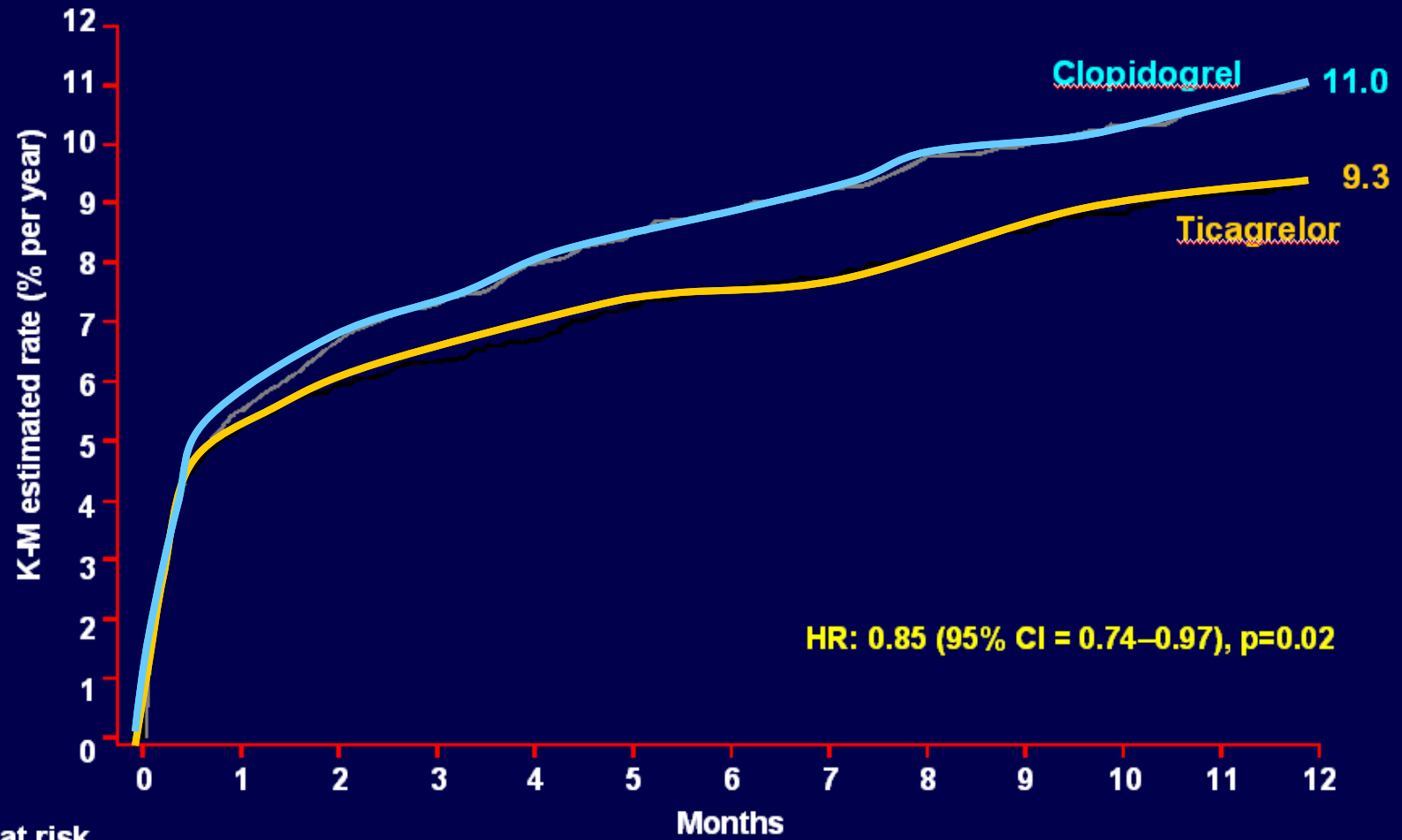
Patient disposition

PLATO STEMI



Primary endpoint: CV death, MI or stroke

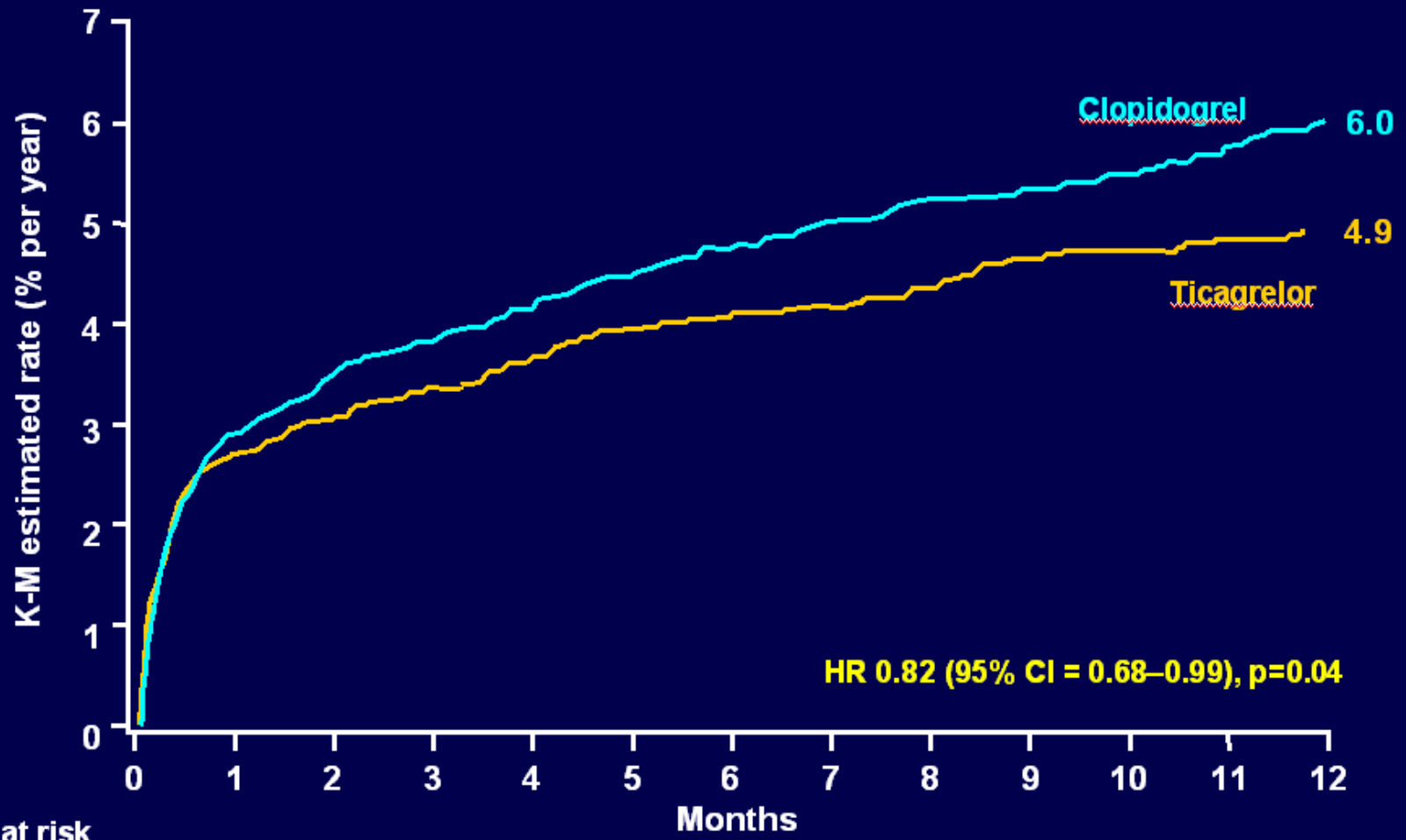
PLATO STEMI



No. at risk							
Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868

All cause mortality

PLATO STEMI



No. at risk							
Ticagrelor	4,201	4,005	3,962	3,876	3,150	2,413	1,993
Clopidogrel	4,229	4,029	3,989	3,912	3,195	2,471	1,980

Hierarchical testing of major efficacy endpoints

PLATO STEMI

Endpoint*	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Primary endpoint, %				
CV death + MI + stroke	9.4	10.8	0.87 (0.75–1.01)	0.07
Secondary endpoints, %				
Total death + MI + stroke	9.8	11.3	0.87 (0.75–1.00)	0.05
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	13.3	15.0	0.87 (0.77–0.99)	0.03
MI (No incluyen peri-ICP)	4.7	5.8	0.80 (0.65–0.98)	0.03
CV death	4.5	5.5	0.83 (0.67–1.02)	0.07
Stroke	1.7	1.0	1.63 (1.07–2.48)	0.07

Trombosis Definitivas o probables

Tic 2.6% vs **Clop** 3.4%

p=0.03

p=0.05

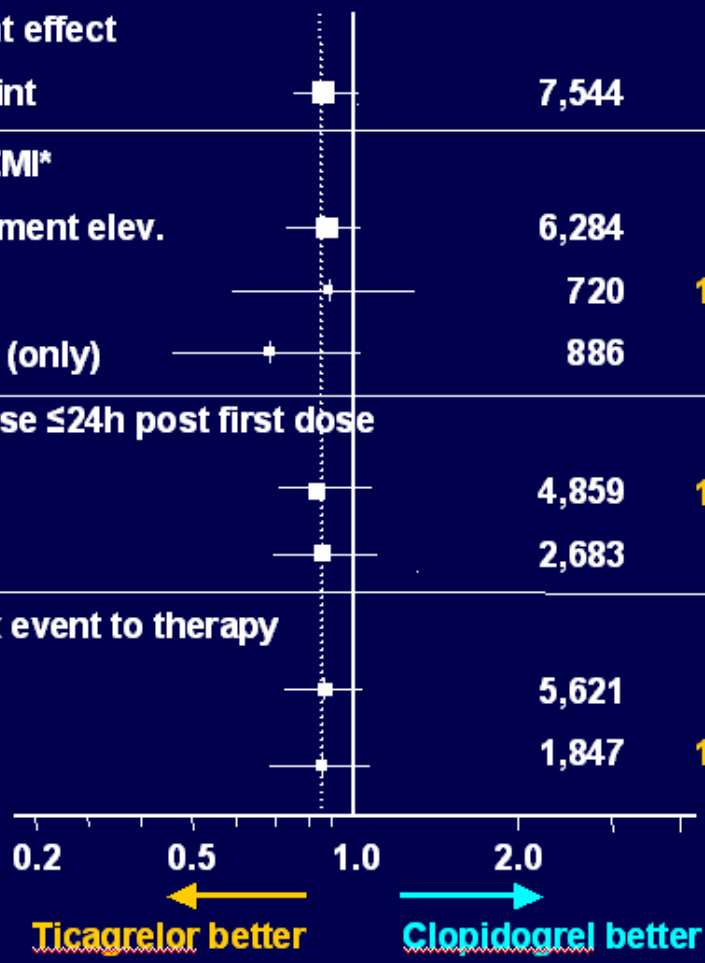
Trombosis Definitivas

Tic 1.6% vs **Clop** 2.4%

Primary efficacy endpoint in selected pre-defined subgroups

PLATO STEMI

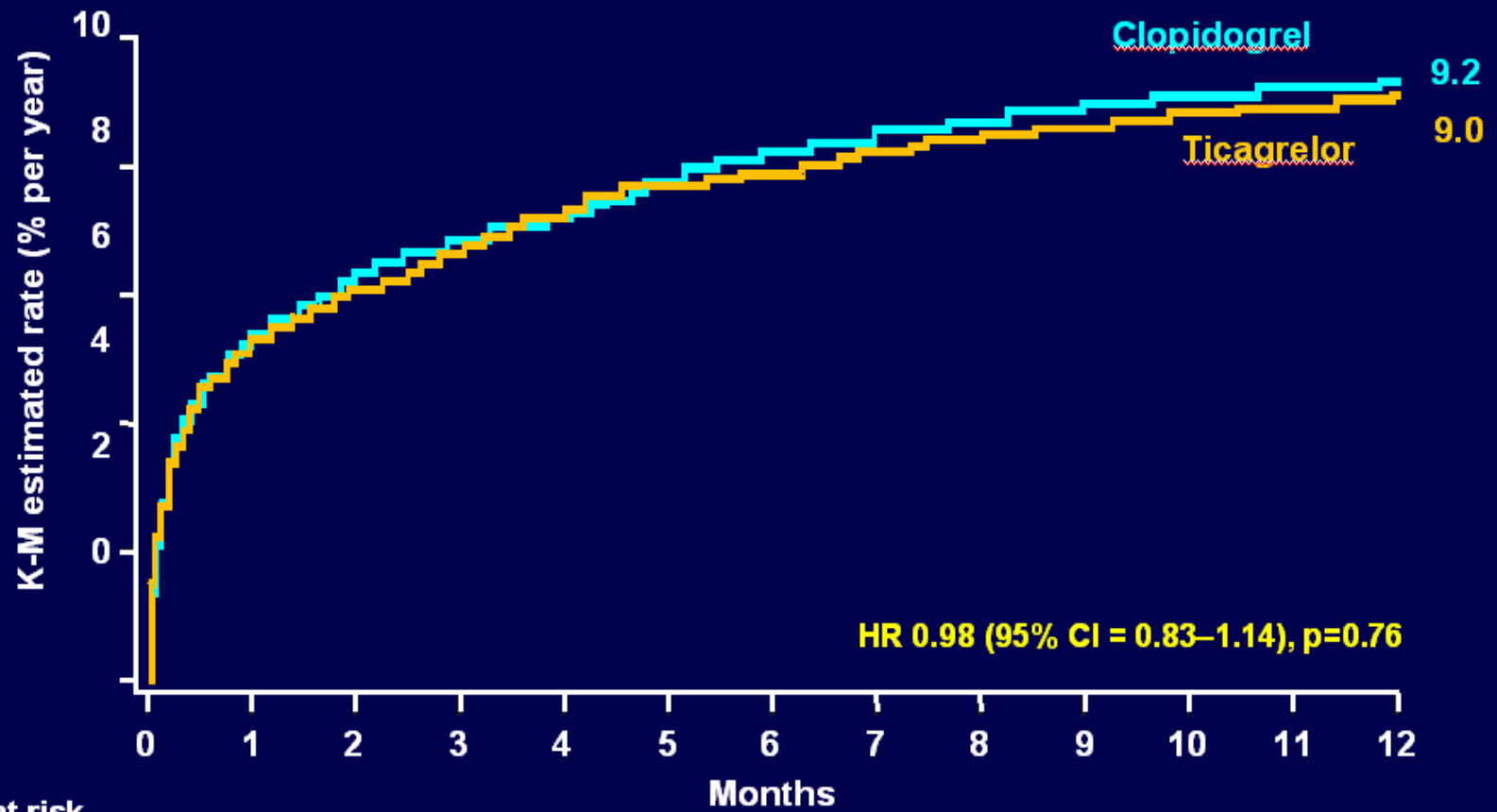
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	p-value (Interaction)
Overall treatment effect						
Primary Endpoint		7,544	9.4	10,8	0.87 (0.75, 1.01)	
Definition of STEMI*						0.91
Persist. ST-segment elev.		6,284	8.9	10.4	0.87 (0.74, 1.02)	
LBBB		720	14.5	14.5	0.89 (0.59, 1.34)	
Final diagnosis (only)		886	8.4	12.5	0.67 (0.44, 1.02)	
Intended clop dose ≤24h post first dose						0.63
300 mg		4,859	10.4	11.6	0.89 (0.75,1.06)	
600 mg		2,683	7.7	9.4	0.82 (0.63, 1.08)	
Time from index event to therapy						0.91
<12 hours		5,621	8.3	9.3	0.89 (0.74, 1.07)	
≥12 hours		1,847	12.8	14.6	0.88 (0.68, 1.13)	



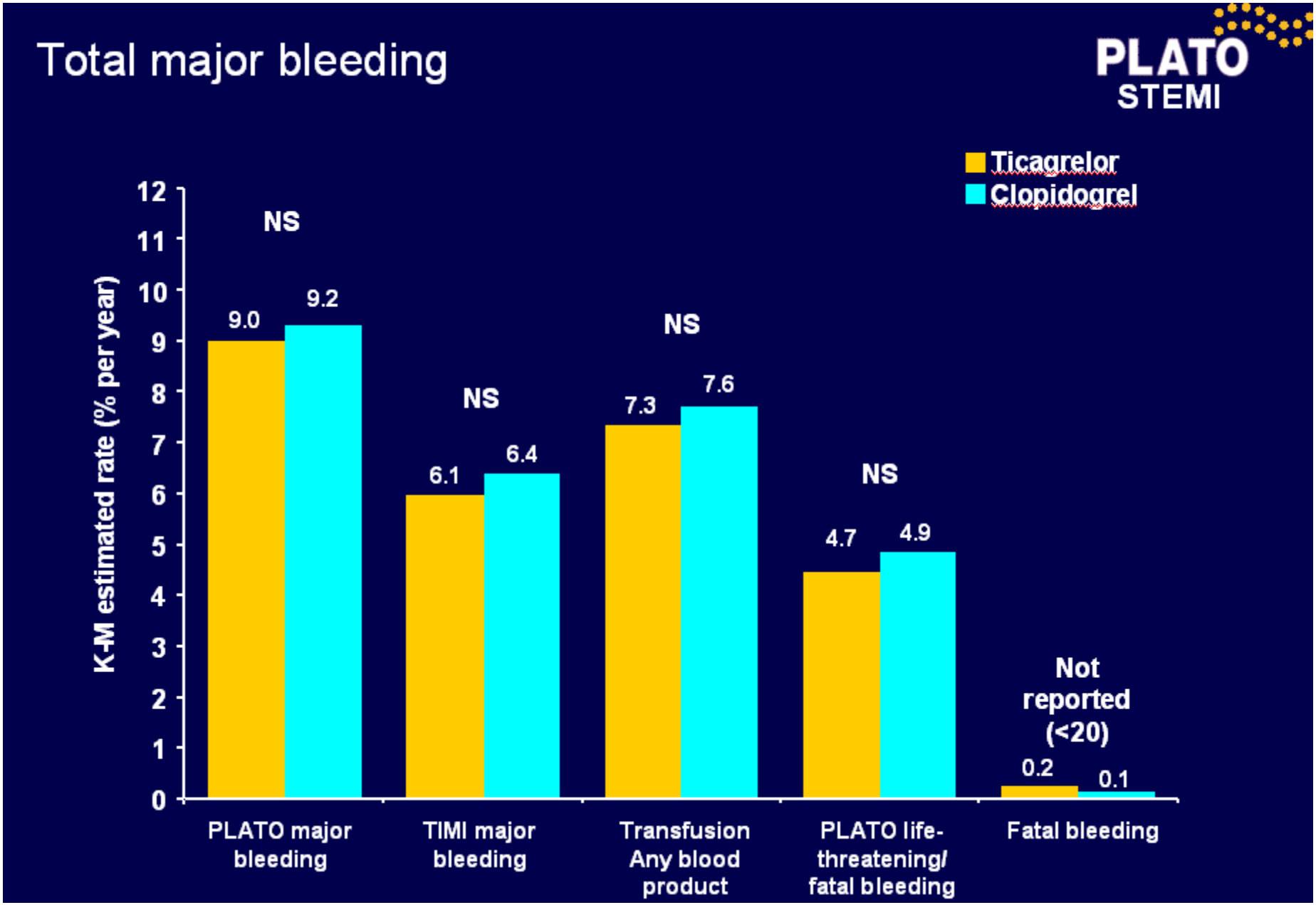
*Patients with LBBB and ST-elevation were classified as LBBB

Primary safety event: major bleeding

PLATO STEMI



No. at risk							
Ticagrelor	3,719	3,079	2,920	2,812	2,183	1,592	1,459
Clopidogrel	3,752 3,092	2,972	2,850	2,202	1,624	1,471	



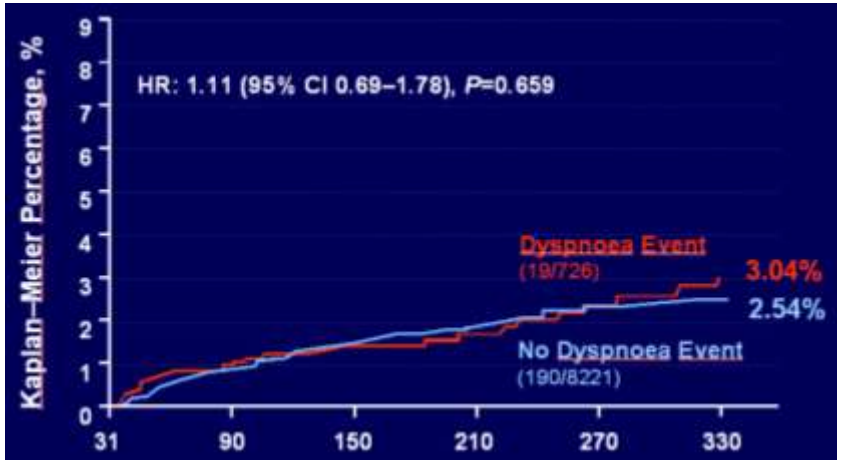
Como en TRITON, perfil de menor riesgo que grupo SCASEST

Other findings

PLATO STEMI

All patients	Ticagrelor (n=4,165)	Clopidogrel (n=4,181)	p-value*
Dyspnoea, %			
Any	12.9	8.3	<0.0001
Requiring discontinuation of study treatment	0.5	0.1	0.0003
Bradycardia-related events, %			
Bradycardia	4.6	4.9	0.57
Pacemaker placement	1.2	1.0	0.35
Syncope	1.0	0.8	0.35
Heart block	1.0	0.9	0.82

Disnea
sin impacto
pronostico

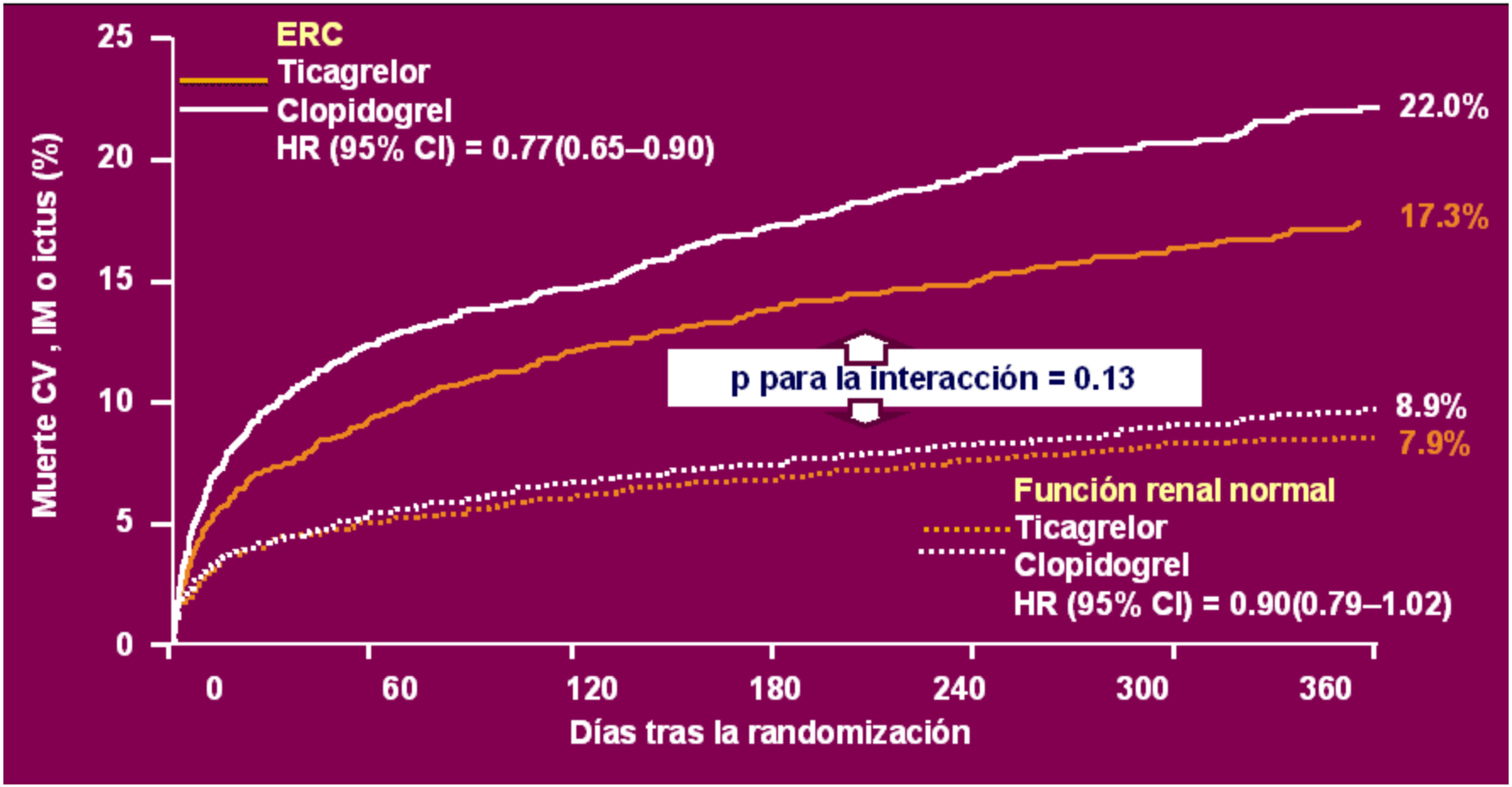


Datos interesantes de la poblacion en PLATO STEMI

- 44% con tratamiento con Clopidogrel previo
- 36% se usaron inh IIb-IIIa

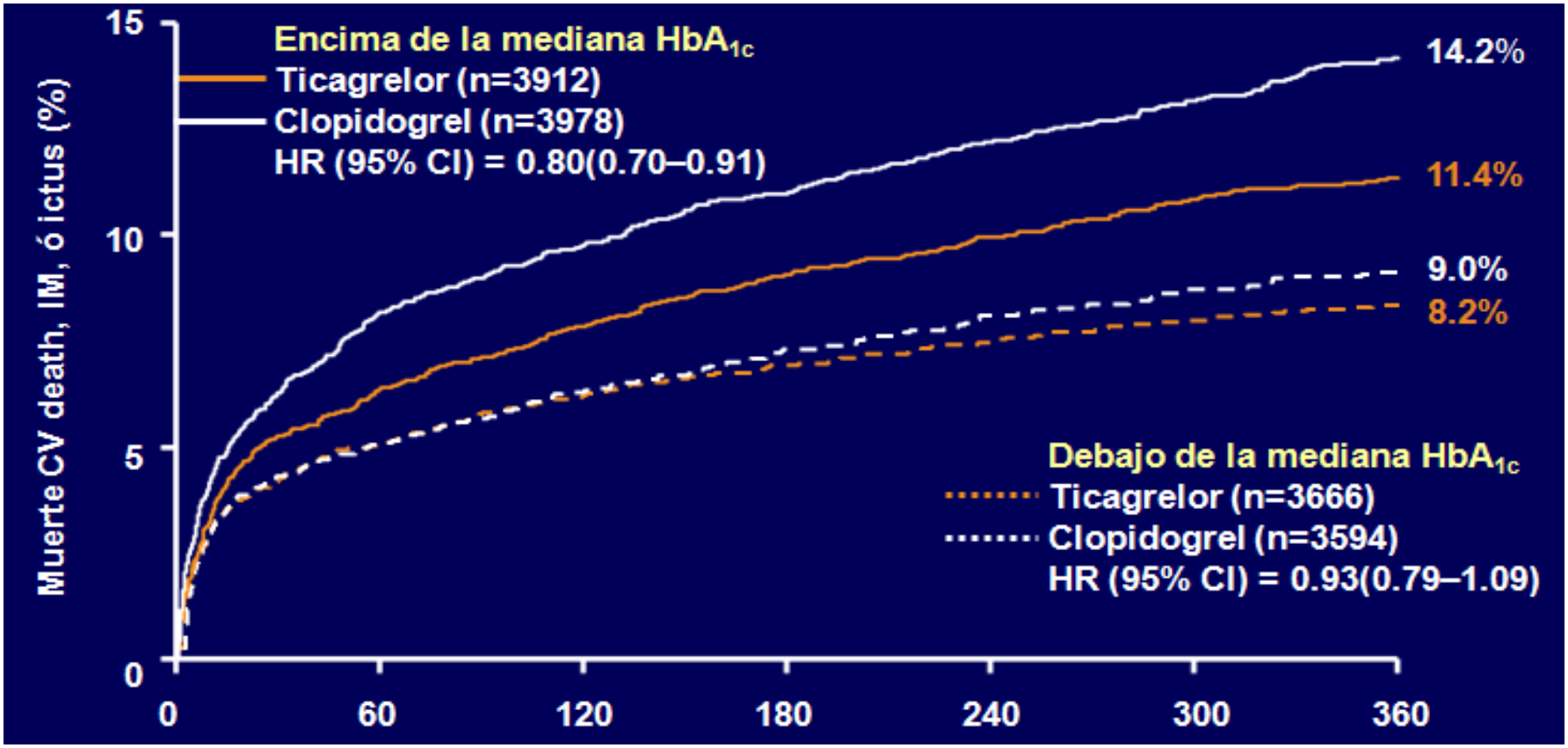
- ICP en < 12 horas de inclusion 72%
- ICP en la hospitalizacion 82%
- CABG 2,5%

Beneficio en IRC



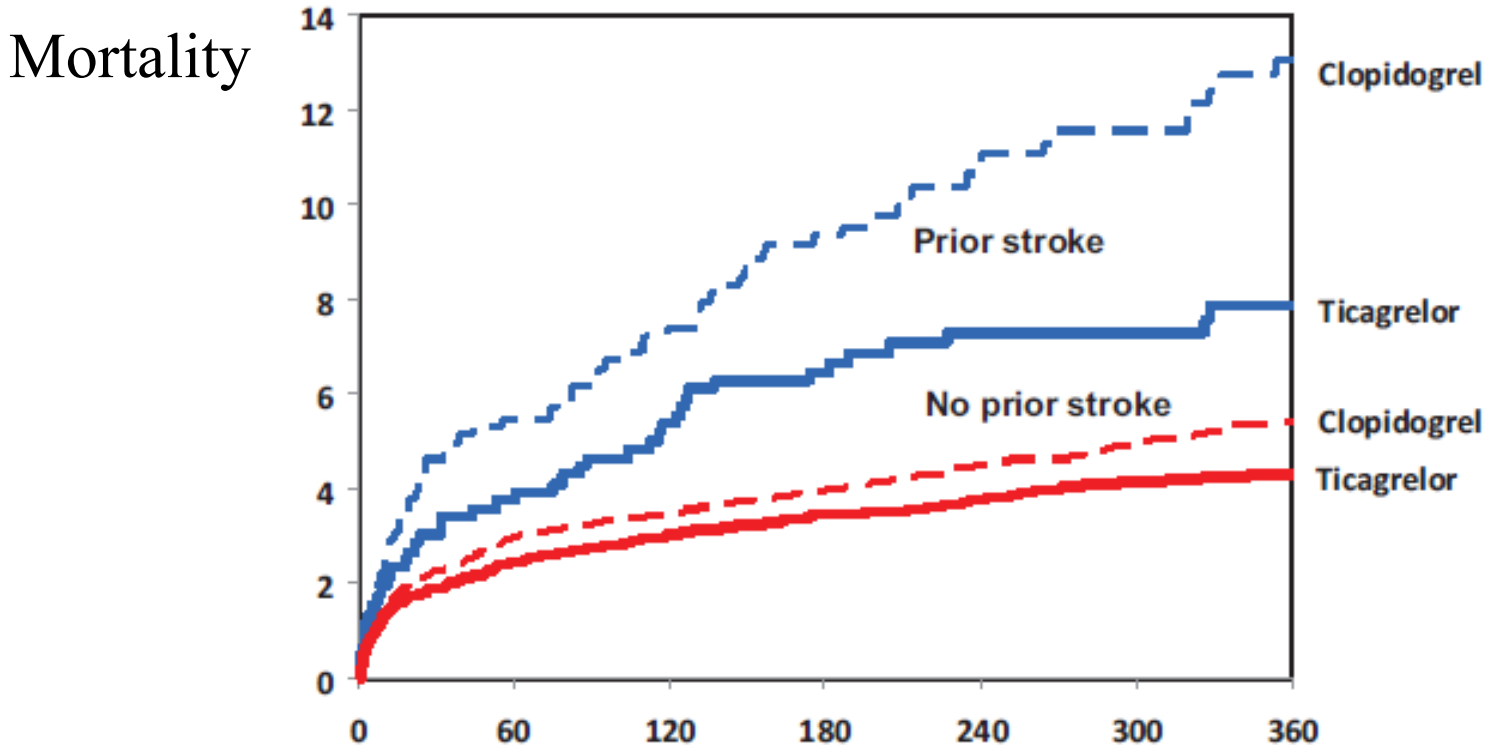
Datos de estudio general

Beneficio en Diabetes



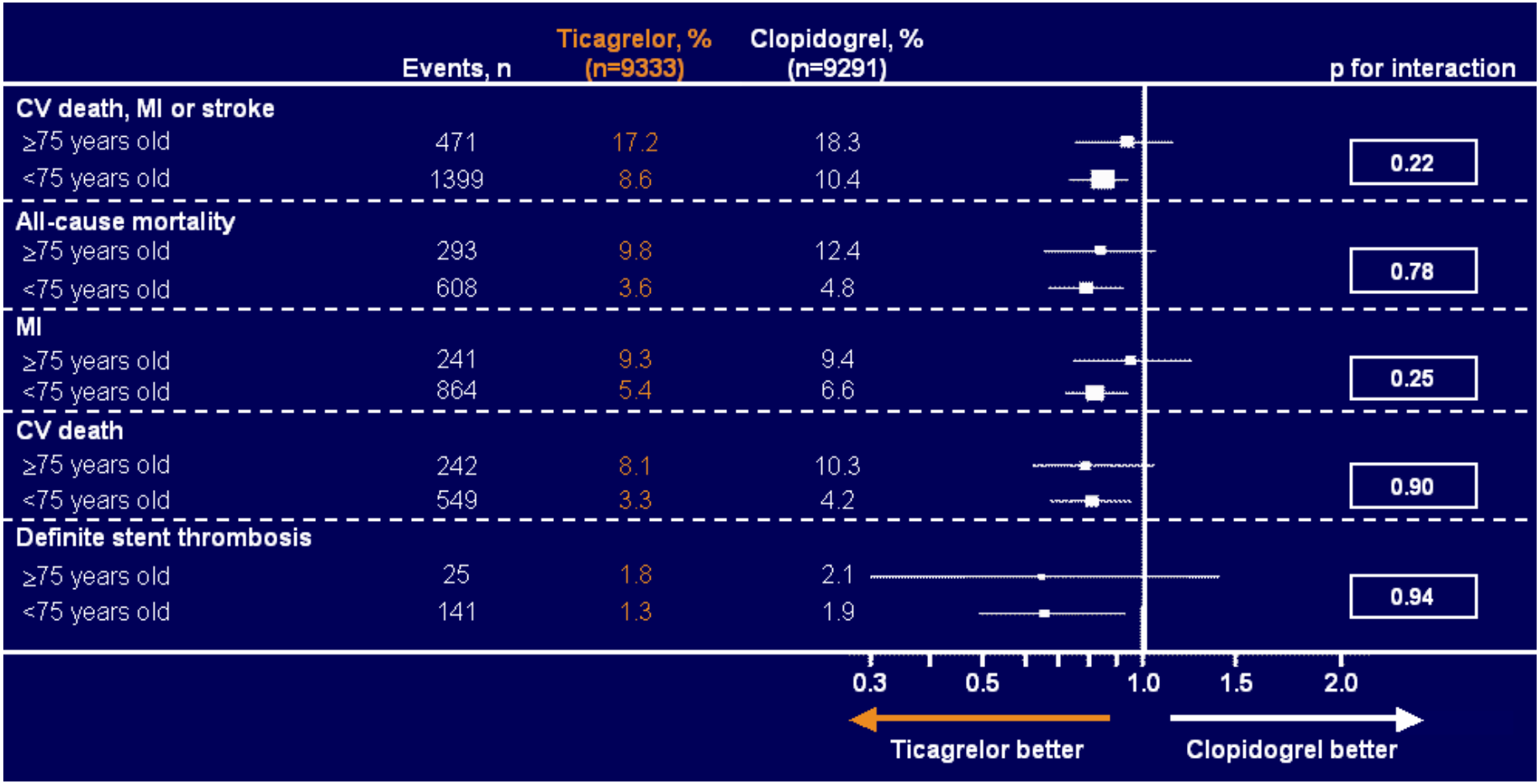
Datos de estudio general

Beneficio con ACVA previo



Datos de estudio general

Beneficio en > 75 años



Datos de estudio general

Diferencias entre estudios

TRITON-STEMI	PLATO-STEMI
• 3.534 pacientes	• 8.410 pacientes
• Infarto hasta 14 días	• Infarto < 24 h
• ICP 97%	• ICP 82%
• No Clopi pre	• Mitad con Clopi pre
• Carga Prasugrel mayoria“en ó tras ICP”	• Carga de Ticagrelor “antes de ICP”
• Mayoria IIb-IIIa	• Minoria IIb-IIIa

Mortalidad CV y total a 12 meses con Clopidogrel:

2,4% y 2,6% 5,5% y 6,1%

¿ Existen **diferencias** entre los **nuevos antiagregantes** que tengan implicaciones de uso en el IAMEST ?

Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients

RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study

Guido Parodi, MD, PhD, Renato Valenti, MD, Benedetta Bellandi, MD, Angela Migliorini, MD, Rossella Marcucci, MD, Vincenzo Comito, MD, Nazario Carrabba, MD, Alberto Santini, MD, Gian Franco Gensini, MD, Rosanna Abbate, MD, David Antoniucci, MD

Florence, Italy

J Am Coll Cardiol 2013;61:1061-6

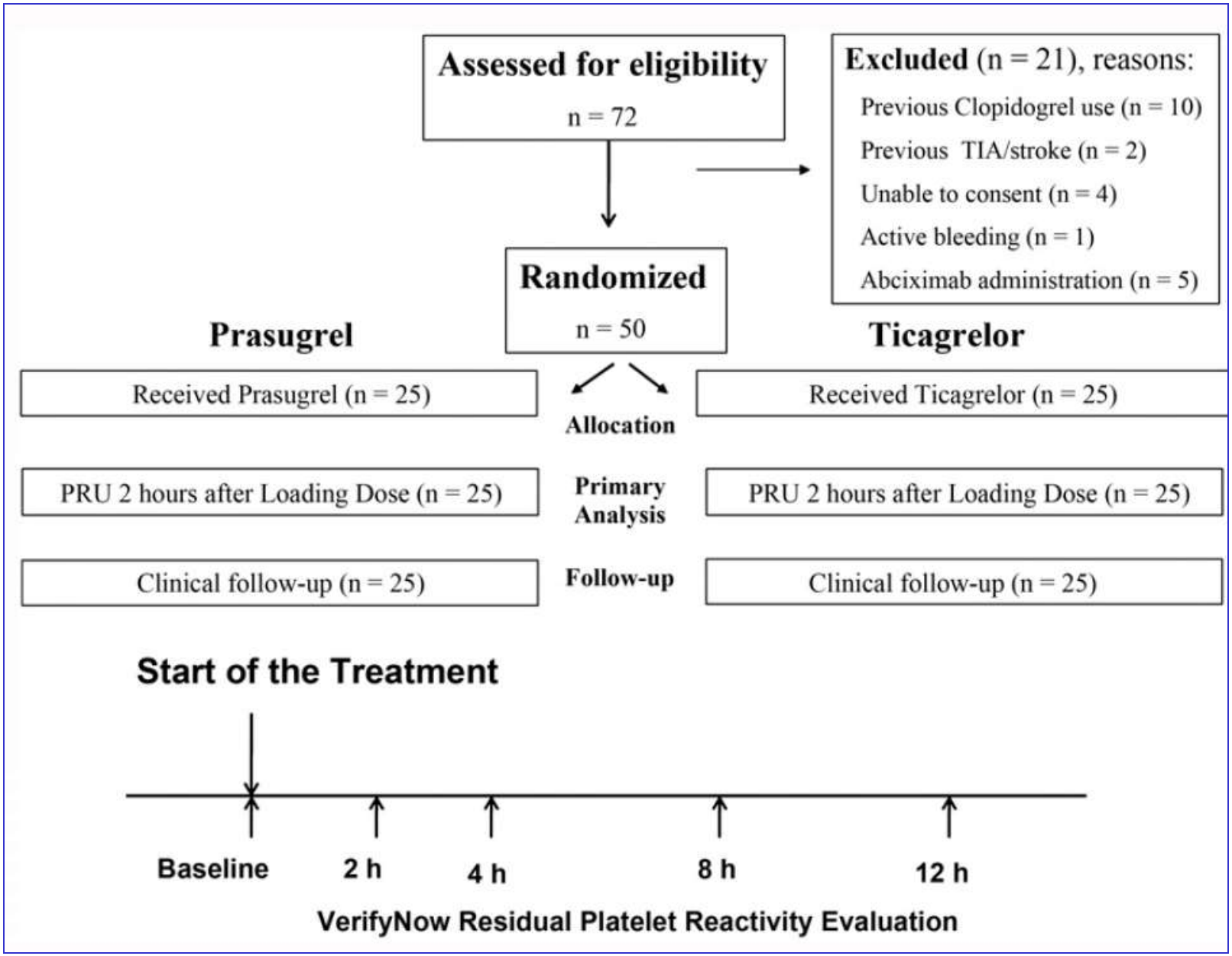
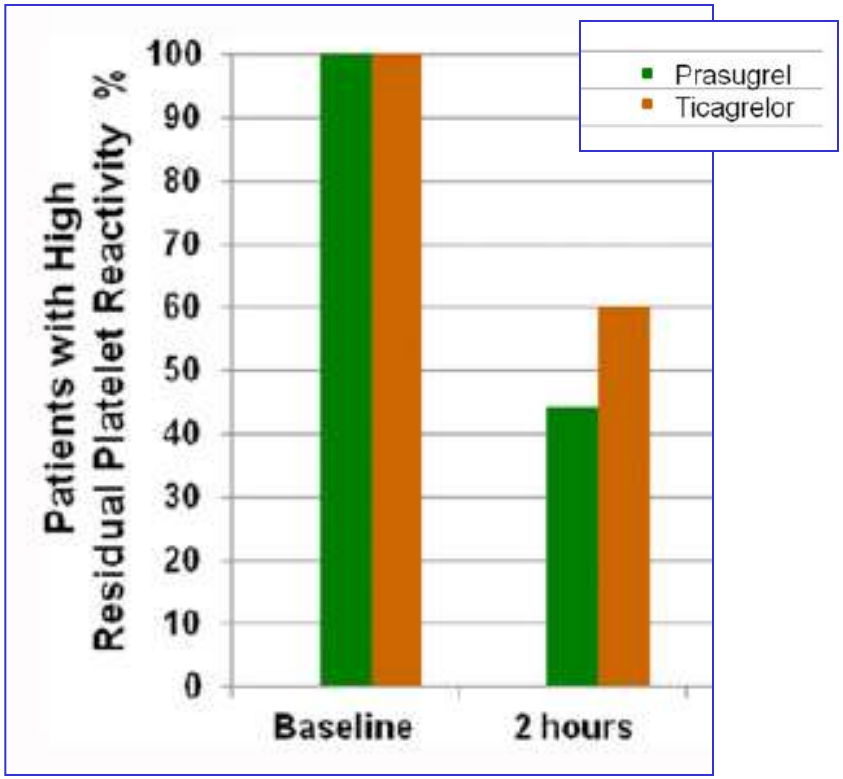
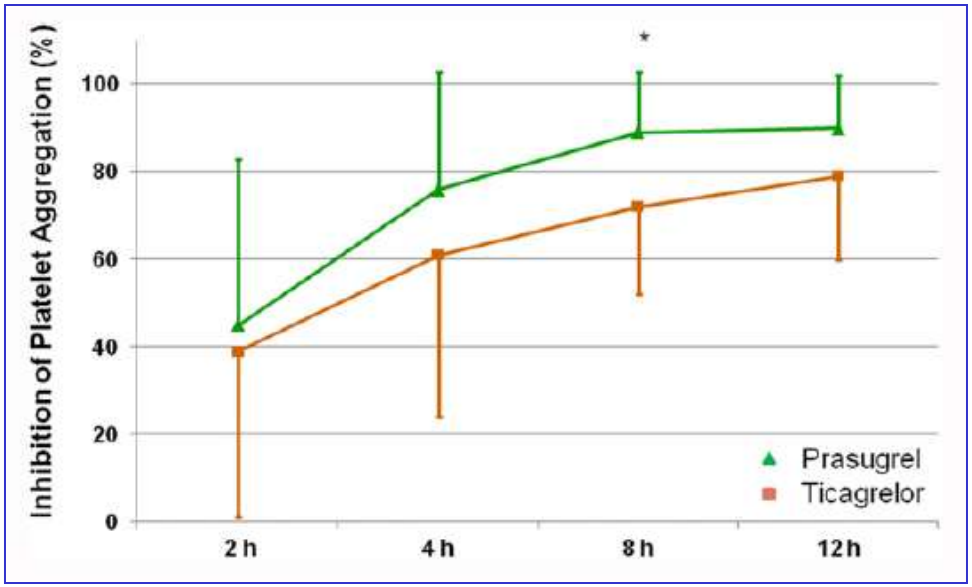

Assessed for eligibility
n = 72
Excluded (n = 21), reasons:
Previous Clopidogrel use (n = 10)
Previous TIA/stroke (n = 2)
Unable to consent (n = 4)
Active bleeding (n = 1)
Abciximab administration (n = 5)
Randomized
n = 50
Prasugrel
Ticagrelor
Received Prasugrel (n = 25)
Allocation
Received Ticagrelor (n = 25)
PRU 2 hours after Loading Dose (n = 25)
Primary Analysis
PRU 2 hours after Loading Dose (n = 25)
Clinical follow-up (n = 25)
Follow-up
Clinical follow-up (n = 25)
Start of the Treatment
Baseline
2 h
4 h
8 h
12 h
VerifyNow Residual Platelet Reactivity Evaluation

Table 1 Baseline Characteristics of Study Patients

Variable	Prasugrel (n = 25)	Ticagrelor (n = 25)	p Value
Age, yrs	67 ± 14	67 ± 10	0.998
Male	20 (80%)	19 (76%)	0.733
Body mass index, kg/m^2	27 ± 4	26 ± 4	0.690
Smoker	9 (36%)	9 (36%)	1
Hypertension	15 (60%)	18 (72%)	0.370
Dyslipidemia	5 (20%)	10 (40%)	0.123
Diabetes mellitus	6 (24%)	3 (12%)	0.269
Previous myocardial infarction	1 (4%)	3 (12%)	0.297
Previous PCI	1 (4%)	3 (12%)	0.297
Previous CABG	0 (0%)	0 (0%)	1.000
Systolic blood pressure, mm Hg	146 ± 33	146 ± 29	0.931
Heart rate, beats/min	73 ± 14	81 ± 28	0.266
Left ventricular ejection fraction, %	44 ± 10	41 ± 12	0.266
Creatine kinase peak value, U/l	1,501 (446–3,484)	2,038 (550–3,399)	0.632
Time creatine kinase peak, h	6 (3–11)	6 (3–7)	0.910
Anterior infarct location	8 (32%)	12 (48%)	0.248
Cardiogenic shock	2 (8%)	5 (20%)	0.221
Unfractionated heparin bolus	4 (16%)	3 (12%)	0.684
Thrombectomy	19 (76%)	16 (64%)	0.355
Infarct artery stenting	25 (100%)	25 (100%)	1.000
Morphine use	12 (48%)	9 (36%)	0.390
Vomit	2 (8%)	1 (4%)	0.552
Discharge therapy			
Aspirin	23 (92%)	22 (88%)	0.637
ACE inhibitors	20 (80%)	19 (76%)	0.733
Beta-blockers	20 (80%)	15 (60%)	0.123
Statins	23 (92%)	22 (88%)	0.637
Proton pump inhibitors	22 (88%)	20 (80%)	0.468



Sin diferencias significativas a las 2 horas



Randomized Assessment of Ticagrelor vs. Prasugrel: Antiplatelet Effects in Patients with STEMI

Single-center study of 55 patients randomized to ticagrelor or prasugrel for 5 days and assessed for platelet reactivity.

P2Y12 Reaction Units	Ticagrelor	Prasugrel	*P* Value
1 Hour	257.3	231.3	0.2
2 Hours	196.1	153.6	0.2
5 Days	25.6	50.3	0.01

Conclusion: Both ticagrelor and prasugrel show evidence of delay in the onset of antiplatelet action in patients with STEMI.

Alexopoulos et al. Circ Cardiovasc Interv. 2012 Dec;5(6):797-804.

Cinetica de accion de los nuevos antiagregantes en el IAMEST

- Mayor reactividad plaquetaria residual a las 2 horas que en pacientes estables, la mitad con reactividad alta:
  - Absorcion menor por alteracion hemodinamica, activacion adrenergica, vasoconstriccion, vomitos,....
- Similar respuesta a las 2 horas con ambos
- A las 4 horas el efecto es mas completo con ambos
- La morfina difiere la accion antiagregante
  - Afecta a motilidad gastro-intestinal ?

Double (360mg) Loading Dose Of Ticagrelor In Patients With ST-elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

D. Alexopoulos, I. Xanthopoulou, V. Gkizas, G. Kassimis, K. Theodoropoulos, G. Tsigkas, I. Chiladakis, A. Damelou, G. Hahalis, P. Davlouros

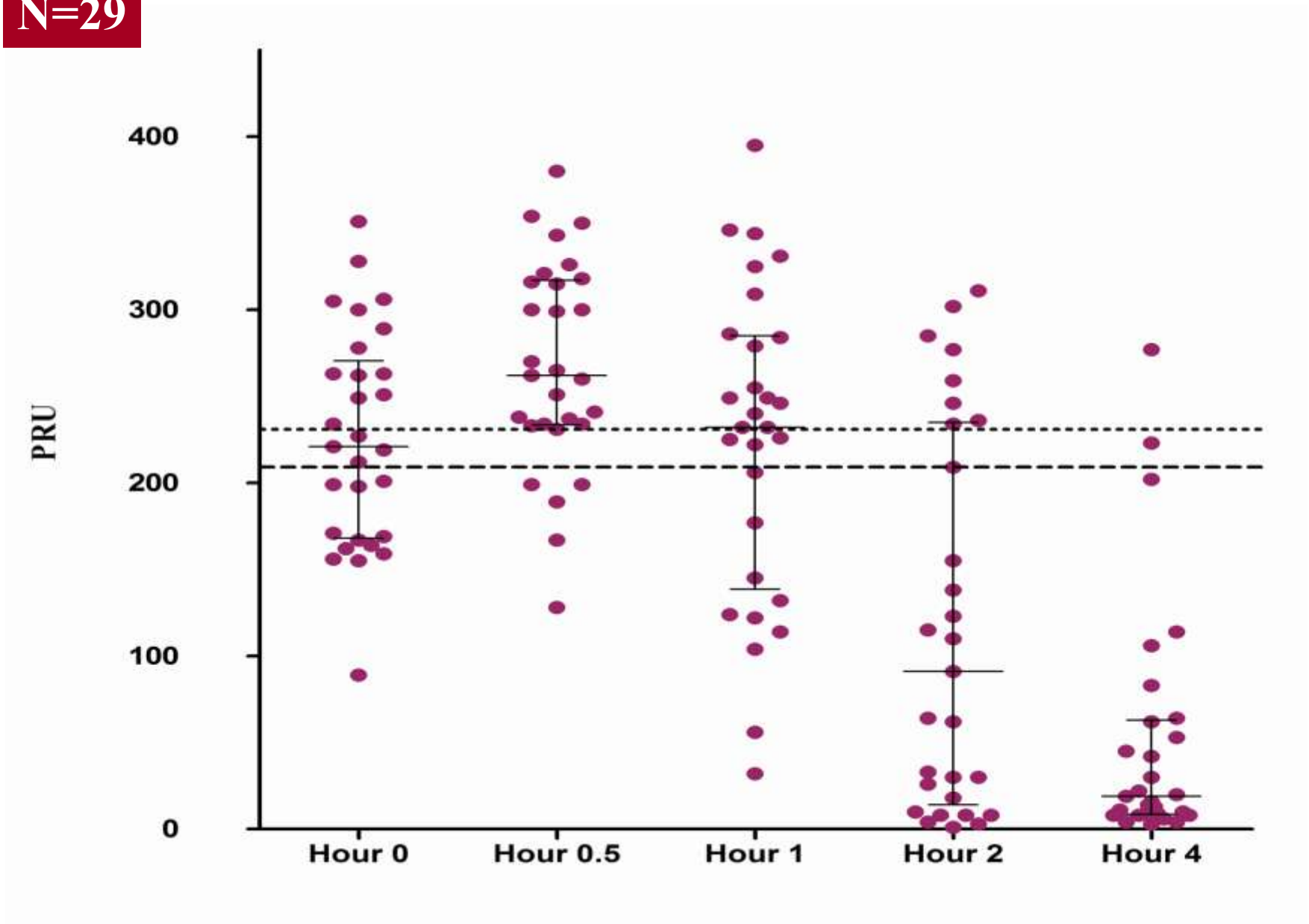
Patras University Hospital, Greece

TCT2012

CARDIOVASCULAR RESEARCH FOUNDATION

Alexopoulos et al. J Am Coll Cardiol. 2013 Jun 7

N=29



Incremento de respuesta en 2ª hora respecto a carga de 180 mgrs

¿ Y si el paciente necesita **cirugia** ?

2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery

4.1. Preoperative Antiplatelet Therapy: Recommendations

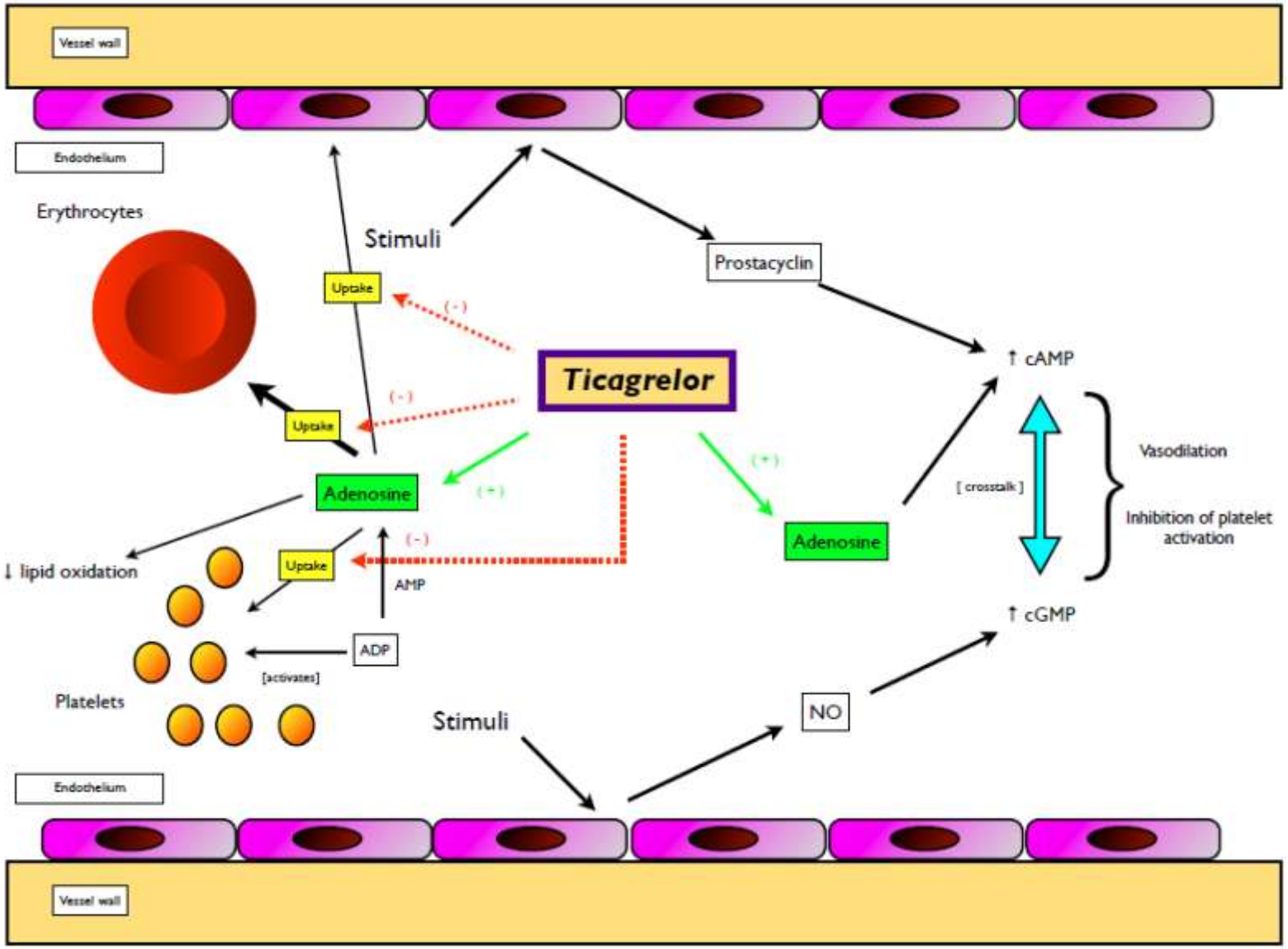
CLASS I

1. Aspirin (100 mg to 325 mg daily) should be administered to CABG patients preoperatively (517–519). (*Level of Evidence: B*)
2. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (520–522) (*Level of Evidence: B*) and prasugrel for at least 7 days (*Level of Evidence: C*) to limit blood transfusions.
3. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications (521,523–525). (*Level of Evidence: B*)

EUROPEAN SOCIETY OF CARDIOLOGY®

In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa

Mas alla de la antiagregacion: via de la adenosina



Por tanto

- Que nos recomiendan las guías
- Como adaptar el uso de los nuevos antiagregantes a un entorno economico restrictivo

European Heart Journal (2012) **33**, 2569–2619
doi:10.1093/eurheartj/ehs215

ESC GUIDELINES

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)

Authors/Task Force Members: Ph. Gabriel Steg (Chairperson) (France)*, Stefan K. James (Chairperson) (Sweden)*, Dan Atar (Norway), Luigi P. Badano (Italy), Carina Blömstrom-Lundqvist (Sweden), Michael A. Borger (Germany), Carlo Di Mario (United Kingdom), Kenneth Dickstein (Norway), Gregory Ducrocq (France), Francisco Fernandez-Aviles (Spain), Anthony H. Gershlick (United Kingdom), Pantaleo Giannuzzi (Italy), Sigrun Halvorsen (Norway), Kurt Huber (Austria), Peter Juni (Switzerland), Adnan Kastrati (Germany), Juhani Knuuti (Finland), Mattie J. Lenzen (Netherlands), Kenneth W. Mahaffey (USA), Marco Valgimigli (Italy), Arnoud van 't Hof (Netherlands), Petr Widimsky (Czech Republic), Doron Zahger (Israel)

	Class	Level
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years	I	B
Ticagrelor	I	B
Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Patrick T. O'Gara, Frederick G. Kushner, Deborah D. Ascheim, Donald E. Casey, Jr, Mina K. Chung, James A. de Lemos, Steven M. Ettinger, James C. Fang, Francis M. Fesmire, Barry A. Franklin, Christopher B. Granger, Harlan M. Krumholz, Jane A. Linderbaum, David A. Morrow, L. Kristin Newby, Joseph P. Ornato, Narith Ou, Martha J. Radford, Jacqueline E. Tamis-Holland, Jacqueline E. Tommaso, Cynthia M. Tracy, Y. Joseph Woo and David X. Zhao

Table 3. Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg load before procedure	I	B
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A
• 81 mg daily is the preferred maintenance dose*	IIa	B
$P2Y_{12}$ inhibitors		
Loading doses		
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B
Maintenance doses and duration of therapy		
DES placed: Continue therapy for 1 y with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
BMS† placed: Continue therapy for 1 y with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B

NICE UK

National Clinical Guideline Centre

Draft for consultation

Myocardial infarction with ST-segment-elevation

The acute management of myocardial infarction with ST-segment-elevation

Clinical guideline <...>

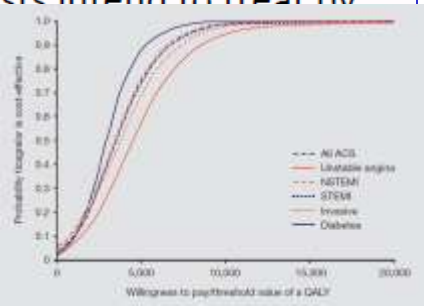
Methods, evidence and recommendations

January 2013

NHS
National Institute for Health and Clinical Excellence

TICAGRELOR

TA236[224] (Ticagrelor for the treatment of acute coronary syndromes) evaluated the role of ticagrelor in the management of people with acute coronary syndrome. In a health economic analysis ticagrelor was found to be cost effective relative to generic clopidogrel (cost of clopidogrel 30-pack = £3.40). TA236 recommends ticagrelor as an option in people with STEMI that cardiologists intend to treat by PPCI. When selecting an ADP receptor antagonist clinicians should be aware tha use of ticagrelor relates to people who were also treated with aspirin, unfractio molecular weight heparin, and a GPI if required.



18. Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in people with STEMI – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary PCI. [This recommendation is adapted from Ticagrelor for the treatment of acute coronary syndromes (NICE technology appraisal guidance 236).]

PRASUGREL

In TA182 a health economic model submitted by the manufacturer compared prasugrel with proprietary clopidogrel (as Plavix). The 1-year cost of proprietary clopidogrel was estimated at £464.05 (based on £1.26 per day). Following publication of TA182 in October 2009 the availability of generic clopidogrel has substantially reduced the cost of treatment. The health economic analysis that underpins the recommendation in TA 182 is therefore outdated and the cost effectiveness of prasugrel relative to generic clopidogrel is uncertain.

¿?

Following consultation NICE Guidance Executive has decided that a review of TA182 should be planned into the appraisal work programme and hence TA182 is undergoing update.[221]

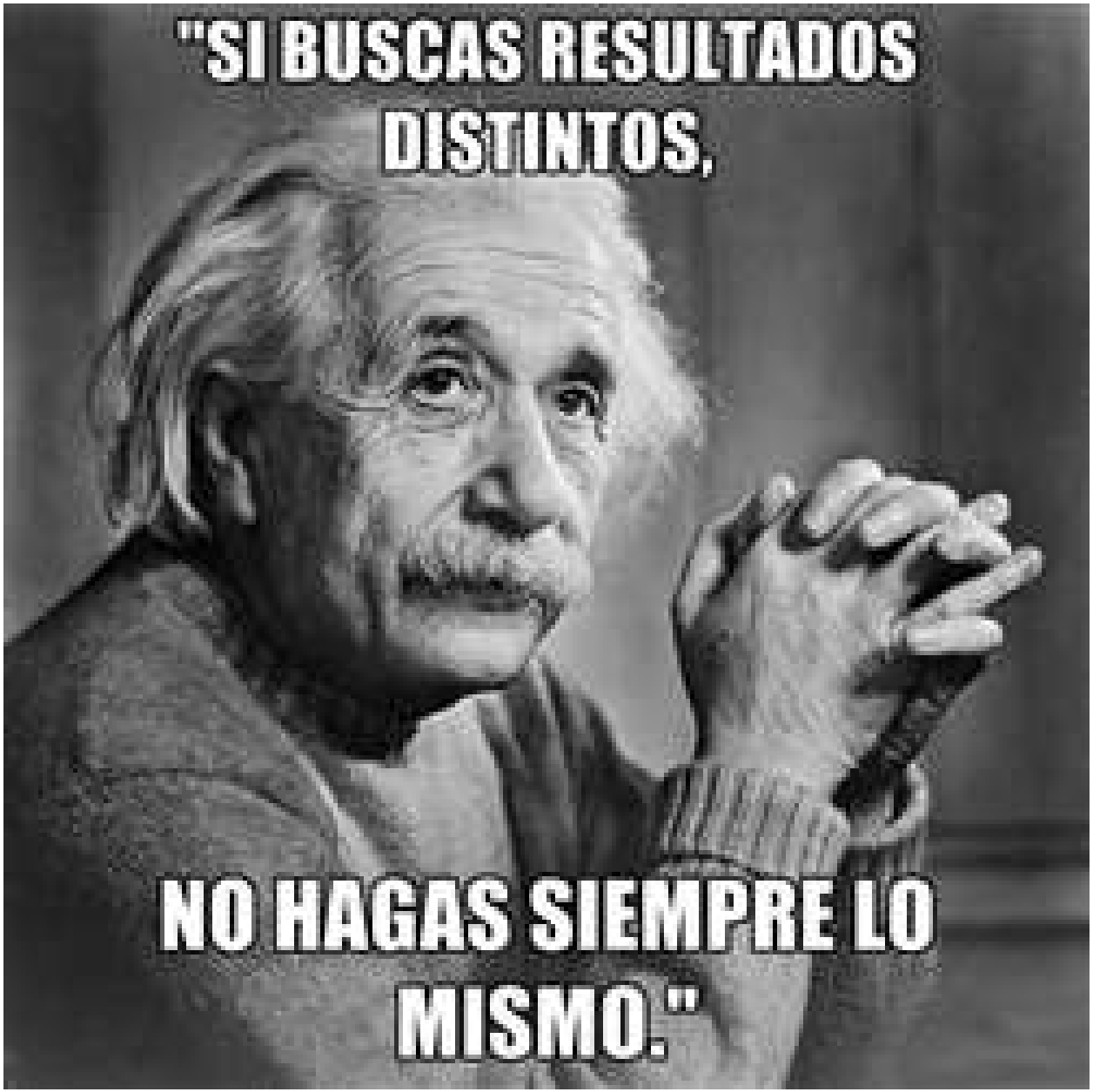
Concluyendo

- Las **guías actuales** recomiendan preferentemente los nuevos antiagregantes sobre el Clopidogrel en la ICP 1ª
- En el periodo actual de **restricción de costos** la utilización de los dos nuevos antiagregantes podría concentrarse en los **grupos de mas riesgo**:
  - Infarto anterior
  - Diabetes
  - Insuficiencia renal crónica
  - Enfermedad coronaria previa (infarto, ICP, CABG)
  - Trombosis de stent
  - Angiografia o ICP primaria de riesgo:
    - Lesiones de tronco
    - Enfermedad multivaso
    - $\geq$ 3 stents
    - Bifurcación con 2 stents
    - Vaso no culpable con oclusión total crónica

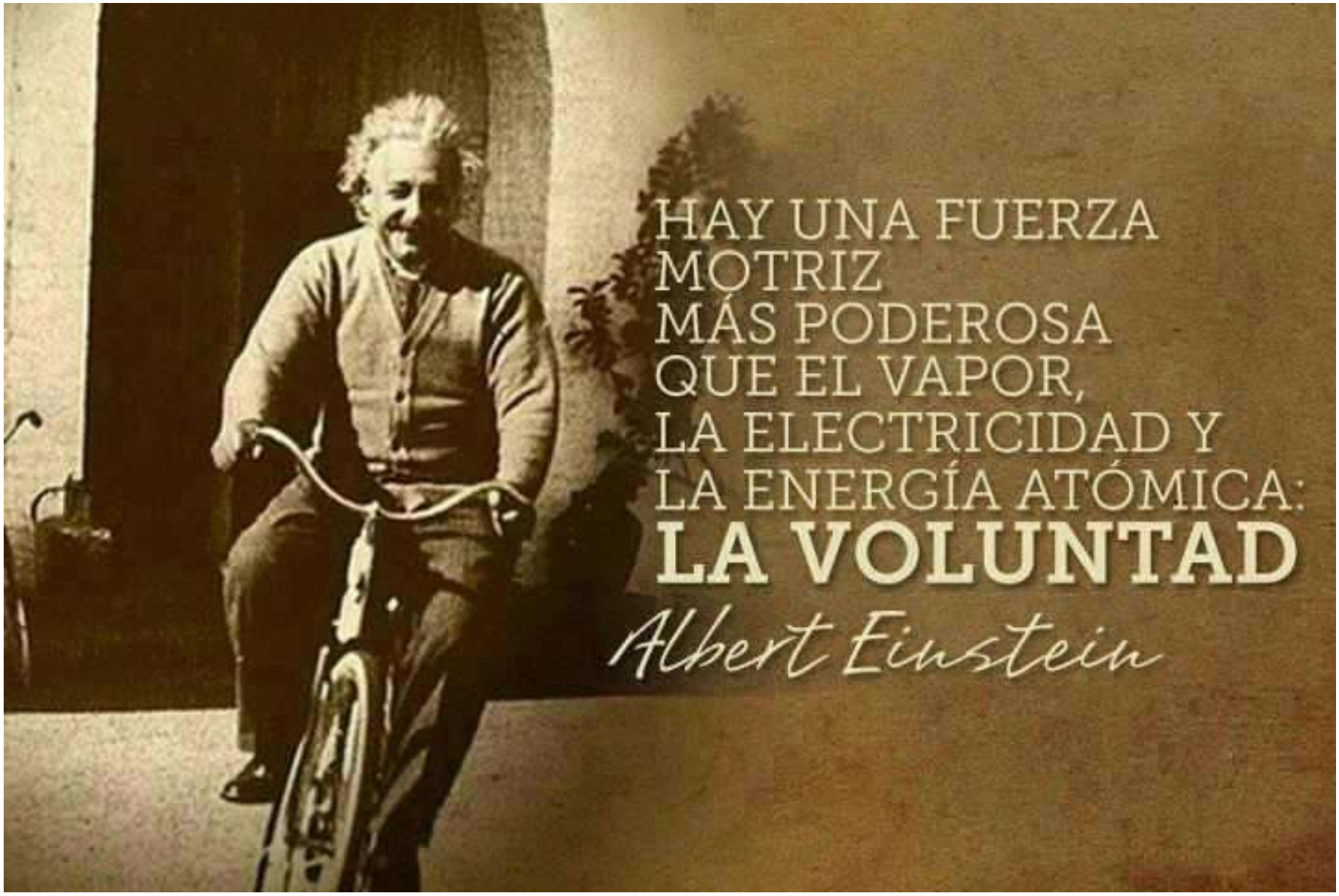
Concluyendo

- **Ambos fármacos** aportan beneficio respecto al Clopidogrel en el IAMEST tratado con **ICP 1ª,** aunque con ciertas diferencias.

- El uso de **Ticagrelor** estaría *especificamente* favorecido en presencia de alguna de las siguientes condiciones:
  - > 75 años de edad
  - < 60 Kgrs de peso
  - Ictus o AIT previo
  - Insuficiencia renal crónica
  - Alergia a tienopiridinas
  - Cirugía posible a corto plazo



Albert Einstein


HAY UNA FUERZA
MOTRIZ
MÁS PODEROSA
QUE EL VAPOR,
LA ELECTRICIDAD Y
LA ENERGÍA ATÓMICA:
LA VOLUNTAD
Albert Einstein

Conclusiones I

- La angioplastia primaria constituye la estrategia optima de reperfusión en el infarto ST alto

- En el ámbito del infarto ST alto la antiagregación combinada de aspirina mas clopidogrel es superior a la antiagregación simple:
  - La precarga oral con 600 mg de Clopidogrel es mejor que con 300 mg
  - Un periodo de antiagregación doble de 9-12 meses es mas beneficioso que por solo 1 mes

Conclusiones II

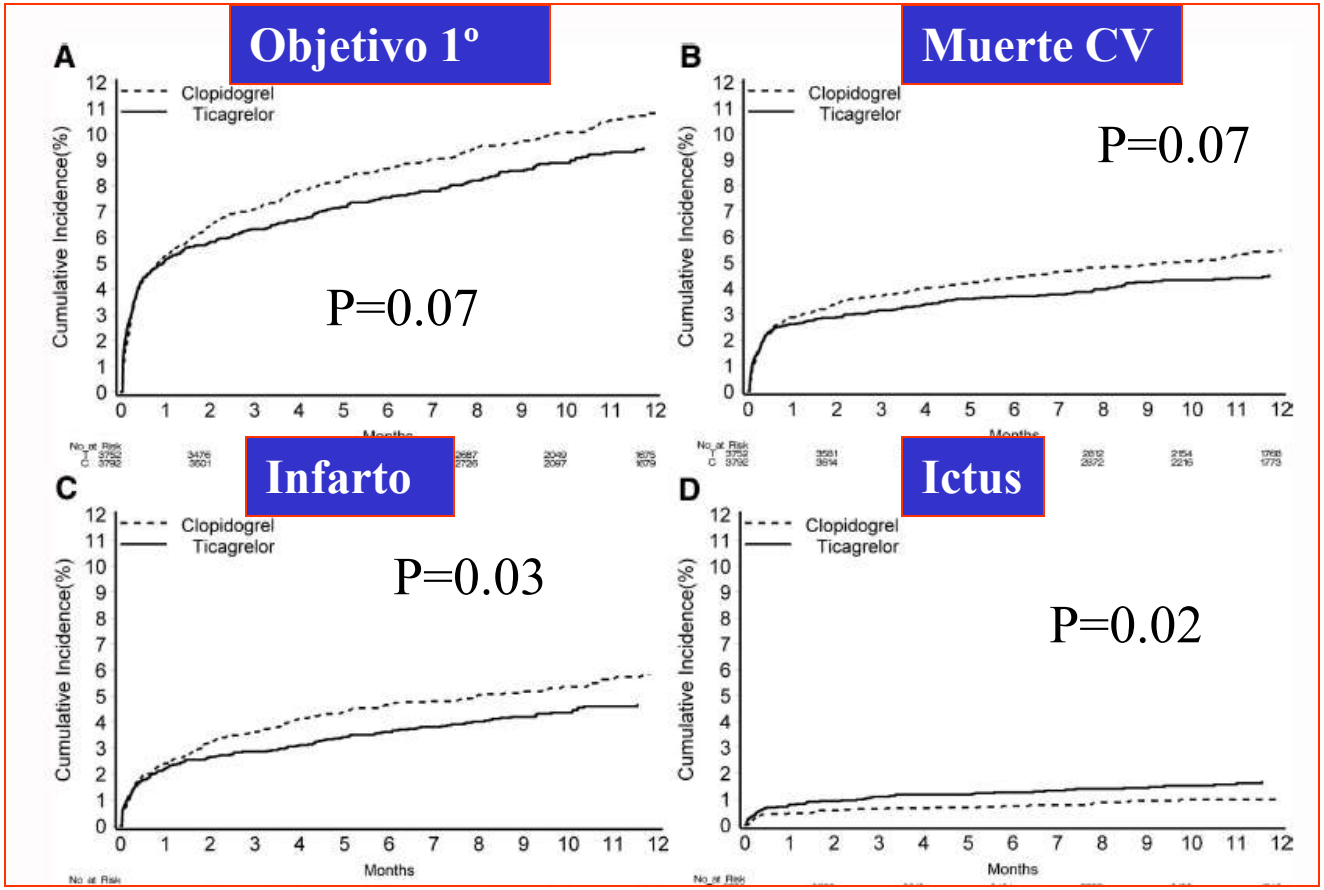
- La tasa de respuesta inadecuada a Clopidogrel en el momento de la angioplastia primaria es muy elevada a pesar de precarga oral.

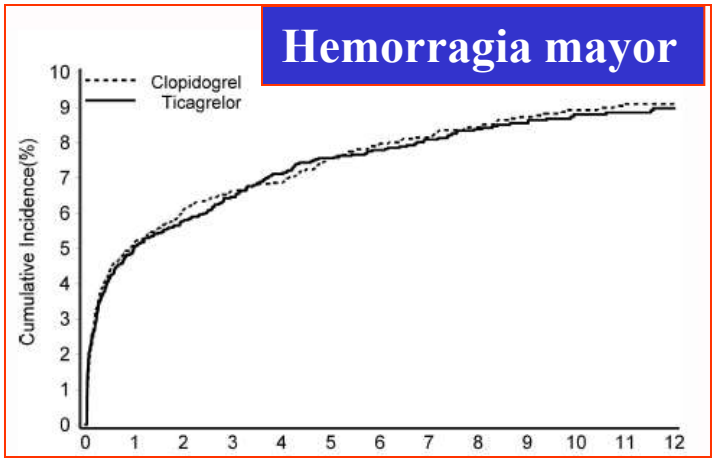
- Los estudios que comparan Clopidogrel con los nuevos antiagregantes Prasugrel y Ticagrelor muestran superioridad de estos últimos en este contexto:
  - El Prasugrel mostro mejores resultados en la angioplastia secundaria (12h – 14 días tras infarto)
  - El Ticagrelor mostro mejores resultados en angioplastia primaria (< 24 h)

Conclusiones III

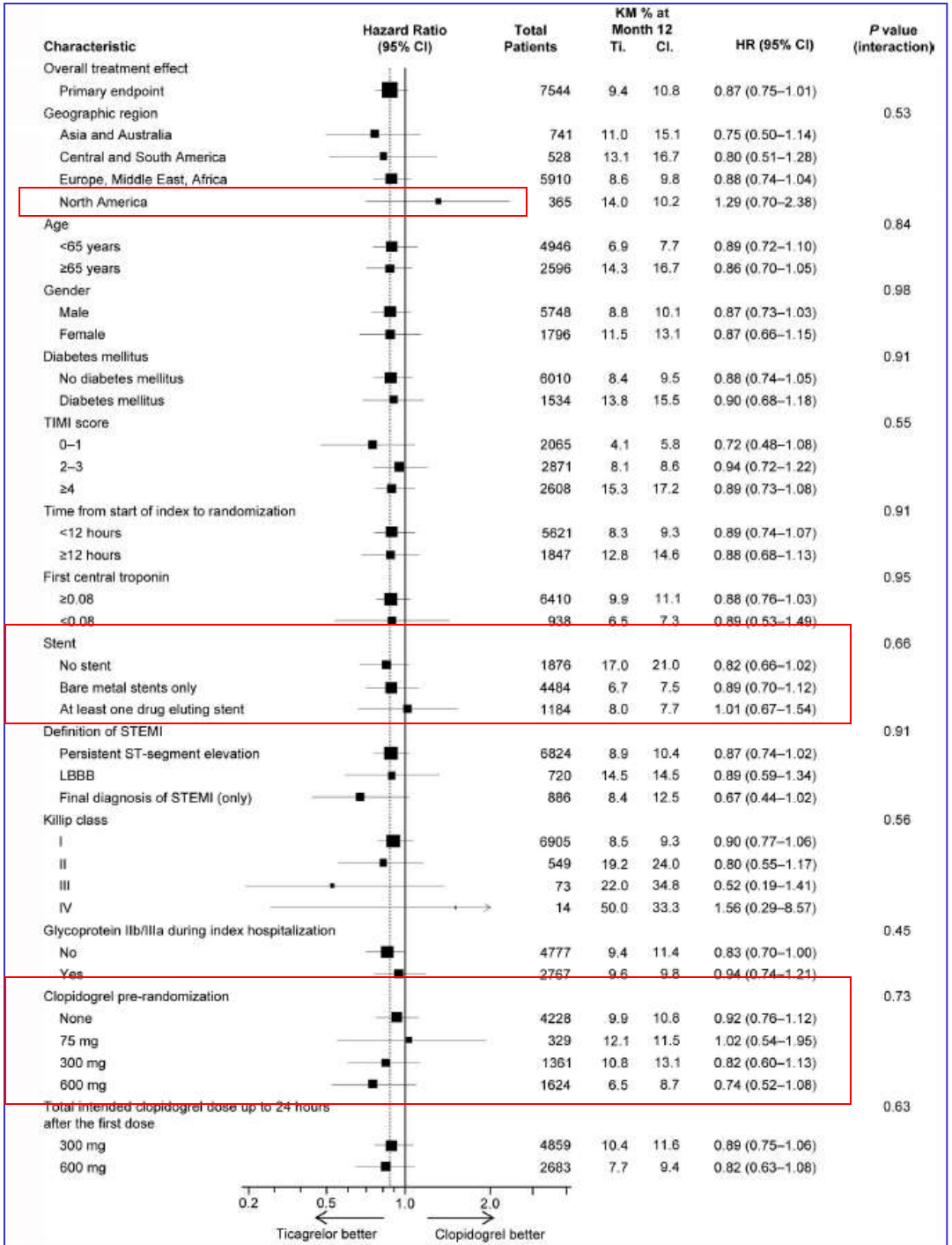
- Los estudios que evalúan la reactividad plaquetaria tras la precarga con los nuevos antiagregantes en pacientes con infarto ST alto no muestran diferencias significativas entre ambos en la tasa de respuesta a las 2 horas de la carga oral

Ticagrelor vs Clopidogrel





Steg et al. Circulartion 2010;122:2131


Characteristic
Hazard Ratio (95% CI)
Total Patients
KM % at Month 12 Ti.
KM % at Month 12 Cl.
HR (95% CI)
P value (interaction)
Overall treatment effect
Primary endpoint 7544 9.4 10.8 0.87 (0.75–1.01)
Geographic region 0.53
Asia and Australia 741 11.0 15.1 0.75 (0.50–1.14)
Central and South America 528 13.1 16.7 0.80 (0.51–1.28)
Europe, Middle East, Africa 5910 8.6 9.8 0.88 (0.74–1.04)
North America 365 14.0 10.2 1.29 (0.70–2.38)
Age 0.84
<65 years 4946 6.9 7.7 0.89 (0.72–1.10)
≥65 years 2596 14.3 16.7 0.86 (0.70–1.05)
Gender 0.98
Male 5748 8.8 10.1 0.87 (0.73–1.03)
Female 1796 11.5 13.1 0.87 (0.66–1.15)
Diabetes mellitus 0.91
No diabetes mellitus 6010 8.4 9.5 0.88 (0.74–1.05)
Diabetes mellitus 1534 13.8 15.5 0.90 (0.68–1.18)
TIMI score 0.55
0–1 2065 4.1 5.8 0.72 (0.48–1.08)
2–3 2871 8.1 8.6 0.94 (0.72–1.22)
≥4 2608 15.3 17.2 0.89 (0.73–1.08)
Time from start of index to randomization 0.91
<12 hours 5621 8.3 9.3 0.89 (0.74–1.07)
≥12 hours 1847 12.8 14.6 0.88 (0.68–1.13)
First central troponin 0.95
≥0.08 6410 9.9 11.1 0.88 (0.76–1.03)
<0.08 938 6.5 7.3 0.89 (0.53–1.49)
Stent 0.66
No stent 1876 17.0 21.0 0.82 (0.66–1.02)
Bare metal stents only 4484 6.7 7.5 0.89 (0.70–1.12)
At least one drug eluting stent 1184 8.0 7.7 1.01 (0.67–1.54)
Definition of STEMI 0.91
Persistent ST-segment elevation 6824 8.9 10.4 0.87 (0.74–1.02)
LBBB 720 14.5 14.5 0.89 (0.59–1.34)
Final diagnosis of STEMI (only) 886 8.4 12.5 0.67 (0.44–1.02)
Killip class 0.56
I 6905 8.5 9.3 0.90 (0.77–1.06)
II 549 19.2 24.0 0.80 (0.55–1.17)
III 73 22.0 34.8 0.52 (0.19–1.41)
IV 14 50.0 33.3 1.56 (0.29–8.57)
Glycoprotein IIb/IIIa during index hospitalization 0.45
No 4777 9.4 11.4 0.83 (0.70–1.00)
Yes 2767 9.6 9.8 0.94 (0.74–1.21)
Clopidogrel pre-randomization 0.73
None 4228 9.9 10.6 0.92 (0.76–1.12)
75 mg 329 12.1 11.5 1.02 (0.54–1.95)
300 mg 1361 10.8 13.1 0.82 (0.60–1.13)
600 mg 1624 6.5 8.7 0.74 (0.52–1.08)
Total intended clopidogrel dose up to 24 hours after the first dose 0.63
300 mg 4859 10.4 11.6 0.89 (0.75–1.06)
600 mg 2683 7.7 9.4 0.82 (0.63–1.08)
0.2
0.5
1.0
2.0
Ticagrelor better
Clopidogrel better

Abstract

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Final Version
Circ Cardiovasc Intervent

2012 Dec;5(6):797-804. doi: 10.1161/CIRCINTERVENTIONS.112.972323. Epub 2012 Nov 20.

ssessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation arction.

hopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G.
gy, Patras University Hospital, Rion, Greece. dalex@med.upatras.gr

cagrelor and prasugrel provide stronger platelet inhibition compared with clopidogrel. Direct pharmacodynamic comparison between een reported in ST-segment-elevation myocardial infarction patients.

ESULTS: In a prospective, single-center, single-blind study, 55 out of 117 (47%) screened consecutive ST-segment-elevation n patients undergoing primary percutaneous coronary intervention were randomized to either ticagrelor 180 mg loading followed by grel 60 mg loading followed by 10 mg od for 5 days. Platelet reactivity (PR) was assessed with the VerifyNow P2Y12 function iplate Analyzer at 0, 1, 2, 6, 24 hours, and 5 days postrandomization. The primary end point, PR with VerifyNow at hour 1, did not etween patients randomized to ticagrelor versus prasugrel (257.3 P2Y12 reaction unit [PRU], 95% CI 230.8-283.8 versus 231.3 -257.4; P=0.2). PR did not differ at 2, 6, and 24 hours, although at day 5 it was lower with ticagrelor than prasugrel (25.6 PRU, ersus 50.3 PRU, 95% CI 36.4-64.1; P=0.01). At hour 2, high on-treatment PR rates (cutoff 208 PRU) were 46.2% and 34.6% for ugrel, respectively, decreased significantly thereafter, whereas did not differ significantly between the 2 agents at all the time points

patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention, both ticagrelor it an initial delay in the onset of their antiplatelet action. Ticagrelor did not appear superior to prasugrel in reducing PR during the segment-elevation myocardial infarction.

REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01463163.

regarding article, "Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation n". [Circ Cardiovasc Interv. 2013]
Kristensen regarding article, "Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-myocardial infarction". [Circ Cardiovasc Interv. 2013]

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es, MeSH Terms, Substances, Secondary Source ID

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Substance (MeSH Keyword)
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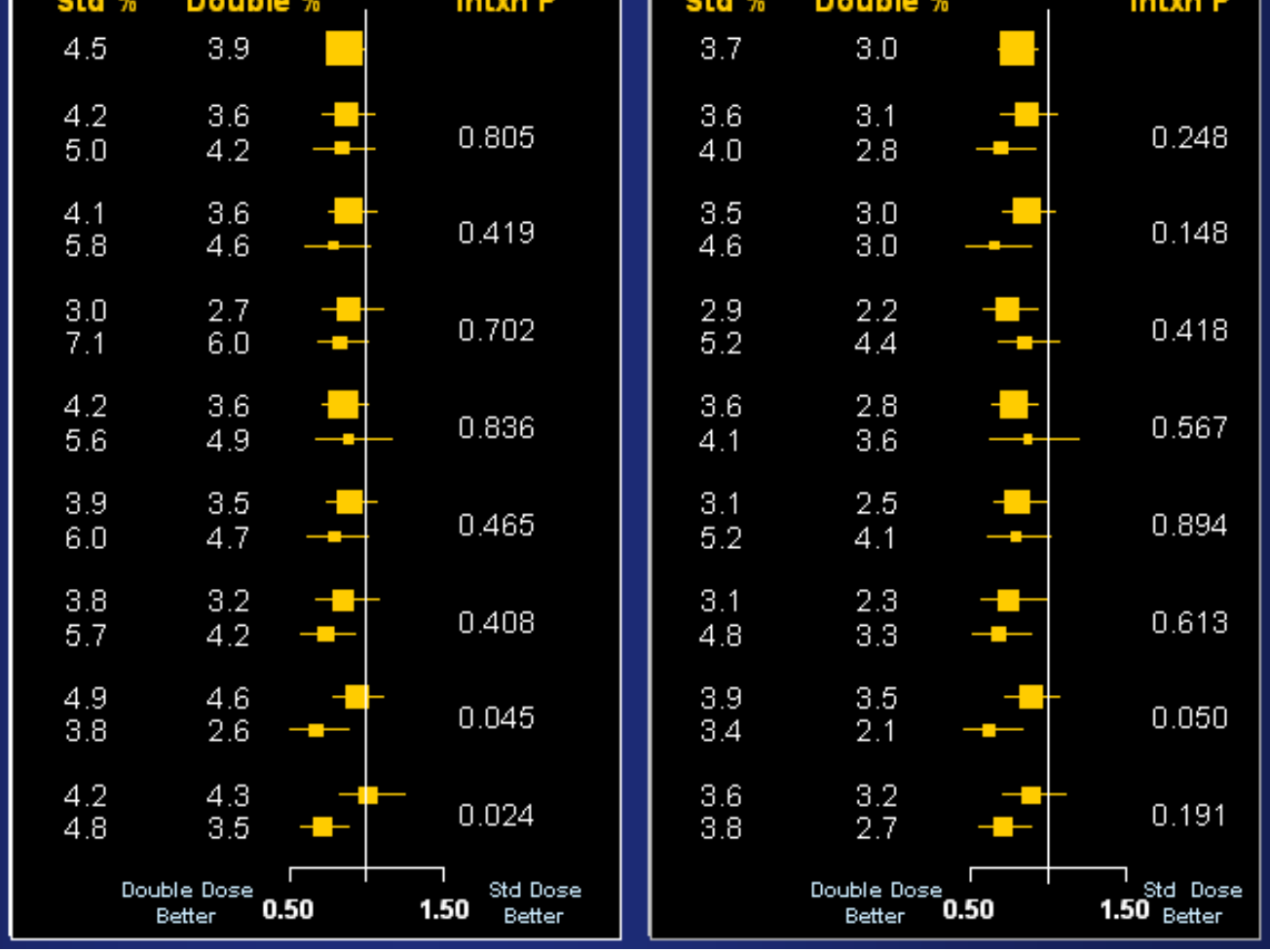
CURRENT

Clopidogrel: Double v Standard Dose PCI Cohort Subgroups

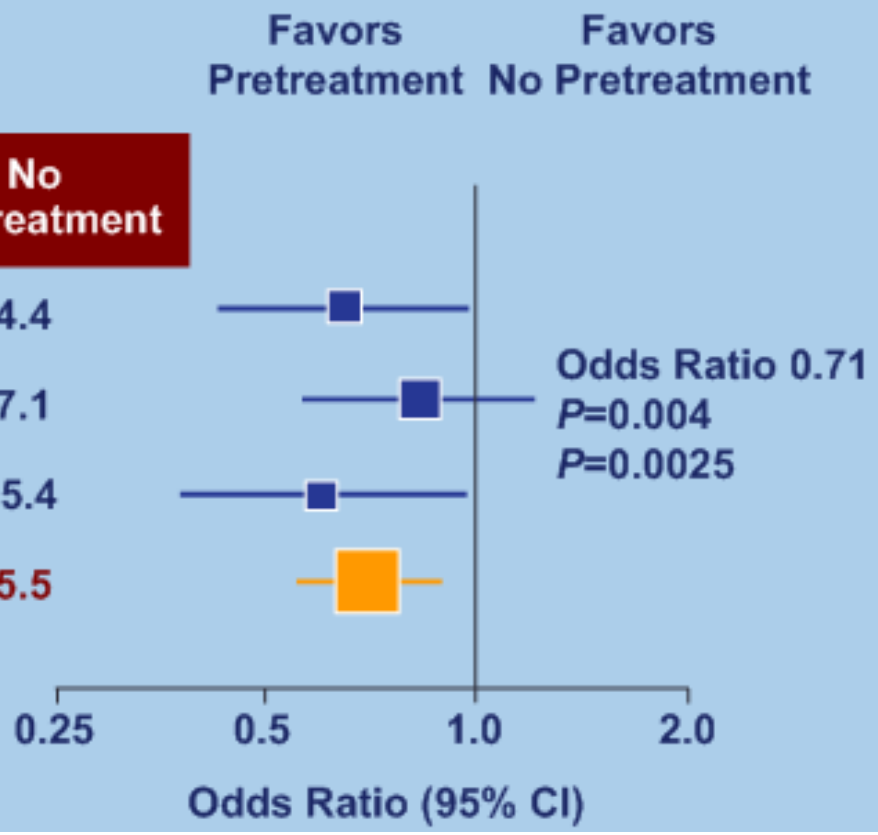
	2N	CV Death, MI or Stroke Std %	CV Death, MI or Stroke Double %	CV Death, MI or Stroke Intxn P	MI or Stent Thrombosis Std %	MI or Stent Thrombosis Double %	MI or Stent Thrombosis Intxn P
Overall	17232	4.5	3.9		3.7	3.0	
NSTEMI/UA	10886	4.2	3.6	0.805	3.6	3.1	0.248
STEMI	6346	5.0	4.2		4.0	2.8	
Male	13009	4.1	3.6	0.419	3.5	3.0	0.148
Female	4223	5.8	4.6		4.6	3.0	
Age <= 65 yrs	10975	3.0	2.7	0.702	2.9	2.2	0.418
Age > 65 yrs	6257	7.1	6.0		5.2	4.4	
Non-Diabetic	13400	4.2	3.6	0.836	3.6	2.8	0.567
Prev Diabetic	3831	5.6	4.9		4.1	3.6	
No Inhosp GPIIb/IIIa	12288	3.9	3.5	0.465	3.1	2.5	0.894
GPIIb in hosp	4936	6.0	4.7		5.2	4.1	
No Prot Pump Inhib	7675	3.8	3.2	0.408	3.1	2.3	0.613
Prot Pump Inhib	5557	5.7	4.2		4.8	3.3	
Non-smoker	10845	4.9	4.6	0.045	3.9	3.5	0.050
Current Smoker	6380	3.8	2.6		3.4	2.1	
ASA Low	8620	4.2	4.3	0.024	3.6	3.2	0.191
ASA High	8612	4.8	3.5		3.8	2.7	



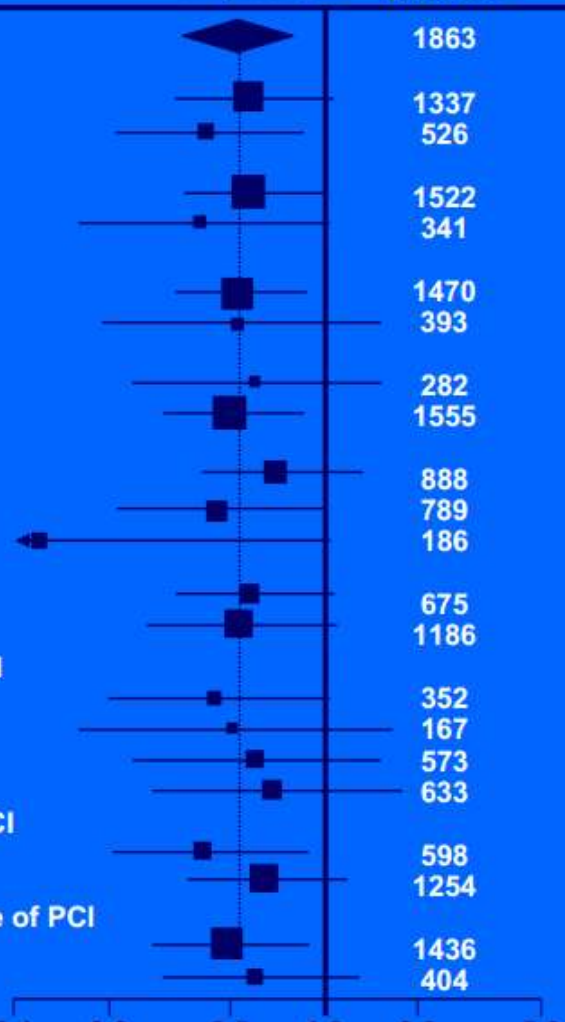
PCI-CLARITY Meta-Analysis of Clopidogrel Pretreatment CV Death or MI After PCI, 30 Days

CV Death or MI After PCI (%)

Trial	Clopidogrel Pretreatment	No Pretreatment
PCI-CURE[a]	2.9	4.4
CREDO	6.0	7.1
PCI-CLARITY[a]	3.3	5.4
Overall	3.9	5.5



PCI-CLARITY: Consistent Results for Primary Endpoint Across Subgroups



Characteristic	OR (95% CI)	Number of patients	Adjusted* OR (95% CI)	Patients with event (%) Clopidogrel	Patients with event (%) Placebo
OVERALL		1863	0.54 (0.35-0.85)	3.6	6.2
Age					
<65 years		1337	0.59 (0.33-1.07)	3.2	4.7
≥65 years		526	0.43 (0.21-0.87)	4.7	10.4
Gender					
Male		1522	0.59 (0.35-0.99)	3.6	5.4
Female		341	0.41 (0.16-1.04)	4.0	10.3
Type of Fibrinolytic Agent					
Fibrin Specific		1470	0.54 (0.33-0.89)	3.5	6.4
Non-fibrin-specific		393	0.54 (0.19-1.53)	4.1	5.6
Diabetes					
Yes		282	0.61 (0.24-1.53)	6.0	10.1
No		1555	0.51 (0.30-0.87)	2.9	5.3
Predominant heparin					
UFH		888	0.72 (0.40-1.32)	5.0	6.5
LMWH		789	0.47 (0.22-1.02)	2.5	5.4
None		186	0.12 (0.01-1.03)	2.2	8.3
PCI					
Urgent		675	0.60 (0.33-1.08)	6.7	9.6
Elective		1186	0.54 (0.27-1.09)	2.1	4.1
Time from randomization to PCI					
<6 hours		352	0.45 (0.20-1.04)	5.3	12.8
6-48 hours		167	0.51 (0.16-1.65)	6.5	11.1
48-96 hours		573	0.61 (0.24-1.53)	3.0	4.5
>96 hours		633	0.70 (0.28-1.78)	2.8	3.9
Gp IIb/IIIa inhibitor at time of PCI					
Yes		598	0.42 (0.21-0.88)	4.2	9.0
No		1254	0.65 (0.36-1.17)	3.4	4.9
Open-label loading dose at time of PCI					
Yes		1436	0.50 (0.28-0.90)	2.9	5.2
No		404	0.62 (0.30-1.29)	6.3	10.1

Abstract

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FULL TEXT ARTICLE (PDF

Jul 1;110(1):110-7. doi: 10.1160/TH13-01-0057. Epub 2013 Apr 25.

etreatment in primary percutaneous coronary intervention: Prevalence of high on-treatment platelet mpact on preprocedural patency of the infarct-related artery.

Berdejo J, Roura G, Gómez-Lara J, Romaguera R, Teruel L, Sánchez-Elvira G, Marcano AL, Gómez-Hospital JA, Angiolillo DJ, Cequier A.

Director of Cardiovascular Research Lab, Heart Diseases Institute, Bellvitge University Hospital - IDIBELL, Feixa Llarga s/n. CP 08907, L'Hospitalet de pain, Tel.: +34 93 260 74 95, Fax: +34 93 260 75 41, E-mail: jlferreiro@bellvitgehospital.cat.

ited data on levels of platelet inhibition achieved in patients with ST-elevation myocardial infarction (STEMI) who are loaded with irin (ASA) prior to undergoing primary percutaneous coronary intervention (P-PCI). The aim of this investigation was to evaluate the MI patients with high on-treatment platelet reactivity (HPR) to clopidogrel at the time of initiating P-PCI and its association with the e infarct-related artery (IRA). This prospective pharmacodynamic study included 50 STEMI patients, previously naïve to oral who received 500-mg ASA and 600-mg clopidogrel loading doses prior to P-PCI. Platelet function assessment was performed at procedure using various assays, including VerifyNow™ system (primary endpoint), light transmission aggregometry and multiple etry. The percentage of patients with suboptimal response to clopidogrel and ASA assessed with the VerifyNow™ system was respectively. Similar results were obtained with the other assays used. A higher percentage of patients with initial patency of the among those patients without HPR compared with those with HPR to clopidogrel (66.7% vs 15.9%; p=0.013), while no differences rding postprocedural angiographic or electrocardiographic outcomes. In conclusion, this study shows that a high percentage of e inadequate levels of clopidogrel-induced and, to a lesser extent, aspirin-mediated platelet inhibition when starting a P-PCI gests that a poor response to clopidogrel might be associated with impaired initial TIMI flow in the IRA.

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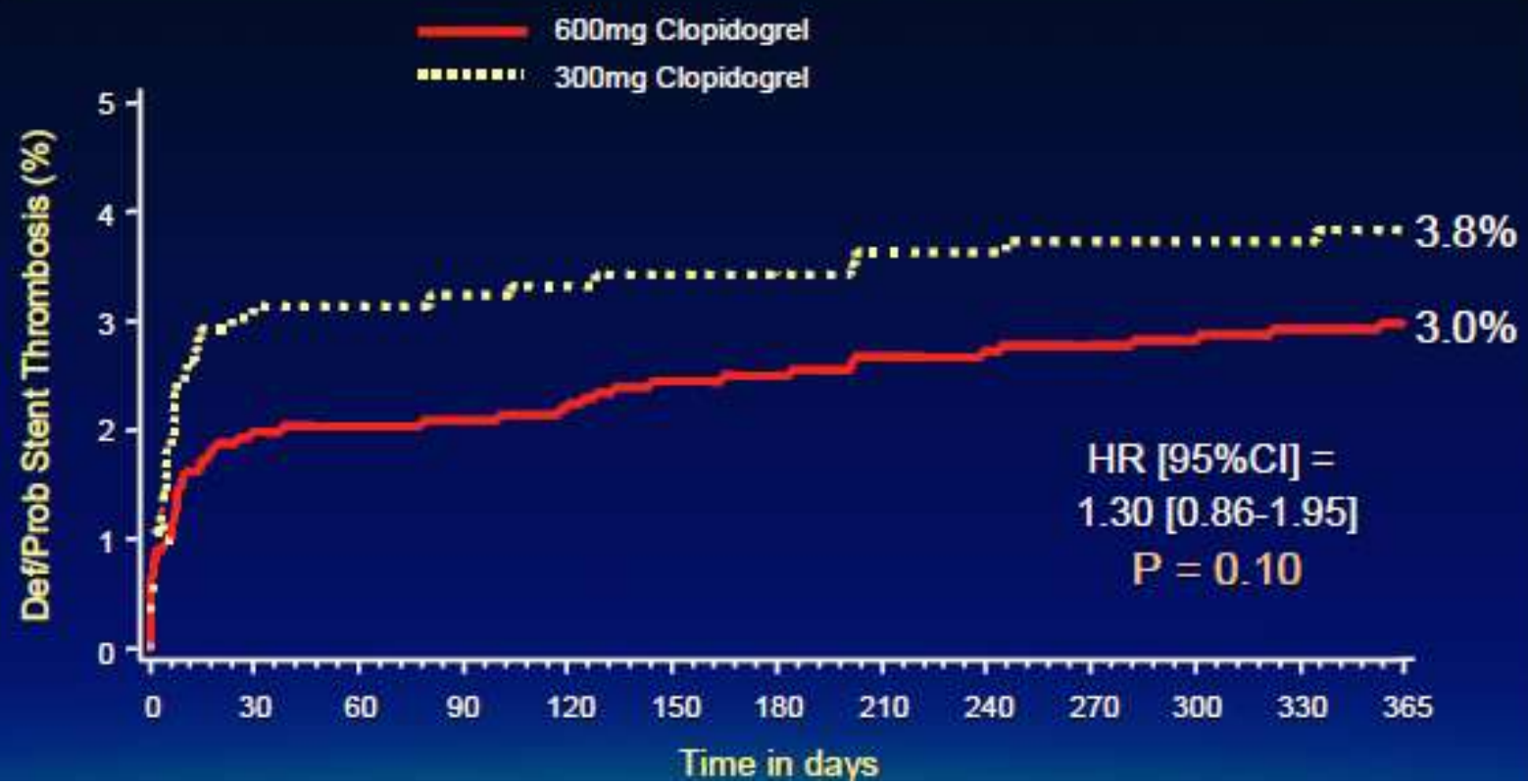
resources

1-Year Stent Thrombosis: Impact of Clopidogrel Loading Dose (all pts)