50 Congreso Sociedad Andaluza de Cardiología
"Congreso Andaluz de las Enfermedades Cardiovasculares"
14 – 16 mayo 2015
Hotel Abades Nevada Palace - Granada

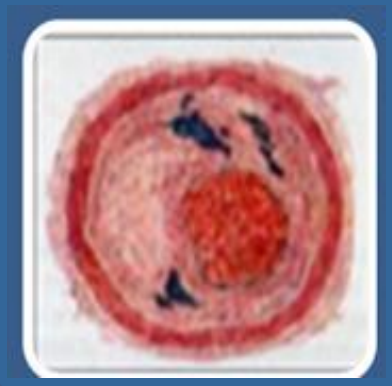
Situación actual de la antiagregación en el Síndrome Coronario Agudo

Alejandro Recio-Mayoral
Unidad Coronaria
UGC Área del Corazón de Sevilla
H.U.V. Macarena

Declaración de potenciales conflictos de intereses

- Relativas a esta presentación existen las siguientes relaciones que podría ser percibidas como potenciales conflictos de intereses:
  - NADA que declarar

Síndrome coronario agudo

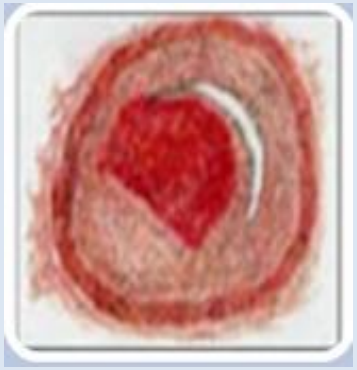


SCACEST

• Fisiopatología: Rotura de placa, formación trombótica y oclusión **total** de la arteria

•Objetivo: Apertura precoz de la arteria para limitar área de necrosis

•Tratamiento: Reperfusión inmediata, mecánica (ICP) o farmacolçogica (fibrinolisis



SCASEST

• Fisiopatología: Rotura de placa, formación trombótica y oclusión **parcial** de la arteria

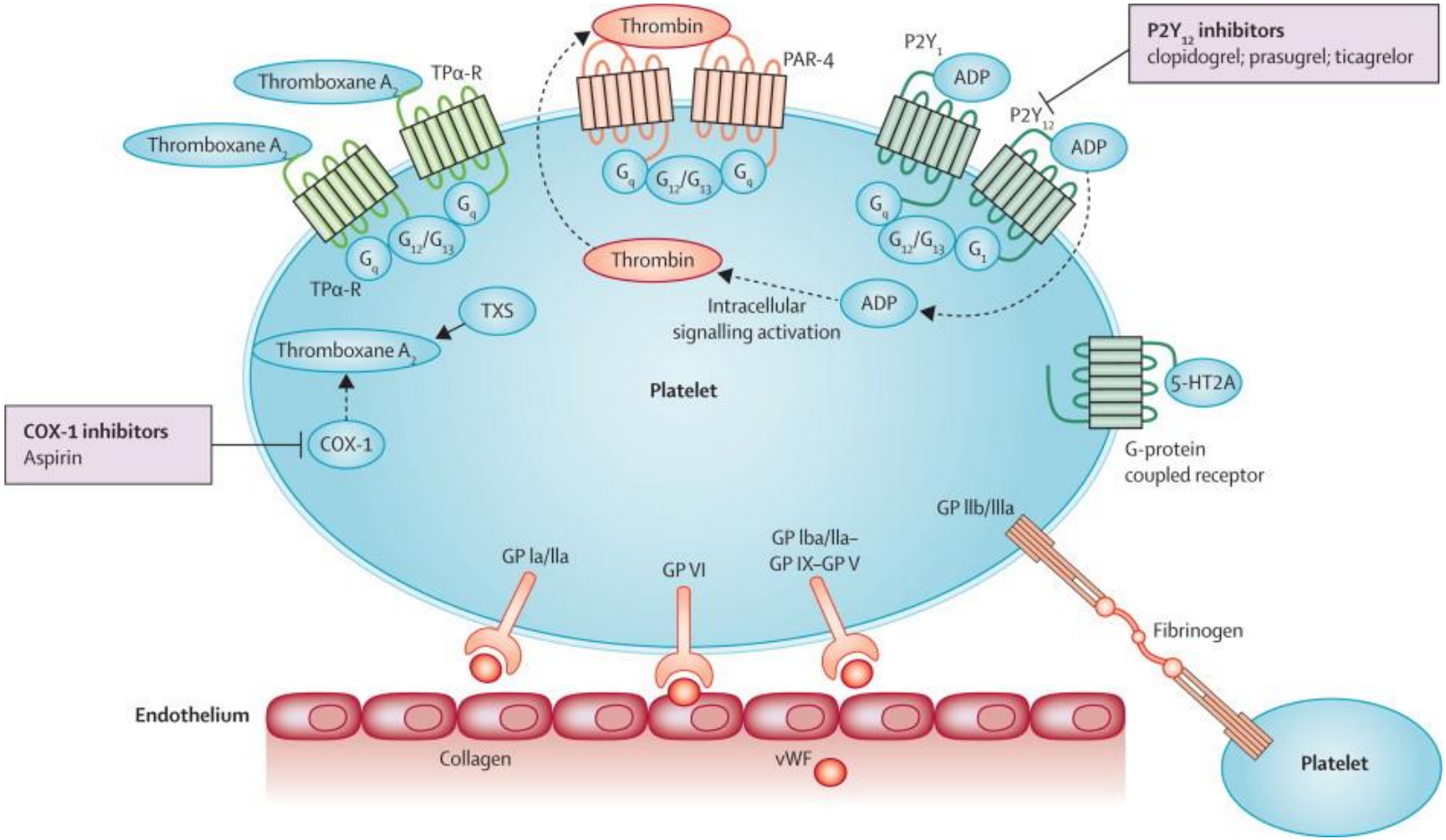
•Objetivo: Impedir oclusión completa para evitar la necrosis

•Tratamiento: Anti-isquémico y antitrombótico precoz, con reperfusión +/- precoz según estratificación de riesgo

Objetivos del tratamiento

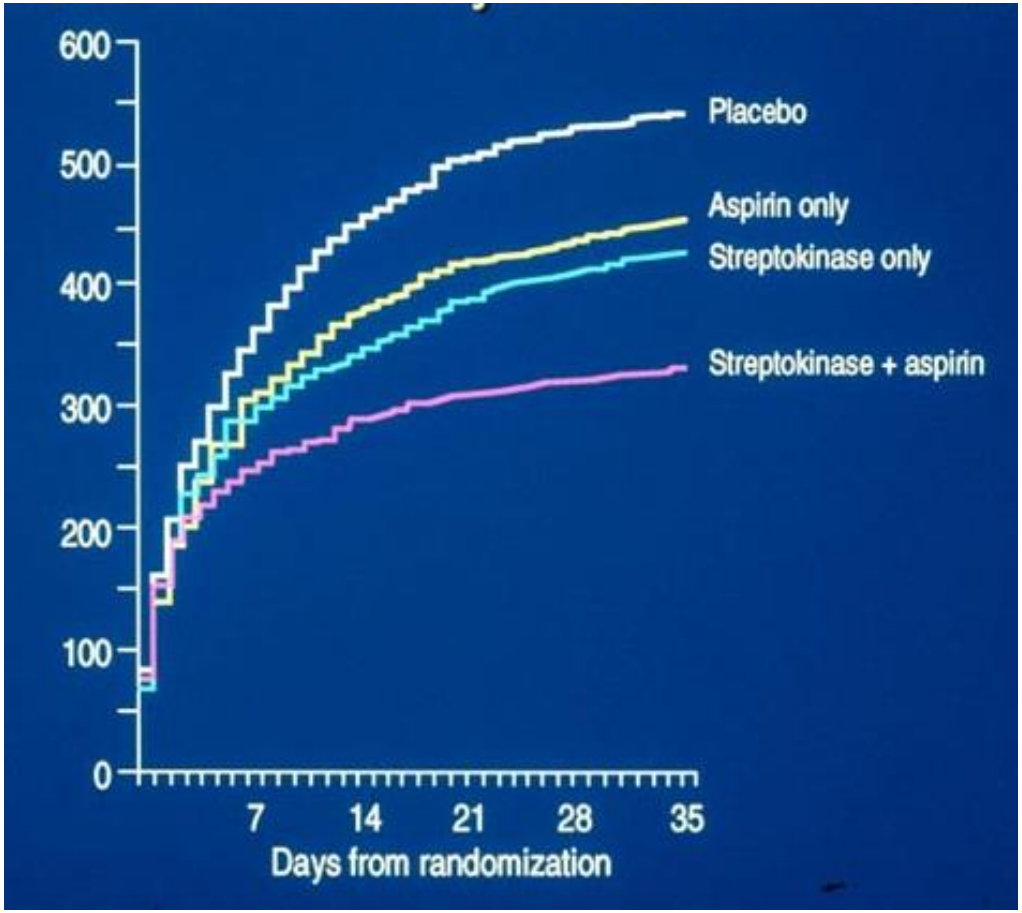
- Inmediato
  - Estabilización de la placa
  - Prevención de la trombosis del stent.
- A largo plazo
  - Prevención de nuevos eventos

Antiagregantes plaquetarios



Jessica L Mega et al. The Lancet 2015; (15)60243-4

Aspirina: ISIS-2



28%

Muerte CV

p<0.00001

ISIS-2 Collaborative Group. Lancet 1988; 2: 349–60

Aspirina: recomendaciones SCA

SCACEST: PPCI

Aspirin oral or i.v. (if unable to swallow) is recommended	I	B

With primary PCI	
Aspirin	Loading dose of 150–300 mg orally or of 80–150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.

Fibrinolisis y No reperfundidos

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

Oral or i.v. aspirin must be administered.	I	B

With fibrinolytic therapy	
Aspirin	Starting dose 150–500 mg orally or i.v. dose of 250 mg if oral ingestion is not possible.
Clopidogrel	Loading dose of 300 mg orally if aged ≤75 years, followed by a maintenance dose of 75 mg/day.
Without reperfusion therapy	
Aspirin	Starting dose 150–500 mg orally.

SCASEST

Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A

Aspirina: ISIS-2, estudio de subgrupos

28%

Muerte CV

p<0.00001

P ns

Muerte CV

9%

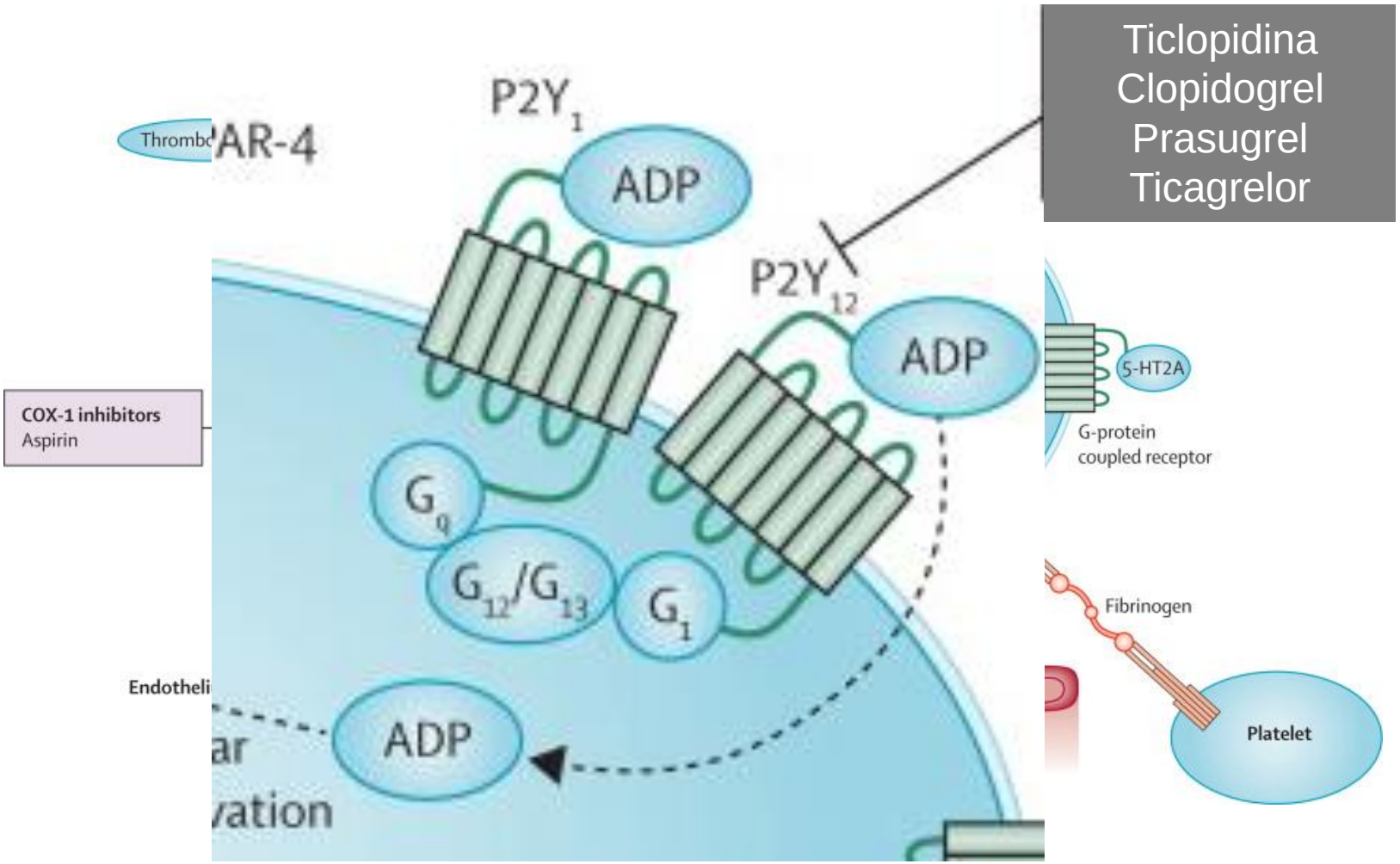
Astrological birth sign	No. of 1-month deaths (aspirin *vs* placebo)	Statistical significance
Libra or Gemini	150 *vs* 147	NS
All other signs	654 *vs* 869	2*P*<0.000001
Any birth sign[a]	804 (9.4%) *vs* 1016 (11.8%)	2*P*<0.000001

ISIS-2 Collaborative Group. Lancet 1988; 2: 349–60

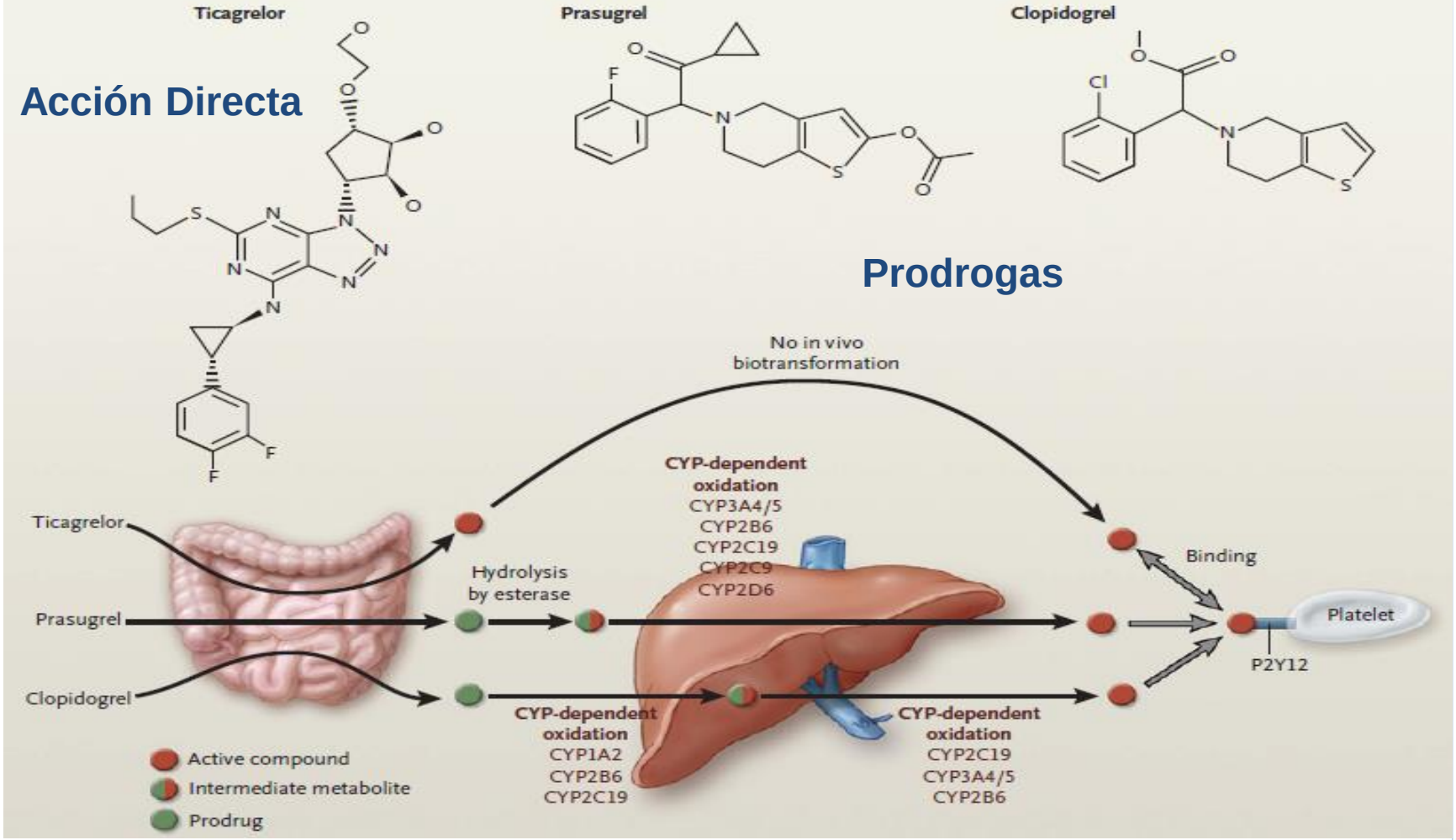
"Es mucho mejor una respuesta aproximada a la pregunta correcta , que es a menudo vaga , que una respuesta exacta a la pregunta equivocada , que siempre se puede hacer precisa."

J W Tukey, 1962

Antagonistas receptores P2Y12



Propiedades farmacocinéticas
Tienopiridinas vs ciclopentil-triazolo-piridina



Albert Shömig. Editorial, N Engl J Med. 2009;361 (11):1108-11.

Clopidogrel en el SCA

AI/SCASEST

RR 20%

Muerte CV+IM+AVC

p<0.001

NEJM 2001

PCI electiva

RR 27%

Muerte CV+IM+AVC

p<0.001

JAMA 2002

SCACEST

RR 21,7%

Muerte CV+IM+OARI

p<0.001

NEJM 2005

RR 9%

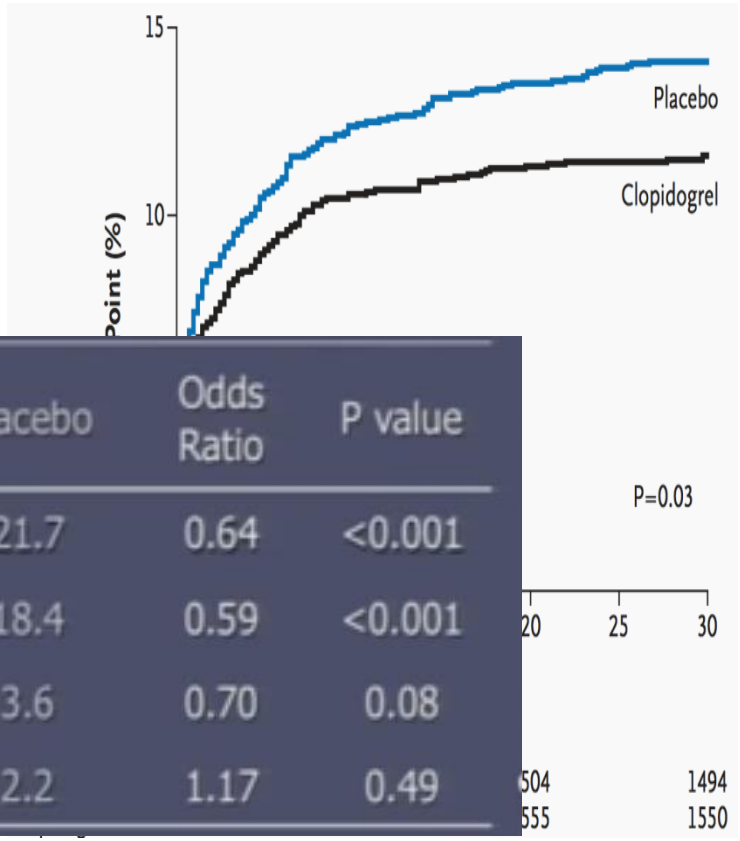
Muerte CV+IM+AVC

P=0.002

Lancet 2005

Clopidogrel en el SCACEST: CLARITY-TIMI 28

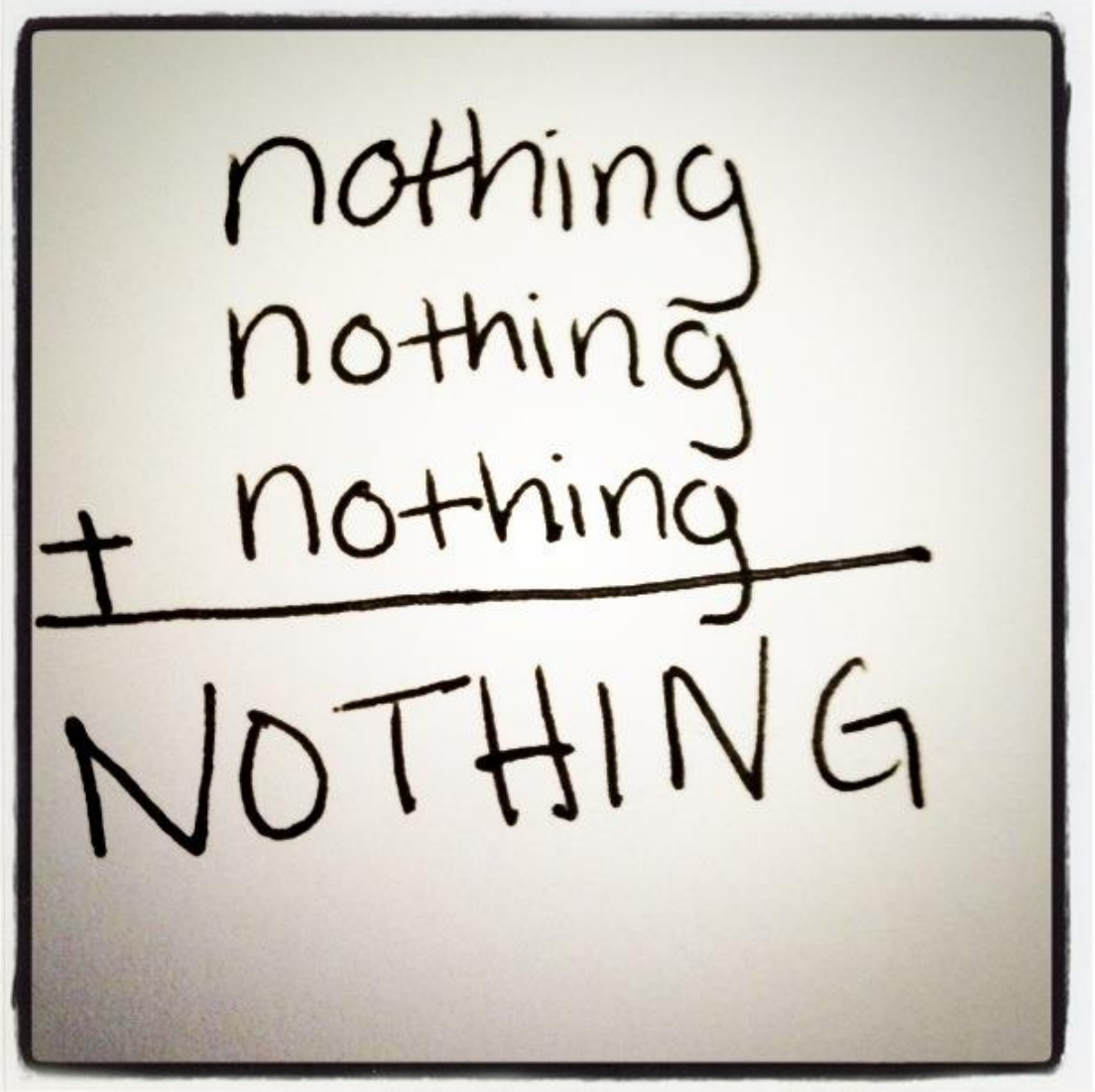
- ✓ 3491 pacientes (18-**75** años) con STEMI sometidos a fibrinolisis en 1ª 12h, randomizados
  - Clopidogrel (300mg ➔ 75mg/día)
  - Placebo
- ✓ PCI en primeras 12 h. Mediana 3.5 días



Outcome	Clopidogrel	Placebo	Odds Ratio	P value
Primary End Point (%)	15.0	21.7	0.64	<0.001
TIMI Flow Grade 0/1	11.7	18.4	0.59	<0.001
MI	2.5	3.6	0.70	0.08
Death	2.6	2.2	1.17	0.49

Sabatine MS. NEJM 2005

Evidencia de clopidogrel en SCACEST PCI



Clopidogrel: guías de practica clínica

SCACEST: Primary percutaneous coronary intervention

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

Periprocedural antithrombotic medication in primary percutaneous coronary intervention

• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

Fibrinolisis

Fibrinolytic therapy

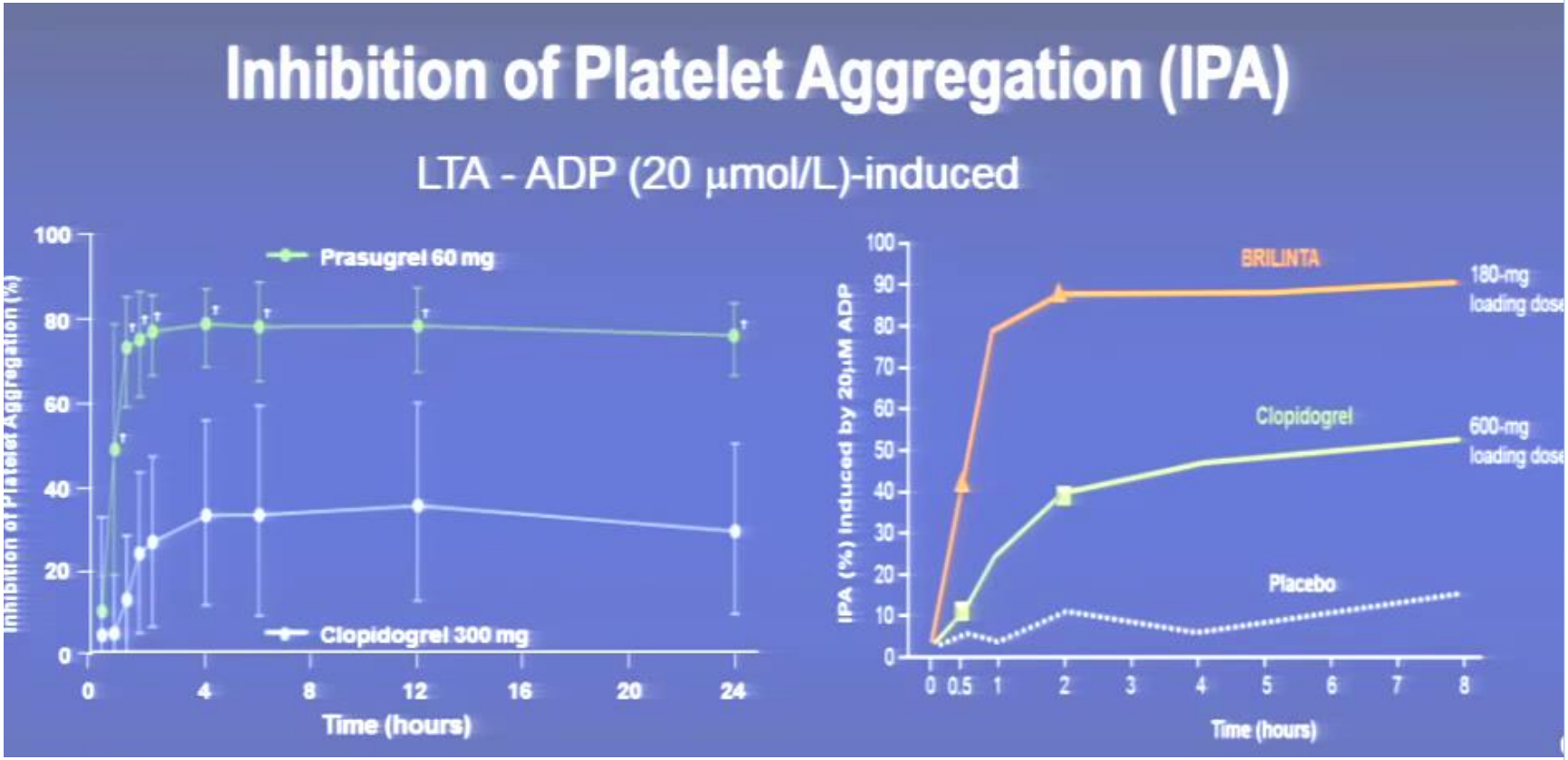
Clopidogrel is indicated in addition to aspirin.	I	A

SCASEST: Primary percutaneous coronary intervention

A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B

Eur Heart J (2012) 33: 2569-2619
Eur Heart J (2011) 32: 2999-3054

Antiagregantes última generación
Farmacodinamia Prasugrel y ticagrelor



Rule of “3P´s”: more Prompt, Potent and Predictable

Even compared with clopidogrel high LD (600-900 mg) and MD (150 mg)

Antiagregantes última generación

Prasugrel y ticagrelor

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

ABSTRACT

BACKGROUND

Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of acute coronary syndromes and percutaneous coronary intervention.

METHODS

To compare prasugrel, a new thienopyridine, with clopidogrel, we randomly assigned 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose), for 6 to 15 months. The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding.

RESULTS

The primary efficacy end point occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; P<0.001). We also found significant reductions in the prasugrel group in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; P<0.001), urgent target-vessel revascularization (3.7% vs. 2.5%; P<0.001), and stent thrombosis (2.4% vs. 1.1%; P<0.001). Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; P=0.03). Also greater in the prasugrel group was the rate of life-threatening bleeding (1.4% vs. 0.9%; P=0.01), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; P=0.23) and fatal bleeding (0.4% vs. 0.1%; P=0.002).

CONCLUSIONS

In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups. (ClinicalTrials.gov number, NCT00097591.)

From Brigham and Women's Hospital and Harvard Medical School, Boston (S.D.W., E.B., C.H.M., S.A.M., C.M.G., E.M.A.); Institut de Cardiologie and INSERM Unit 856, Pitié–Salpêtrière University Hospital, Paris (G.M.); Instytut Kardiologii, Warsaw, Poland (W.R.); Bikur Cholim Hospital, Jerusalem, Israel (S.G.); Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany (F.-J.N.); Azienda Ospedaliero–Universitaria di Parma, Parma, Italy (D.A.); Azienda Ospedaliera Civile di Legano, Legano, Italy (S.D.S.); and Eli Lilly Research Laboratories, Indianapolis (J.R., G.W.). Address reprint requests to Dr. Antman at the Cardiovascular Division, Brigham and Women's Hospital, TIMI Study Group, 350 Longwood Ave., 1st Fl., Boston, MA 02115, or at eantman@rics.bwh.harvard.edu.

*The members of the Steering and Operations Committees of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 are listed in the Appendix. The TRITON–TIMI 38 Investigators are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa0706482) was published at www.nejm.org on November 4, 2007.

N Engl J Med 2007;357:2001-15.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

ABSTRACT

BACKGROUND

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel.

METHODS

In this multicenter, double-blind, randomized trial, we compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation.

RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of death from any cause was also reduced with ticagrelor (4.5% vs. 5.9% with clopidogrel; P<0.001). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43), but ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.

CONCLUSIONS

In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding. (ClinicalTrials.gov number, NCT00391872.)

From the Uppsala Clinical Research Center, Uppsala, Sweden (L.W., C.H., S.J.); Duke Clinical Research Institute, Durham, NC (R.C.B., K.W.M., R.A.H.); Grochowski Hospital, Warsaw, Poland (A.B.); Thrombolysis in Myocardial Infarction Study Group, Brigham and Women's Hospital, Boston (C.P.C., B.M.S.); AstraZeneca Research and Development, Mölndal, Sweden (H.E.), and Wilmington, DE (J.H.); Århus University Hospital, Århus, Denmark (S.H.); Universitätsklinikum Heidelberg, Heidelberg, Germany (H.K.); Worldwide Clinical Trials U.K., Nottingham, United Kingdom (A.S.); INSERM Unité 698, Assistance Publique–Hôpitaux de Paris and Université Paris 7, Paris (P.G.S.); and the University of Sheffield, Sheffield, United Kingdom (R.F.S.). Address reprint requests to Dr. Wallentin at Uppsala Clinical Research Center, University Hospital, 75185 Uppsala, Sweden, or at lars.wallentin@ucr.uu.se.

*The Study of Platelet Inhibition and Patient Outcomes (PLATO) Investigators are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

This article (10.1056/NEJMoa0904327) was published on August 30, 2009, at NEJM.org.

N Engl J Med 2009;361:1045-57.

Antiagregantes última generación
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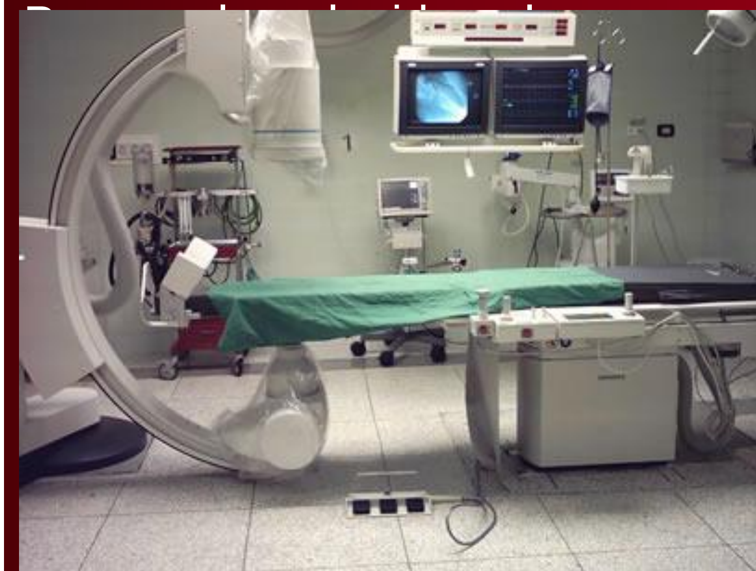


Inicio DAPT antes de la ICP
Prasugrel y ticagrelor

	Drug allocation		PCI		
	Clopidogrel (n=1765)	Prasugrel (n=1769)	Primary (n=2438)	Secondary (n=1094)	p
Timing of study drug administration					<0·0001
Before PCI	453 (27%)	455 (27%)	704 (31%)	204 (19%)	..
During PCI	1213 (72%)	1221 (72%)	1571 (68%)	863 (80%)	..
After PCI	21 (1%)	15 (1%)	28 (1%)	8 (1%)	..

Data are number of patients (%), unless otherwise stated. Data for some characteristics are missing for some patients. *Definitions, see reference 15.

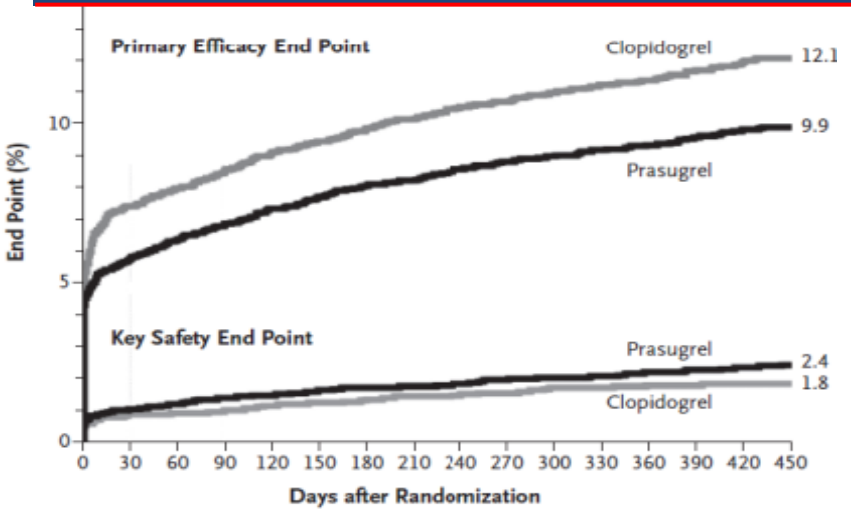
Table 1: Baseline characteristics of STEMI cohort, by drug allocation and type of PCI

-TRITON: De 2438 pacientes SCACEST que fueron a ICPp, sólo 704 recibieron la dosis de carga antes de la ICP.

- PLATO: >7500 pacientes SCACEST, con intención de ICPp, y todos ellos recibieron la dosis de carga antes de la ICP.

Montalescot et al. Lancet 2009; 373: 723-31

Antiagregantes última generación
Prasugrel y ticagrelor



Prasugrel

Efficacy end point (cardiovascular death, MI, stroke)

OR 0.81 (0.73-0.90); <0.001

Safety end point

OR 1.32 (1.03-1.68); 0.03

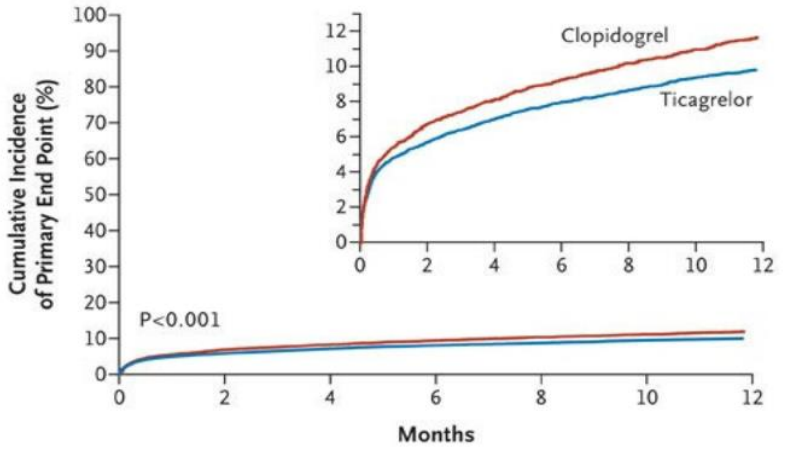
Ticagrelor

Efficacy end point (cardiovascular death, MI, stroke)

OR 0.84 (0.77-0.92); 0.0003

Safety end point

OR 1.04 (0.95-1.13); 0.43



TRITON-TIMI 38: Variables eficacia

End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes ✗	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI √	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke ✗	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

Seguimiento 15 meses

Wiviott et al. NEJM 2007;357:2001-5

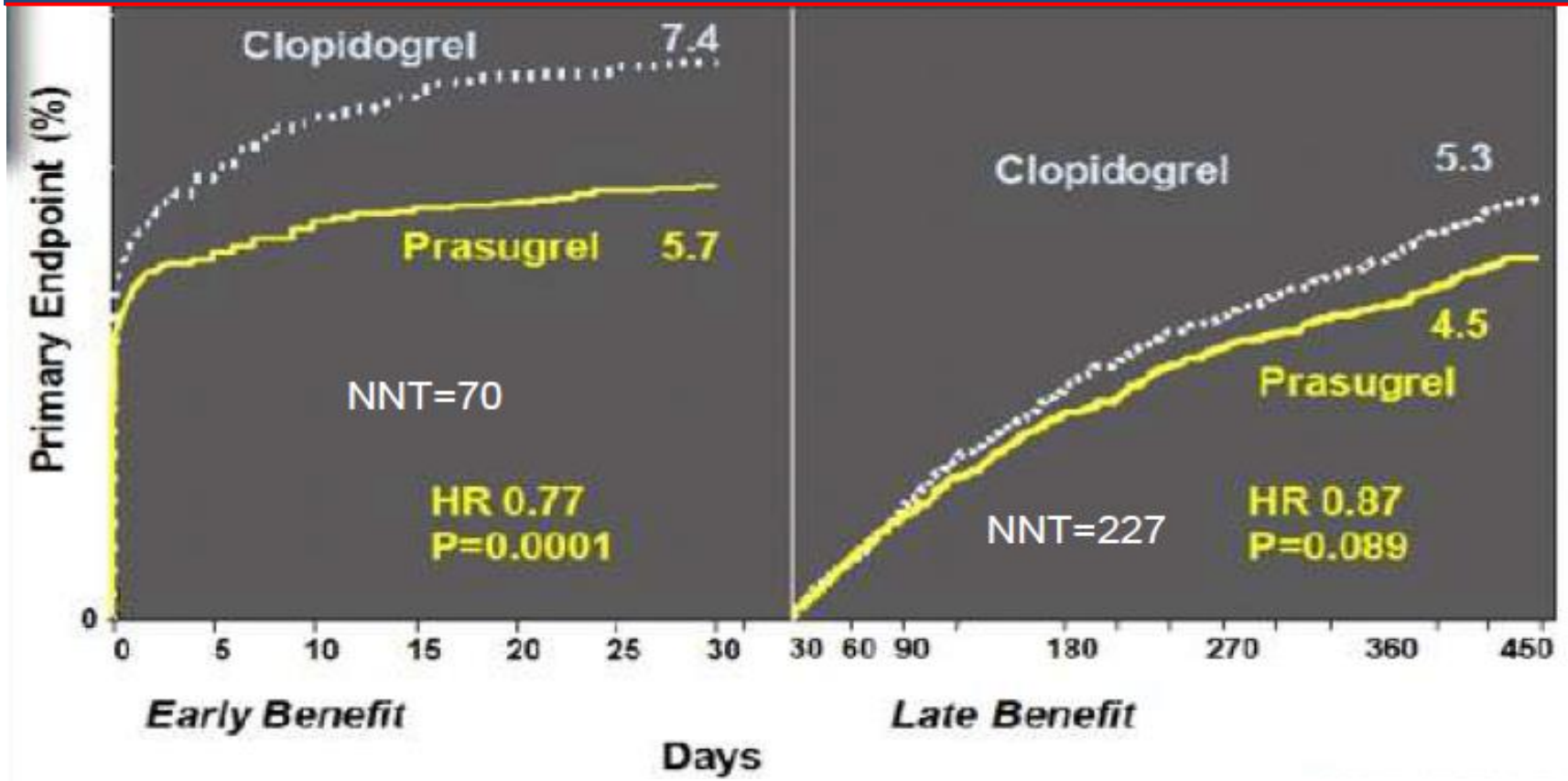
PLATO: Variables eficacia

End Point		Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†	
MI	√	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡	
Death from vascular causes	√	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡	
Stroke	×	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22	
Unknown		10/9333 (0.1)	2/9291 (0.02)		0.04	
Other events — no./total no. (%)						
Death from any cause		399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001	
Death from causes other than vascular causes		46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08	
Severe recurrent ischemia		302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08	

Seguimiento 12 meses

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

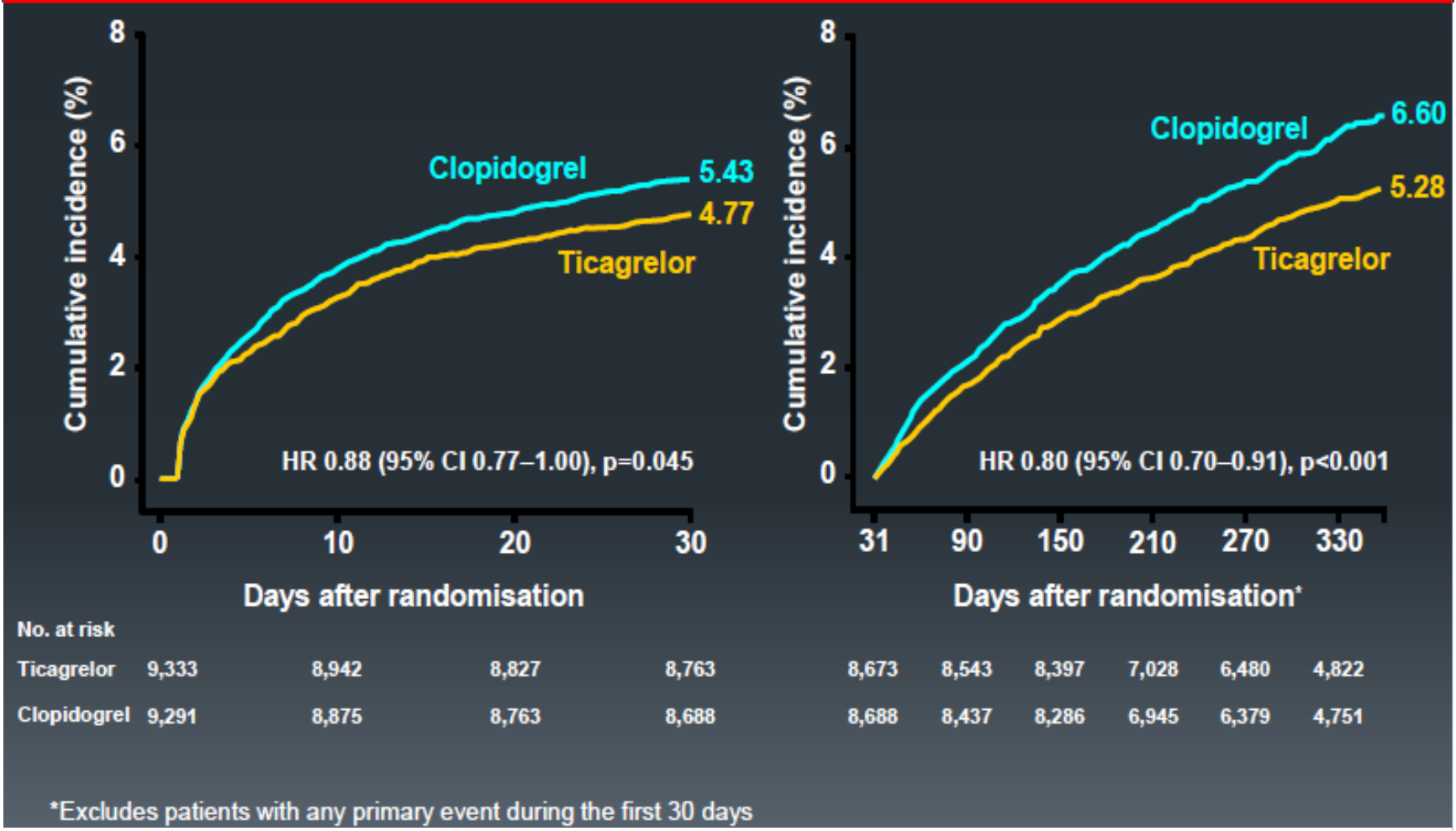
TRITON-TIMI 38: eficacia y tiempo



Outcome	Randomization to 30 days				>30 days to end of trial			
	Pras	Clop	HR (95% CI)	P value	Pras	Clop	HR (95% CI)	P value
CV death, MI, stroke	5.7%	7.4%	0.77 (0.68–0.88)	0.0001	5.3%	4.5%	0.87 (0.74–1.02)	0.089
TIMI major bleeding	1.03%	0.87%	1.19 (0.83–1.70)	0.34	1.42%	0.97%	1.48 (1.04–2.10)	0.028
Adjusted NNT	70	227						

Antman E

PLATO: eficacia y tiempo



*Excludes patients with any primary event during the first 30 days

Wallentin L et al. N Engl J Med 2009;361:1045-57.

Guías de practica clínica

2012 ESC STEMI Guidelines

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

2011 ESC NSTE-ACS Guidelines

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).	I	B
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 life-threatening bleeding or other contraindications.[d]	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A

SCASEST: Prasugrel vs Ticagrelor

- Prasugrel
  - TRITON-TIMI 38
    - Solo PCI, sin pretratar
  - TRYLOGY ACS
    - SCASEST no invasivo
  - ACCOAST
    - Manejo invasivo con pretratamiento

- Ticagrelor
  - PLATO
    - Todo el expectro SCA

TRILOGY: PRASUGREL NSTEMI MANEJO MÉDICO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization

CONCLUSIONS

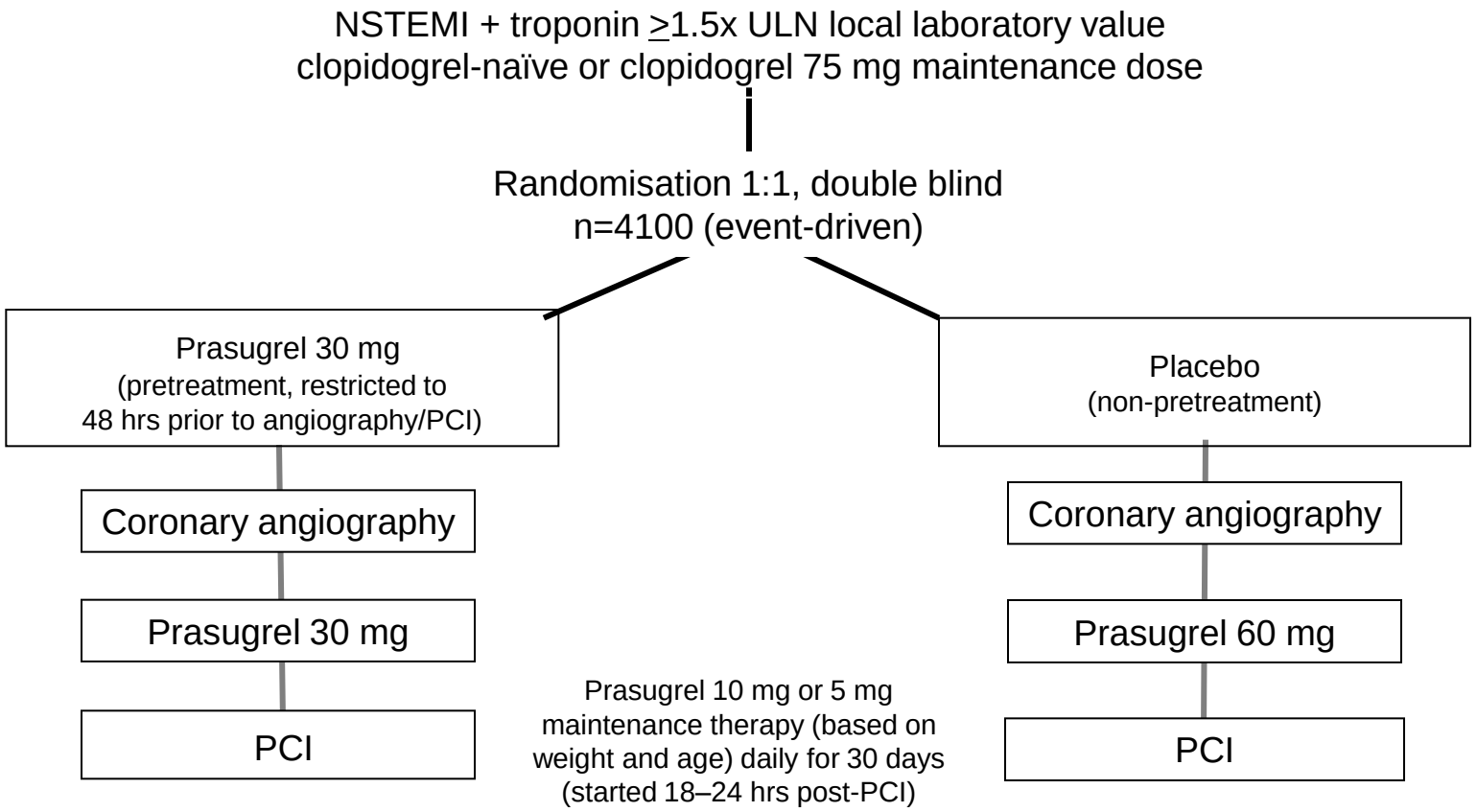
Among patients with unstable angina or myocardial infarction without ST-segment elevation, prasugrel did not significantly reduce the frequency of the primary end point, as compared with clopidogrel, and similar risks of bleeding were observed. (Funded by Eli Lilly and Daiichi Sankyo; TRILOGY ACS ClinicalTrials.gov number, NCT00699998.)

Mircea Cinteză, M.D., Ph.D., R. Craig McLendon, R.N., Kenneth J. Winters, M.D., Eileen B. Brown, Ph.D., Yuliya Lokhnygina, Ph.D., Philip E. Aylward, B.M., B.Ch., Ph.D., Kurt Huber, M.D., Judith S. Hochman, M.D., and E. Magnus Ohman, M.B., Ch.B., for the TRILOGY ACS Investigators*

Roe M.T et al. N Engl Med 2012 Oct 4;367(14):1297-309

SCACEST: ACCOAST

Estudio de pretratamiento o tratamiento antes versus despues de conocer anatomía coronaria en SCASEST



PRIMARY ENDPOINTS

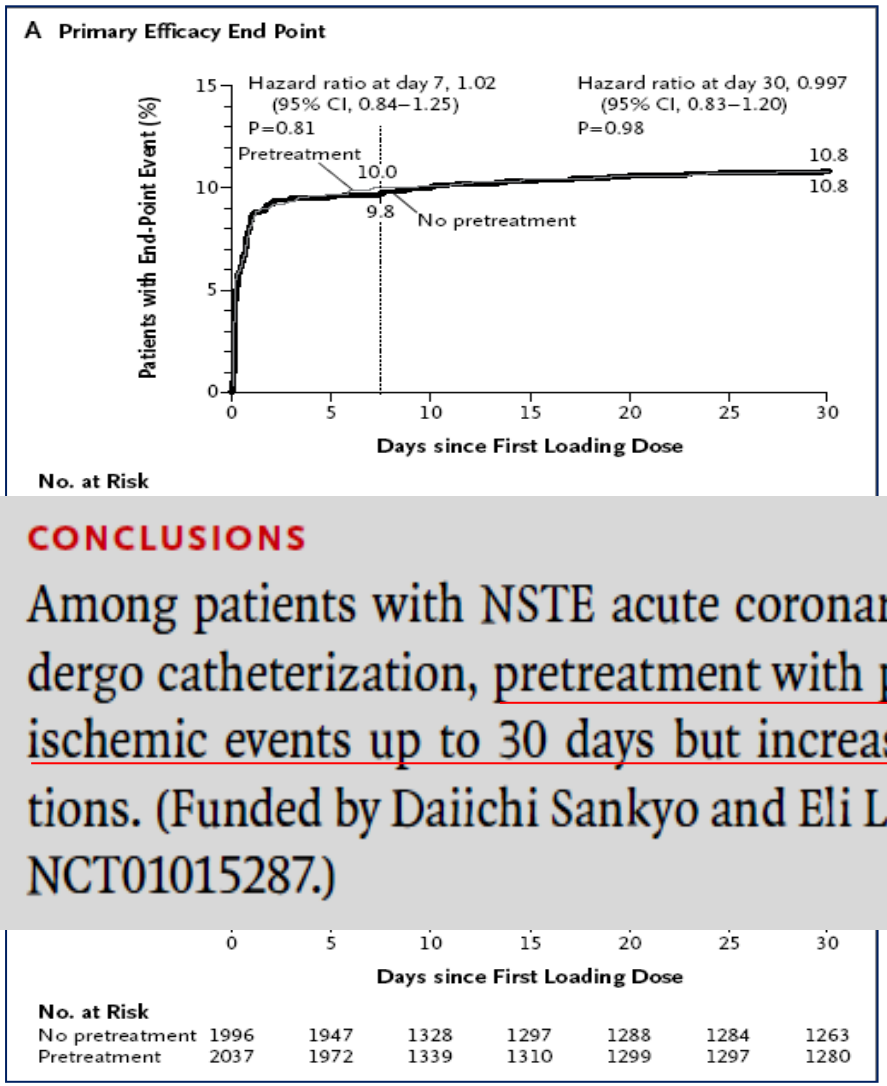
EFFICACY: CV death, MI, stroke, urgent revascularisation. GPIIb/IIIa inhibitor bailout at 7 days

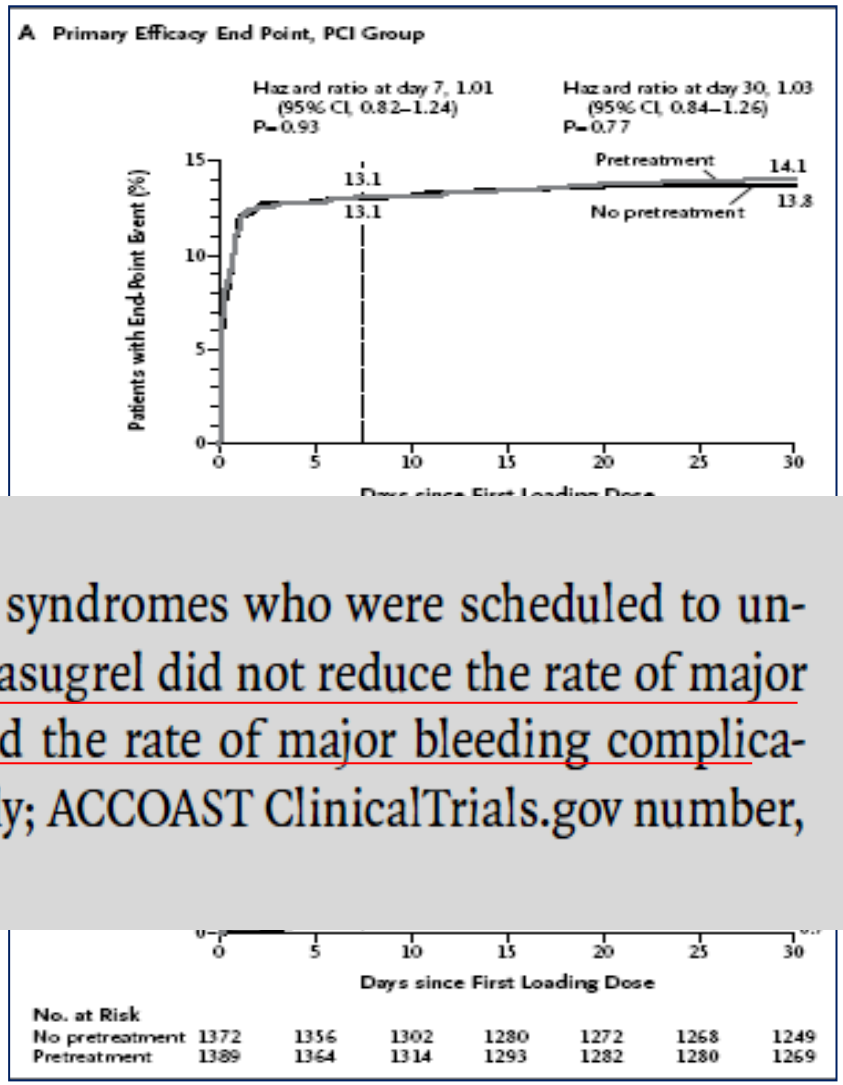
SAFETY: TIMI major and minor bleeding

Montalescot G, et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1308075.

SCACEST: ACCOAST

Resultados





CONCLUSIONS

Among patients with NSTE acute coronary syndromes who were scheduled to undergo catheterization, pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications. (Funded by Daiichi Sankyo and Eli Lilly; ACCOAST ClinicalTrials.gov number, NCT01015287.)

Montalescot G, et al. N Engl J Med 2013..

European Heart Journal
doi:10.1093/eurheartj/ehu160

CLINICAL RESEARCH
Acute coronary syndromes

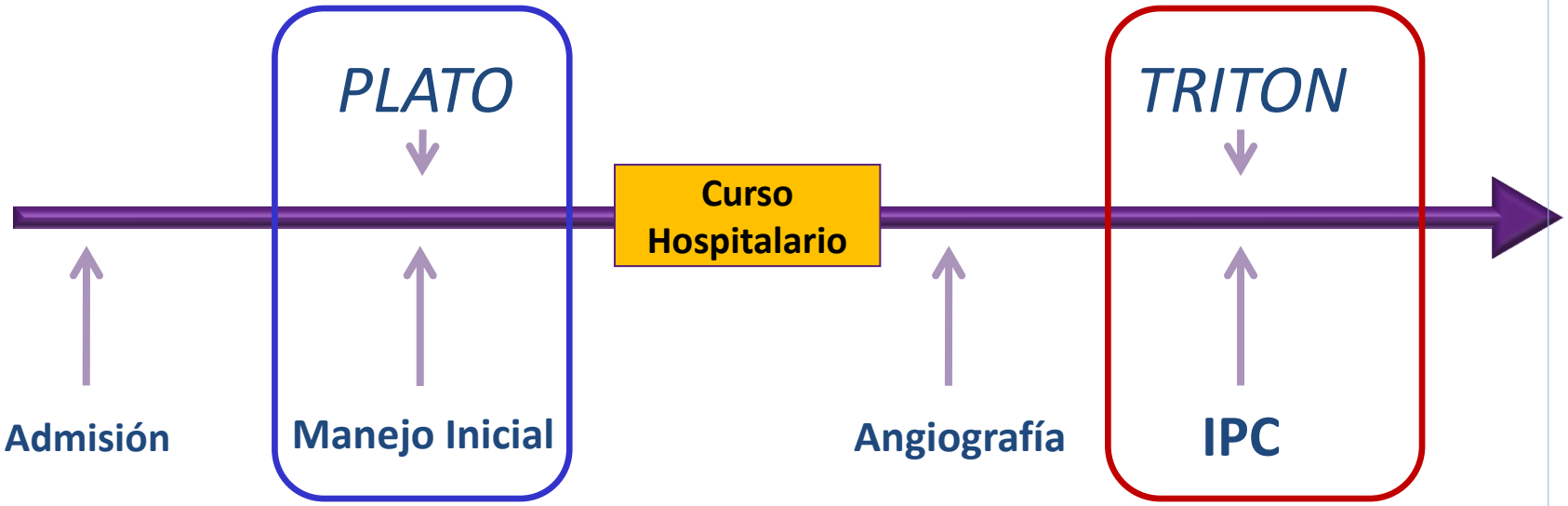
Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial

Daniel Lindholm[1], Christoph Varenhorst[1], Christopher P Cannon[2], Robert A Harrington[3], Anders Himmelmann[4], Juan Maya[5], Steen Husted[6], Philippe Gabriel Steg[7,8,9,10], Jan H Cornel[11], Robert F Storey[12], Susanna R Stevens[13], Lars Wallentin[1], and Stefan K James[1]*

[1]Department of Medical Sciences, Cardiology and Uppsala Clinical Research Center, Uppsala University, MTC Building, Uppsala Science Park, Dag Hammarskjölds väg 14B, SE-752 37 Uppsala, Sweden; [2]TIMI Study Group, Brigham and Women's Hospital, Boston, MA, USA; [3]Department of Medicine, Stanford University, Stanford, CA, USA; [4]AstraZeneca Research and Development, Mölndal, Sweden; [5]AstraZeneca Research and Development, Wilmington, DE, USA; [6]Medical Department, Hospital Unit West, Herning/Holstbro, Denmark; [7]INSERM-Unité 1148, Paris, France; [8]Assistance Publique-Hôpitaux de Paris, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Paris, France; [9]NHLI Imperial College, ICMS, Royal Brompton Hospital, London, UK; [10]Université Paris-Diderot, Sorbonne-Paris Cité, Paris, France; [11]Department of Cardiology, Medisch Centrum Alkmaar, Alkmaar, The Netherlands; [12]Department of Cardiovascular Science, University of Sheffield, Sheffield, UK; and [13]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA

Received 21 August 2013; revised 27 February 2014; accepted 19 March 2014

SCASEST: PLATO vs TRITON
Momento de inclusión



PLATO:
- Manejo Invasivo y Conservador antes de A.C.

TRITON:
- Sólo ICP después de A.C.

Resultados PLATO SCASEST

Table 2 **Efficacy and safety outcomes in patients with NSTE-ACS**

	Ticagrelor % (*n*)	Clopidogrel % (*n*)	HR (95% CI)	*P*-value
Efficacy endpoints				
CV death/MI (excluding silent)/stroke	10.0 (533)	12.3 (630)	0.83 (0.74, 0.93)	0.0013
All-cause death/MI(excl. silent)/stroke	10.5 (557)	13.0 (664)	0.82 (0.73, 0.92)	0.0006
CV death/MI(all)/stroke/severe recurrent ischaemia/recurrent ischaemia/TIA/arterial thrombotic event	15.5 (824)	17.8 (918)	0.88 (0.80, 0.96)	0.0058
Myocardial infarction (excluding silent)	6.6 (345)	7.7 (392)	0.86 (0.74, 0.99)	0.0419
Cardiovascular death (includes vascular and unknown deaths)	3.7 (194)	4.9 (247)	0.77 (0.64, 0.93)	0.0070
Stroke	1.3 (69)	1.4 (71)	0.95 (0.69, 1.33)	0.79
All-cause death	4.3 (224)	5.8 (290)	0.76 (0.64, 0.90)	0.0020
Safety endpoints				
Major bleeding (study criteria)	13.4 (660)	12.6 (618)	1.07 (0.95, 1.19)	0.26
Major or minor bleeding (study criteria)	18.2 (900)	16.3 (794)	1.14 (1.03, 1.25)	0.0078
Non-CABG related major bleeding (study criteria)	4.8 (225)	3.8 (176)	1.28 (1.05, 1.56)	0.0139
Fatal bleeding	0.3 (13)	0.4 (18)	0.72 (0.35, 1.47)	0.37
Life threatening or fatal bleeding (study criteria)	6.6 (331)	6.5 (315)	1.05 (0.90, 1.22)	0.56
Intracranial bleeding	0.3 (14)	0.2 (7)	2.01 (0.81, 4.99)	0.13
Other major bleeding	7.2 (344)	6.6 (318)	1.08 (0.93, 1.25)	0.34

Lindholm et al. European Heart Journal 2014. doi:10.1093/eurheartj/ehu160

PLATO SCASEST: Beneficio independientemente si se ralizó o no revascularización

Conclusions

In this substudy of the PLATO trial, ticagrelor compared with clopidogrel consistently reduced the rates of ischaemic events and mortality without any difference in overall major bleeding in patients with an entry diagnosis of NSTE-ACS, and this effect was independent of whether or not early revascularization was performed. These results harmonize with the European Society of Cardiology (ESC) NSTE-ACS guidelines, which recommend ticagrelor in all patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy.[1]

Days from day 10 post-randomization

C, no rv	2590	2501	2472	2207	1948	1426	1194
C, revasc	2804	2740	2718	2467	2239	1649	1397
T, no rv	2627	2541	2505	2265	2028	1493	1239
T, revasc	2842	2789	2767	2478	2251	1663	1412

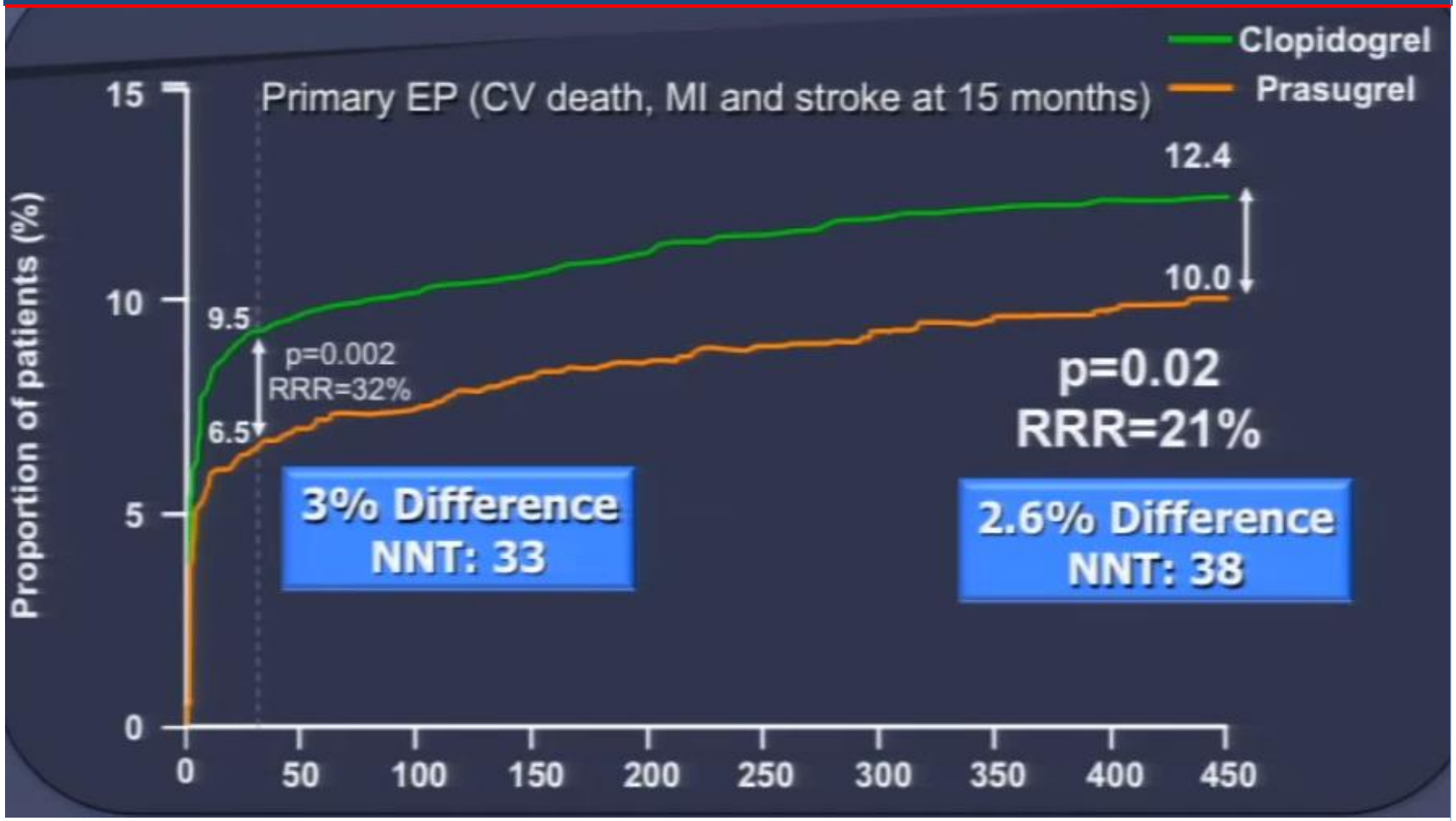
Lindholm et al. European Heart Journal 2014. doi:10.1093/eurheartj/ehu160

SCACEST: Prasugrel vs Ticagrelor

- Prasugrel
  - TRITON-TIMI 38
    - Solo PCI, sin pretratar

- Ticagrelor
  - PLATO
    - Todo el expectro SCA
  - ATLANTIC
    - Inicio extrahospitalario

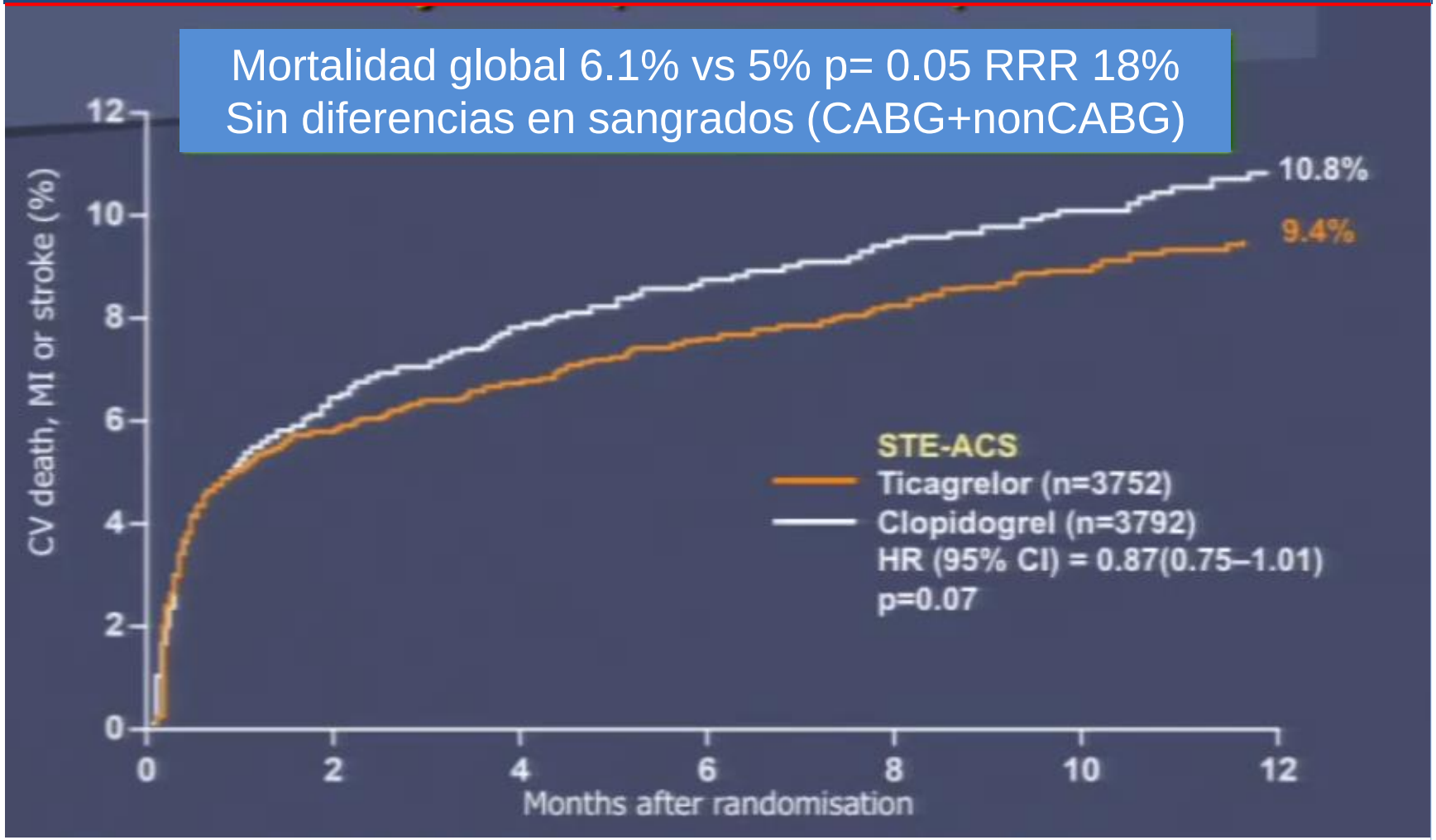
SCACEST: TRITON STEMI



Montalescot; Lancet 2009; 373: 723-31

SCACEST: PLATO STE-ACS

Mortalidad global 6.1% vs 5% p= 0.05 RRR 18%
Sin diferencias en sangrados (CABG+nonCABG)



El beneficio con ticagrelor respecto al endpoint primario fue consistente con los resultados globales del estudio PLATO

SCACEST: Prasugrel vs Ticagrelor
Consideraciones metodológicas

- Prasugrel y Ticagrelor han sido investigados en SCA de alto riesgo con manejo invasivo
- En ambos estudios no se detectaron interacciones en el análisis del subgrupo SCACEST
- Por tanto, la correcta interpretación de los resultados de ambos estudios es que los beneficios y riesgos observados en la cohorte completa son consistentes también en el SCACEST

SCACEST: Inicio DAPT en el entorno extra-hospitalario Estudio ATLANTIC

The NEW ENGLAND JOURNAL of MEDICINE

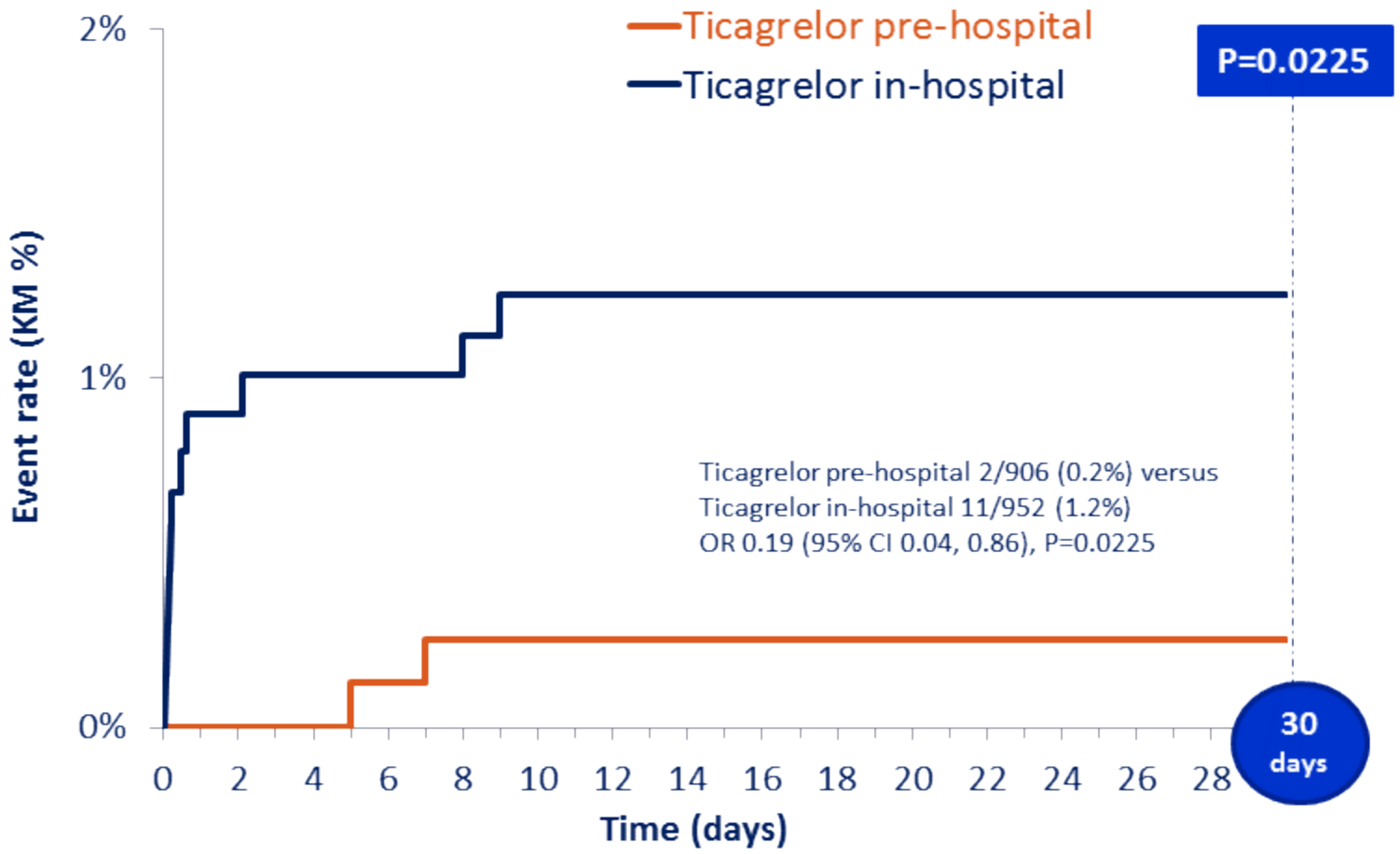
ORIGINAL ARTICLE

Pre-hospital ticagrelor administration a short time before PCI in patients with ongoing STEMI is safe but does not improve pre-PCI coronary reperfusion. It may, however, reduce the risk of post-PCI stent thrombosis.

Anne Tsatsaris, M.D., Eric Vicaut, M.D., Ph.D., and Christian W. Hamm, M.D., Ph.D.,
for the ATLANTIC Investigators*

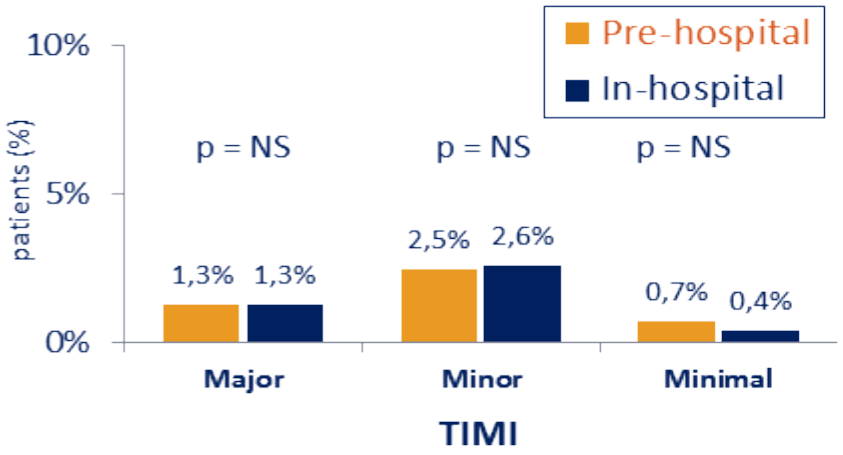
N Engl J Med. 2014 Sep 11;371(11):1016-27

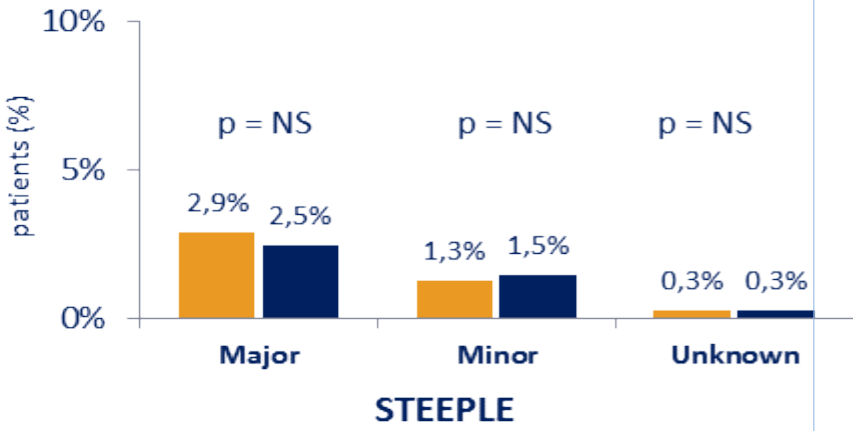
SCACEST: Estudio ATLANTIC
Trombosis stent definitiva a 30 días

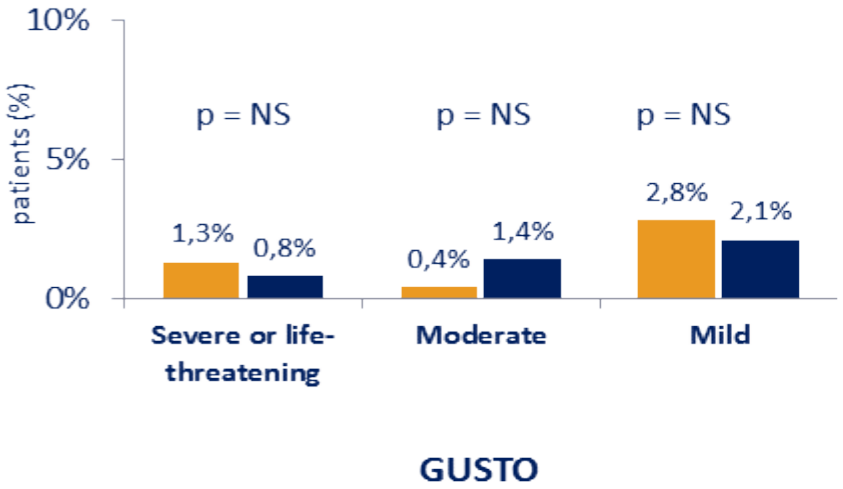


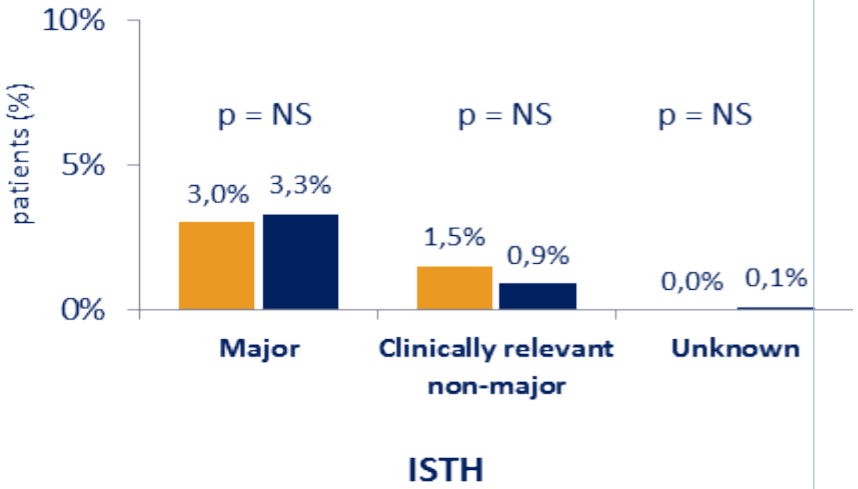
N Engl J Med. 2014 Sep 11;371(11):1016-27

SCACEST: Estudio ATLANTIC
Seguridad









Non-CABG-related bleeding events
(TIMI, STEEPLE, GUSTO and ISTH definitions) - Safety population

N Engl J Med. 2014 Sep 11;371(11):1016-27

Facilidad de uso

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Ticagrelor or prasugrel for pre-hospital protocols in STEMI?☆

Nathalie Fournier [a], Richard Toesca [a], Jacques Bessereau [a], Anne Champenois [a], André Mazille [b], Stéphane Luigi [b], Serge Yvorra [c], Franck Paganelli [d], Pierre-Marie Brun [e], Pierre Michelet [a], Daniel Meyran [e], Jean-Pierre Auffray [a], Laurent Bonello [e,*]

[a] Pole RUSH, hôpital de la Timone, Marseille, France
[b] Service d'accueil des urgences, Hôpital de Martigues, France
[c] Service de cardiologie, Hôpital de Martigues, Martigues, France
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[e] SMUR de Marseille, Bataillon des Marins Pompiers, Marseille, France

Int J Cardiol. 2013 Oct 9;168(4):4566-7

Facilidad de uso

Ticagrelor or prasugrel for pre-hospital protocols in STEMI?☆

Protocol A

Ticagrelor LD: 180mg /Clopidogrel 600mg
Contrainidcation for Ticagrelor use:

- Fibrinolysis
- Recent surgery
- High Bleeding Risk
- Dialysis

Protocol B

Prasugrel LD: 60mg/Clopidogrel 600mg
Contrainidcation for Prasugrel use:

- >75 años
- <60kg
- History Ictus
- Fibrinolysis
- Recent surgery
- High Bleeding Risk

The present study suggests that a STEMI protocol using ticagrelor allows a higher proportion of patients to receive a novel P2Y12-ADP receptor antagonist compared to a protocol based on prasugrel. Further the limited number of contra-indication is also associated with a higher adhesion to the protocol by emergency practitioners.

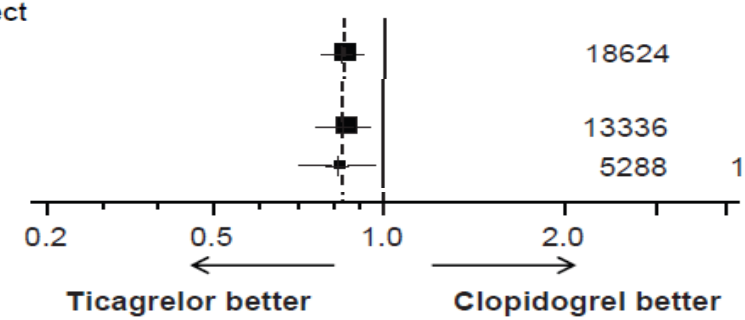
76 Received Ticagrelor according to protocol	26 Received Prasugrel according to protocol
6 had CI to Ticagrelor	17 had a CI to Prasugrel
0 Received Ticagrelor despite CI	3 Received Prasugrel despite CI
1 did not receive Ticagrelor despite the protocol	7 did not receive Prasugrel despite the protocol

Fig. 1. Flow chart of the study and main results. STEMI: ST-elevation myocardial infarction. PCI: percutaneous coronary intervention.

Int J Cardiol. 2013 Oct 9;168(4):4566-7

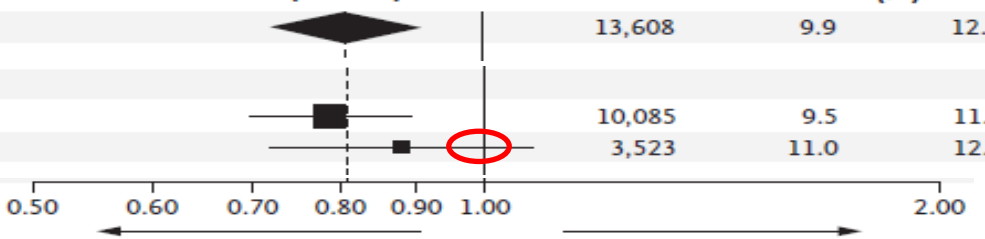
Sexo femenino: PLATO vs TRITON

PLATO



Characteristic	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	*P* value (Interaction)
Overall Treatment Effect					
Primary Endpoint	18624	9.8	11.7	0.84 (0.77, 0.92)	
Sex					0.82
Male	13336	9.2	11.1	0.85 (0.76, 0.95)	
Female	5288	11.2	13.2	0.83 (0.71, 0.97)	

TRITON



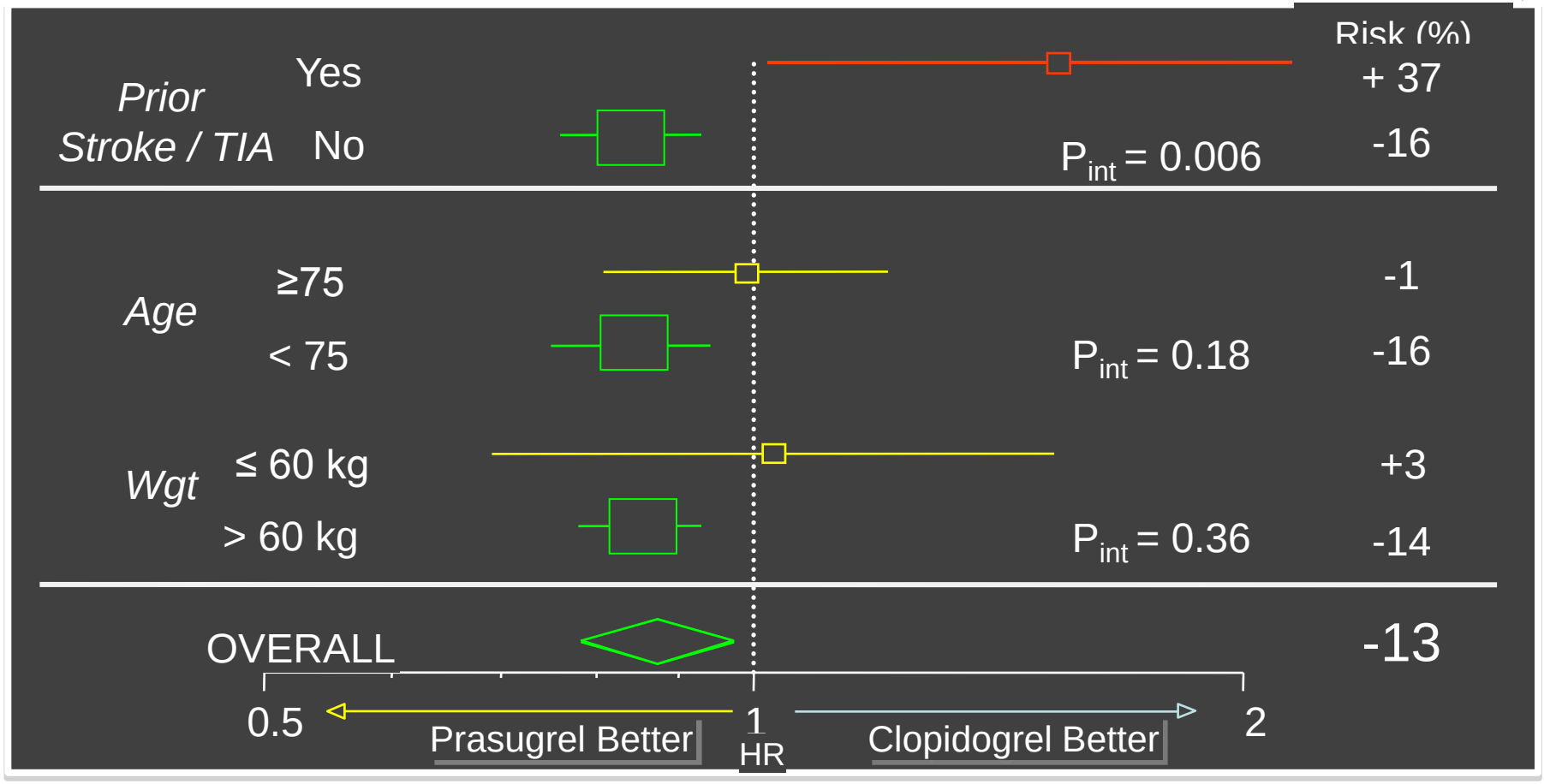
Baseline Characteristics	Total No. of Patients	Prasugrel (%)	Clopidogrel (%)	Reduction in Risk (%)
Overall	13,608	9.9	12.1	19
Sex				
Male	10,085	9.5	11.9	21
Female	3,523	11.0	12.6	12

P interaction ns

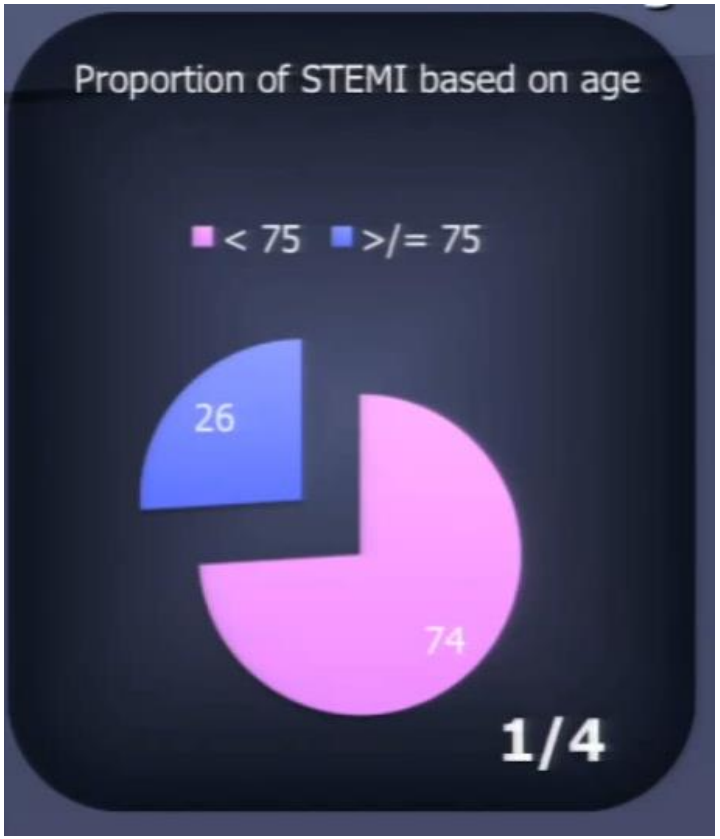
Wallentin L, et al. N Engl J Med 2009;361:1045–1057; Wiviott, S et al. N Engl J Med 2007;357:2001-15

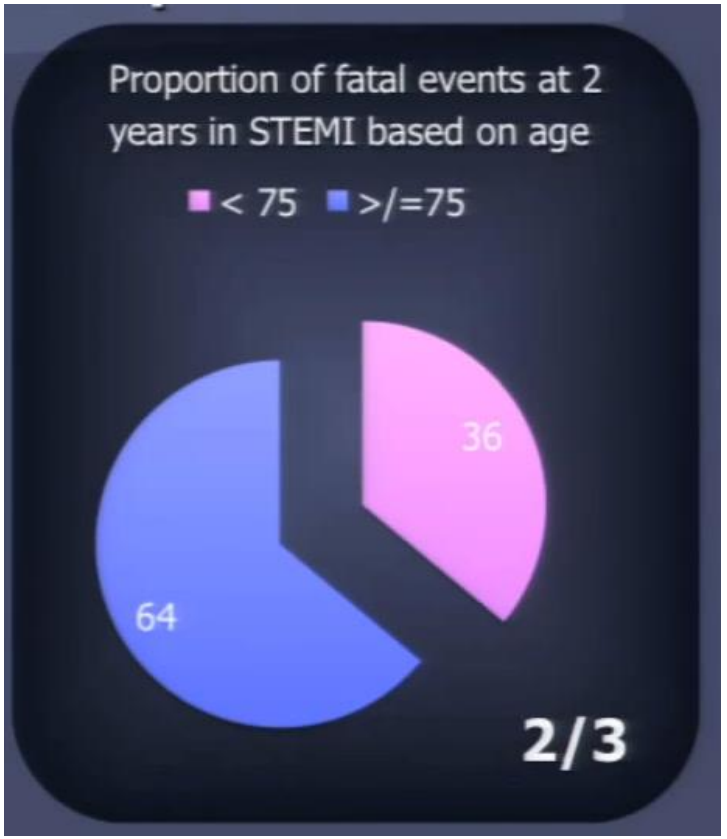
Eficacia y seguridad en grupos especiales

TRITON-TIMI 38 Study
Subgroup analysis by bleeding risk



SCACEST y edad

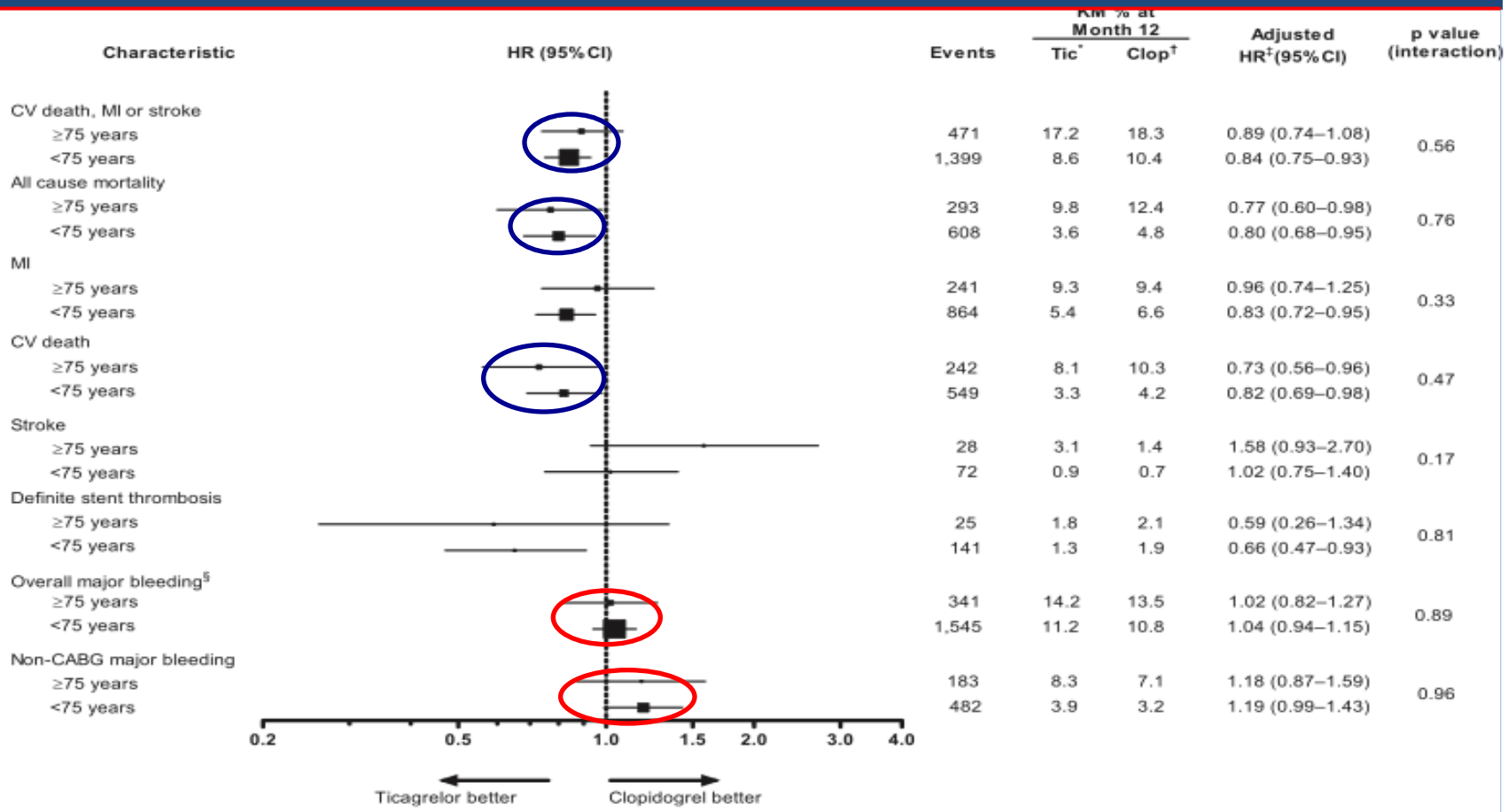




¿Estamos tratando bien a los pacientes de mayor riesgo?

PRODIGY dataset

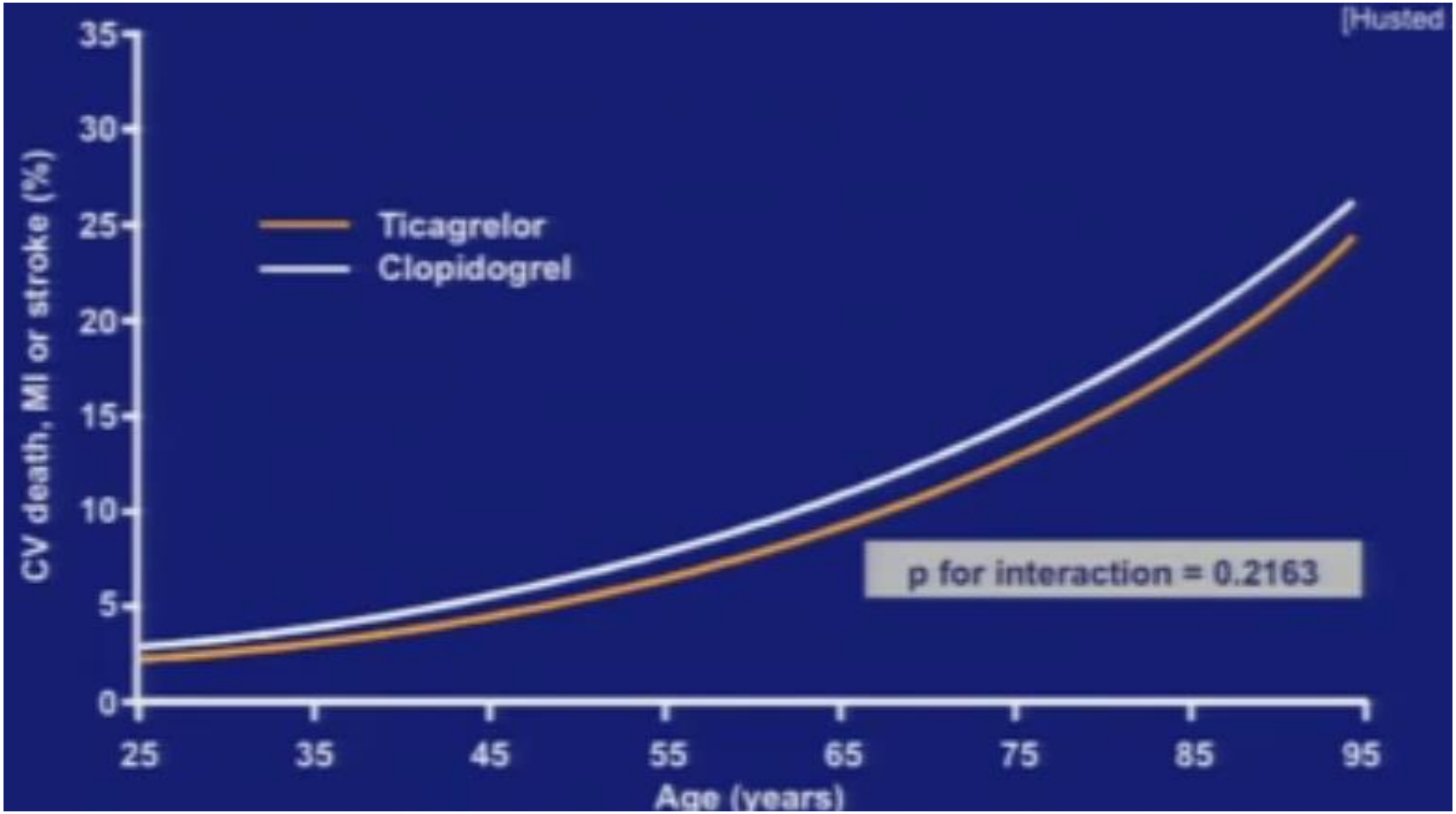
SCA y edad
PLATO



Pacientes ≥75 y <75 años, reducción significativa de la mortalidad CV y mortalidad total SIN aumento de los sangrados mayores y NO relacionados con CABG

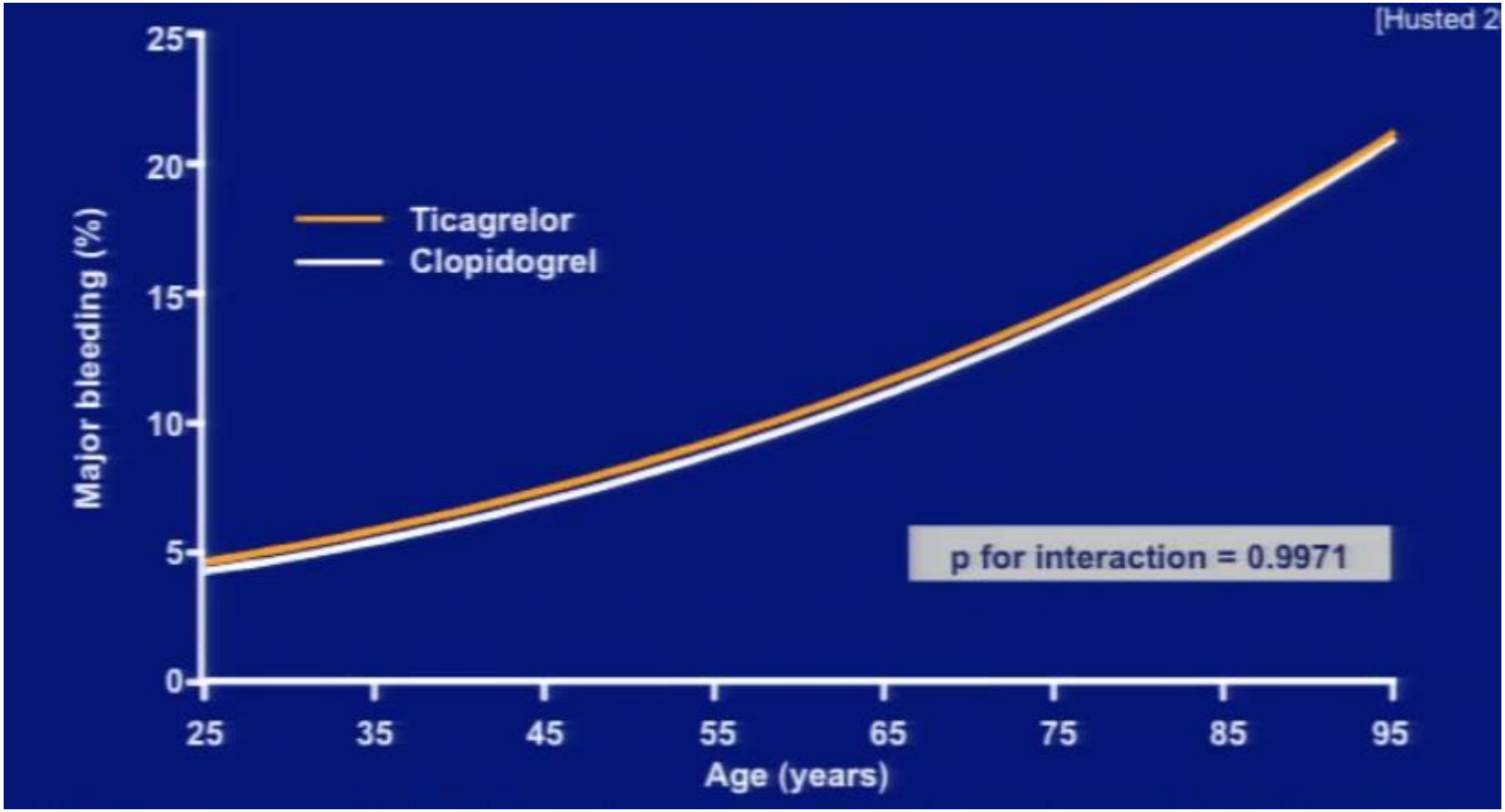
Steen Husted, et al. Circ Cardiovasc Qual Outcomes 2012.

Estudio PLATO-ancianos
Endpoint primario acorde a la edad



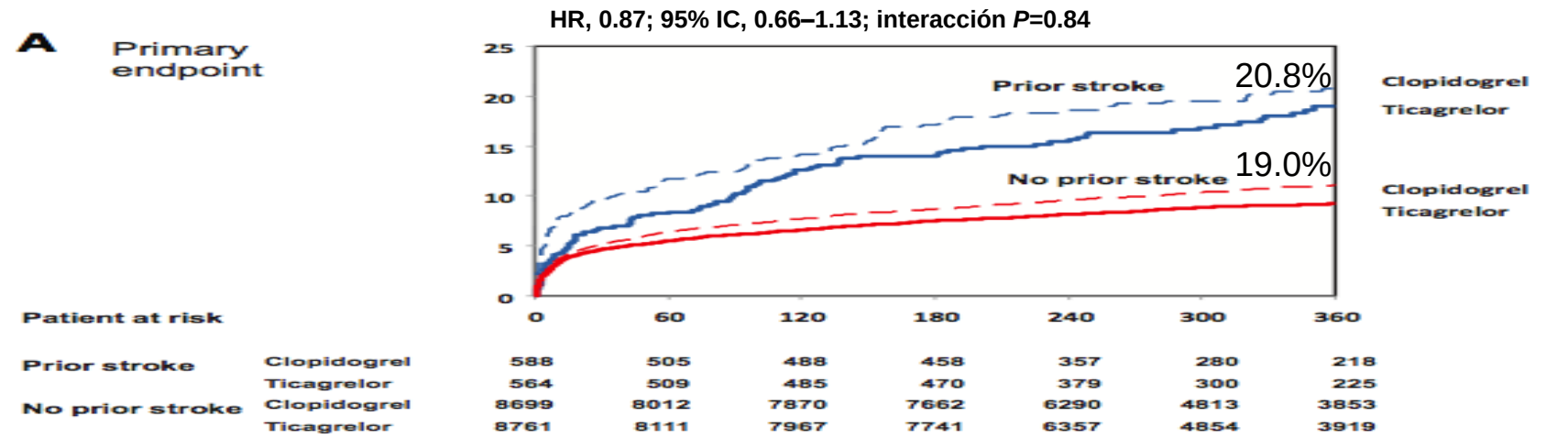
Beneficio con ticagrelor consistente con los resultados del estudio principal

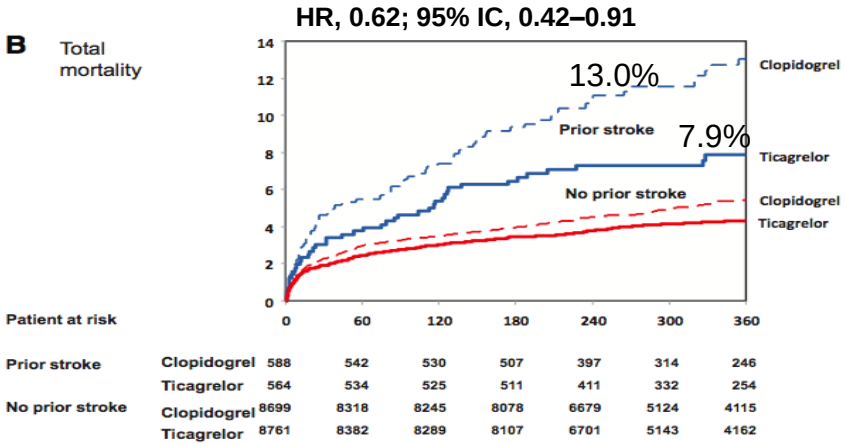
Estudio PLATO-ancianos
Hemorragia acorde a la edad

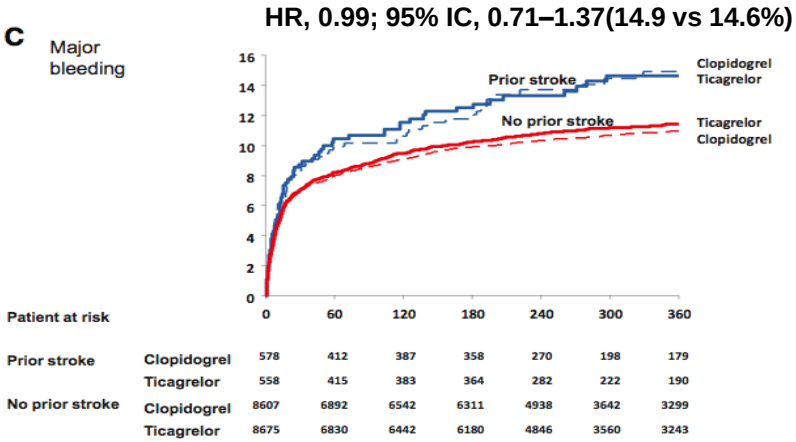


Frecuencia de hemorragias similares a los resultados del estudio principal

SCA y AVC

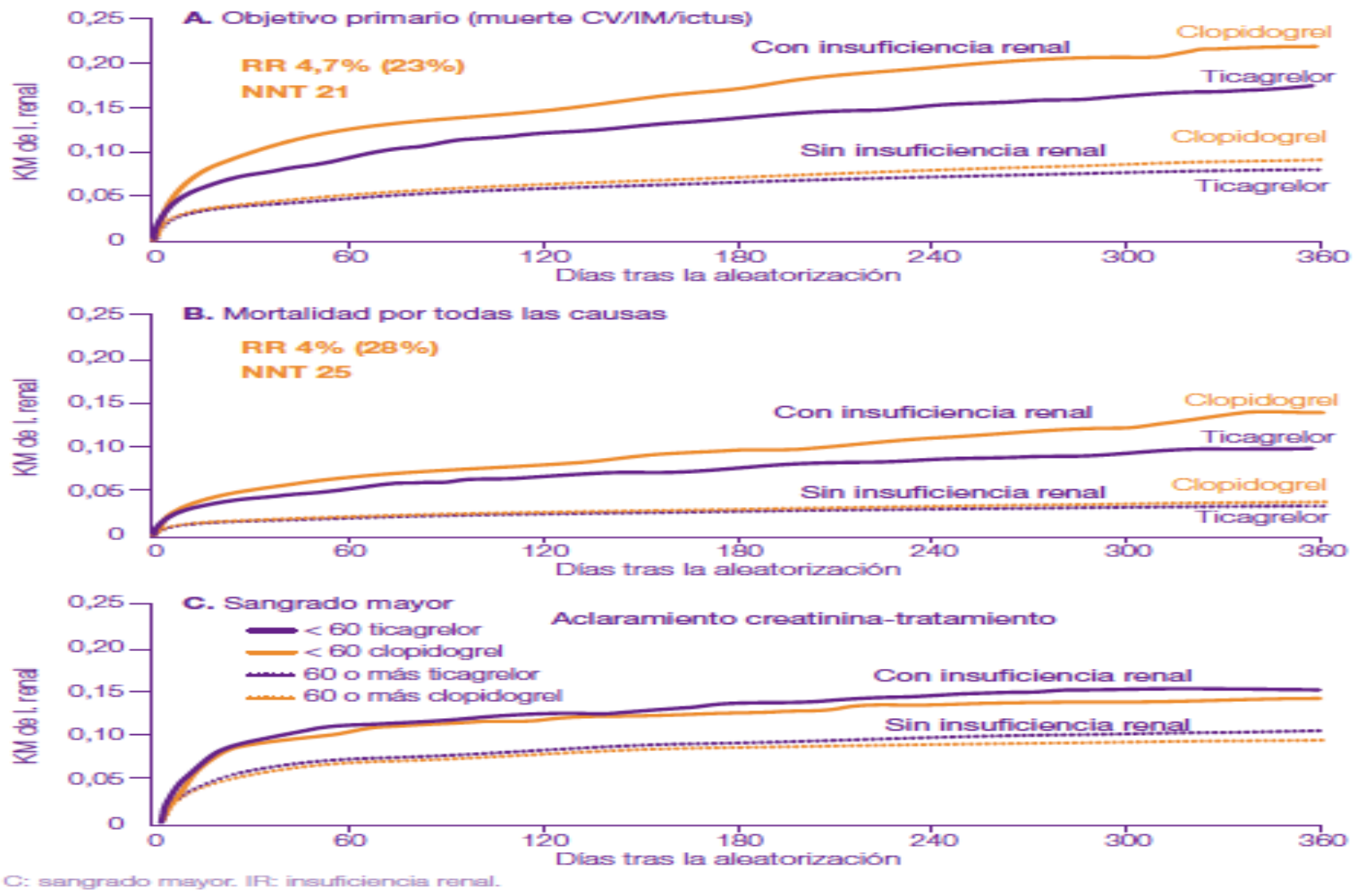






Stefan K. James et al. Circulation. 2012;125:2914-2921 .

Estudio PLATO: Insuficiencia renal

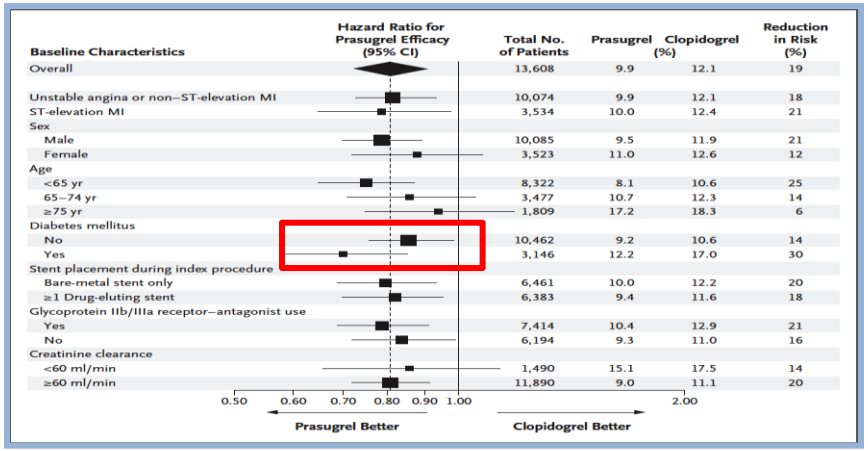


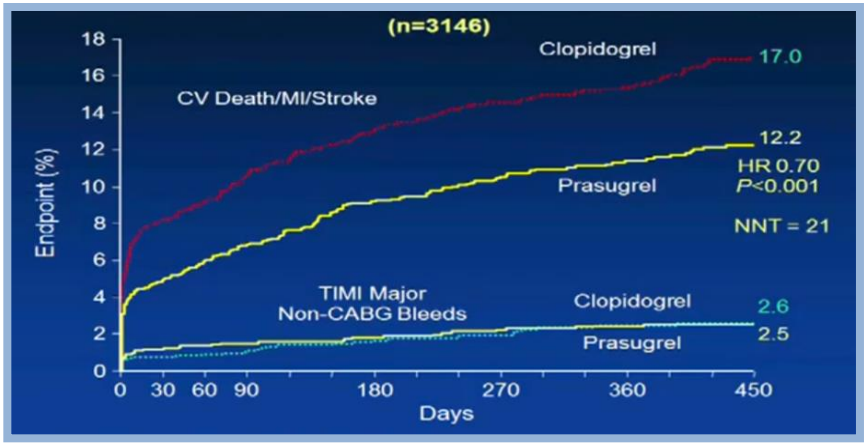
C: sangrado mayor. IR: insuficiencia renal.

Wallentin L et al. N Engl J Med 2009; 361: 1045-1057.

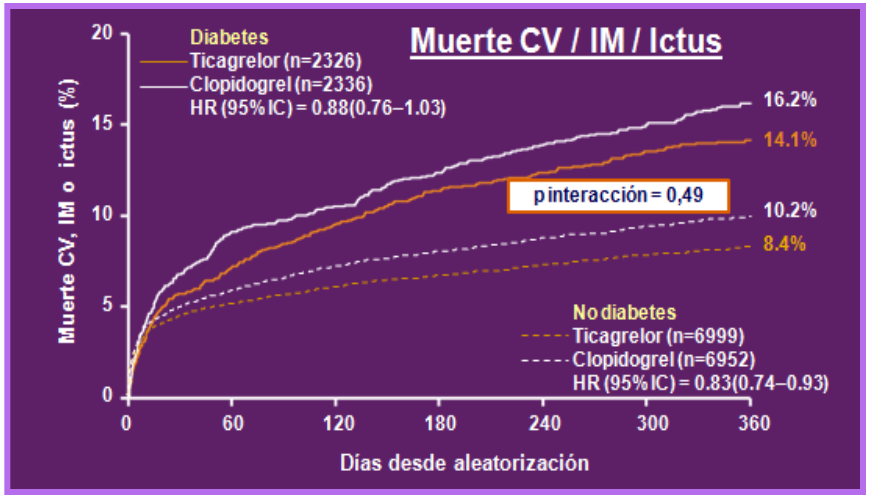
Estudio PLATO: Diabetes

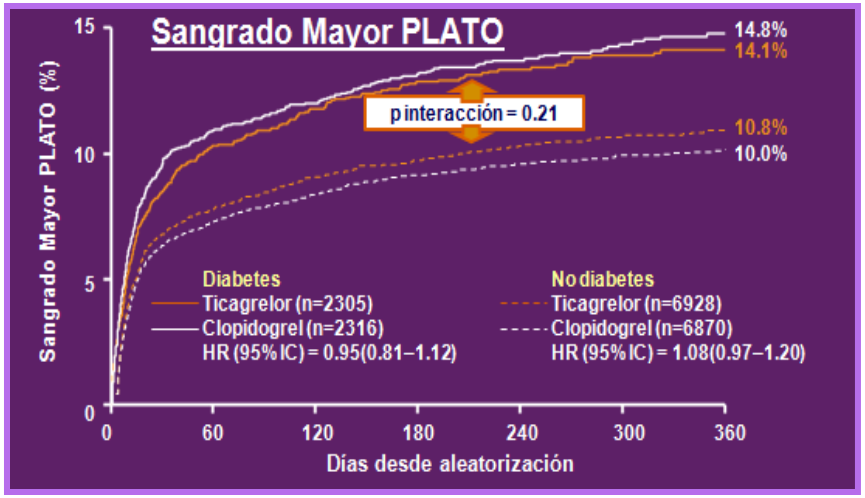
TRITON-TIMI 38





PLATO Study





Wiviott SD. N Engl J Med 2007; 357: 2001-15.

James S et al. Eur Heart J 2010;31:3006-1

DAPT en DM: SCASEST

European Heart Journal (2011) 32, 2999–3054
doi:10.1093/eurheartj/ehr236

ESC GUIDELINES

ESC Guidelines for the management of acute coronary syndromes in patients pre g without persistent ST-segment

The Task Force for the management dromes (ACS) in patients presenting witho elevation of the European Soci

Sin comentarios específicos para DM

Recommendations		Level [b]
Aspirin should be given to all patients without contrai maintenance dose of 75–100 mg daily long-term		A
A $P2Y_{12}$ inhibitor should be added to a contraindications such as excessi	I	A
Ticagrelor (180-mg lo ischaemic event clopidogrel (whi -high risk of ing those pre-treated with	I	B
Prasugrel (60-mg l diabetics) in whom threatening bleeding $_{12}$-inhibitor-naïve patients (especially ceeding to PCI unless there is a high risk of life-	I	B
Clopidogrel (300-mg l dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600-mg loading dose o opidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B

DAPT en DM: SCACEST

European Heart Journal
doi:10.1093/eurheartj/ehs215

ESC GUIDELINES

ESC Guidelines for the manageme…cute myocardial infarction in patie…g with ST-segment elevatio…

The Task Force on the mana…n acute myocardial infarction of t… (ESC)

Sin comentarios específicos para DM

Aspirin oral or i.v. (if unable to swallow) is…	I	B
An ADP-receptor blocker is rec…	I	A
• Prasugrel in clopid…	I	B
• Ticagrelo…	I	B
• Clopidogr… contraindicated.	I	C
GP IIb/IIIa inhibit… …iographic evidence of massive thrombus, slow or no-reflow	IIa	C
Routine use of a G… …y PCI performed with unfractionated heparin may be considered in patien…	IIb	B
Upstream use of a G… …-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B
Options for GP IIb/IIIa i… …tors are (with LoE for each agent):		
• Abciximab		A
• Eptifibatide (with double bolus)		B
• Tirofiban (with a high bolus dose)		B

¿Qué hacemos en nuestra práctica clínica habitual?

Registro retrospectivo PROMETHEUS

19,914 ACS patients included

80% treated with clopidogrel

Los pacientes tratados con Prasugrel fueron más jóvenes y "sanos" que aquellos que recibieron clopidogrel

Respecto a los eventos (MACE) disminuyeron en un 44% a 90 días en el análisis univariado, disminuciones del 49% en IM y 79% en mortalidad por todas las causas

En el multivariado, no hubo diferencias en los MACE entre los dos grupos

La incidencia de sangrado fue menor en los pacientes tratados con prasugrel, pero la reducción no fué significativa tras ajustar por las potenciales variables confusoras

Stent thrombosis after STEMI treated with primary PCI and dual antiplatelet therapy with ticagrelor or clopidogrel

Aims: Stent thrombosis is a life-threatening. Newer P2Y12 antagonists have been developed to increase safety in patients with acute coronary syndromes. We compared one-year risk of definite stent thrombosis and cardiac death in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) and dual antiplatelet therapy with aspirin and either ticagrelor or clopidogrel for 12 months.

Methods and results: From June 2010 to June 2012 all patients with STEMI treated with primary PCI at Odense University Hospital were identified from the Western Denmark Heart Registry. From June 2010 to June 2011 the standard dual antiplatelet therapy was aspirin and clopidogrel (600-mg loading dose, 75 mg daily thereafter): "clopidogrel group" and from June 2011 to June 2012 the standard dual antiplatelet therapy was changed to aspirin and ticagrelor (180-mg loading dose, 90 mg twice daily thereafter): "ticagrelor group". This change in use of type of P2Y12 antagonist was performed simultaneously in the

Conclusiones: En este estudio observacional con mas de 1100 pacientes, Ticagrelor comparado con Clopidogrel, redujo la tasa de muerte cardiovascular y la trombosis definitiva de stent.

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clopidogrel treated patients (p=0.63) had TIMI 3 flow in the infarct related coronary artery before the intervention. In the ticagrelor group 545 (91.4%) of the patients were treated with a drug-eluting stent compared to 526 (89.5%) in the clopidogrel group (p=0.25). Overall, at 1 year, 13 events (1.1%) of definite stent thrombosis were recorded. Ticagrelor compared with clopidogrel reduced definite stent thrombosis (3 [0.5%] versus 10 [1.8%] events [HR=0.29 95% Confidence Interval (CI) 0.08-1.06]. The definite stent thrombosis in the ticagrelor treated patients occurred acute (n=1), and subacute (n=2) and in the clopidogrel treated patients the definite stent thrombosis occurred acute (n=4), subacute (n=5) and late (n=1). One-year cardiac mortality rate was significant lower in the "ticagrelor group" n=25 (4.2%) compared to the "clopidogrel group" n=42 (7.1%) [HR=0.58 95% CI: 0.36-0.95].

euro PCR 2014

TICAGRELOR VERSUS CLOPIDOGREL IN THE REAL-WORLD PATIENTS WITH STEMI: 1-YEAR RESULTS BY A PROPENSITY SCORE ANALYSIS

Matteo Vercellino[1], Federico Ariel Sànchez[1], Sergio Suppo[2], Valentina Boasi[1],

•**Methods**. From the single-center "CARDIO-STEMI SANREMO" registry, patients with a diagnosis of STEMI were selected between Feb 2011 and Jun 2013.

•**Results**.

-Out of 416 patients: 401 were STEMI:

-In the T group (n=142), 100% of patients received the loading dose, administered in 98% of cases before the cath-lab.

- In the C group (n=259), 91% received the loading dose (38% >300 mg), administered in 94% before the cath-lab.

-All-cause mortality at 1 year after STEMI remained significantly lower for TICAGRELOR [Hazard risk=0.29 (0.08-0.99); p=0.048].

•**Conclusions: In our single-center experience about a real-world population, ticagrelor resulted in improved survival at 1 year in patients with STEMI, even after correction, by propensity score, of interference related to the lack of randomization.**

Vercellino M. G ITAL CARDIOL | VOL 15 | SUPPL 2 AL N 4 2014

SCASEST

AAS (250-300 mg)+Enoxaparina (1mg/kg/12 h, si ClCr<30 1 mg/kg/día)

Balance riesgo isquémico/hemorrágico

Riesgo isquémico moderado-alto
GRACE≥109
TIMI≥3

Riesgo isquémico bajo
GRACE<109
TIMI<3

Contraindicaciones nuevos antiP2Y12,
Riesgo hemorrágico muy alto (CRUSADE≥50) *

No

SI

Clopidogrel * 300/600 mg DC

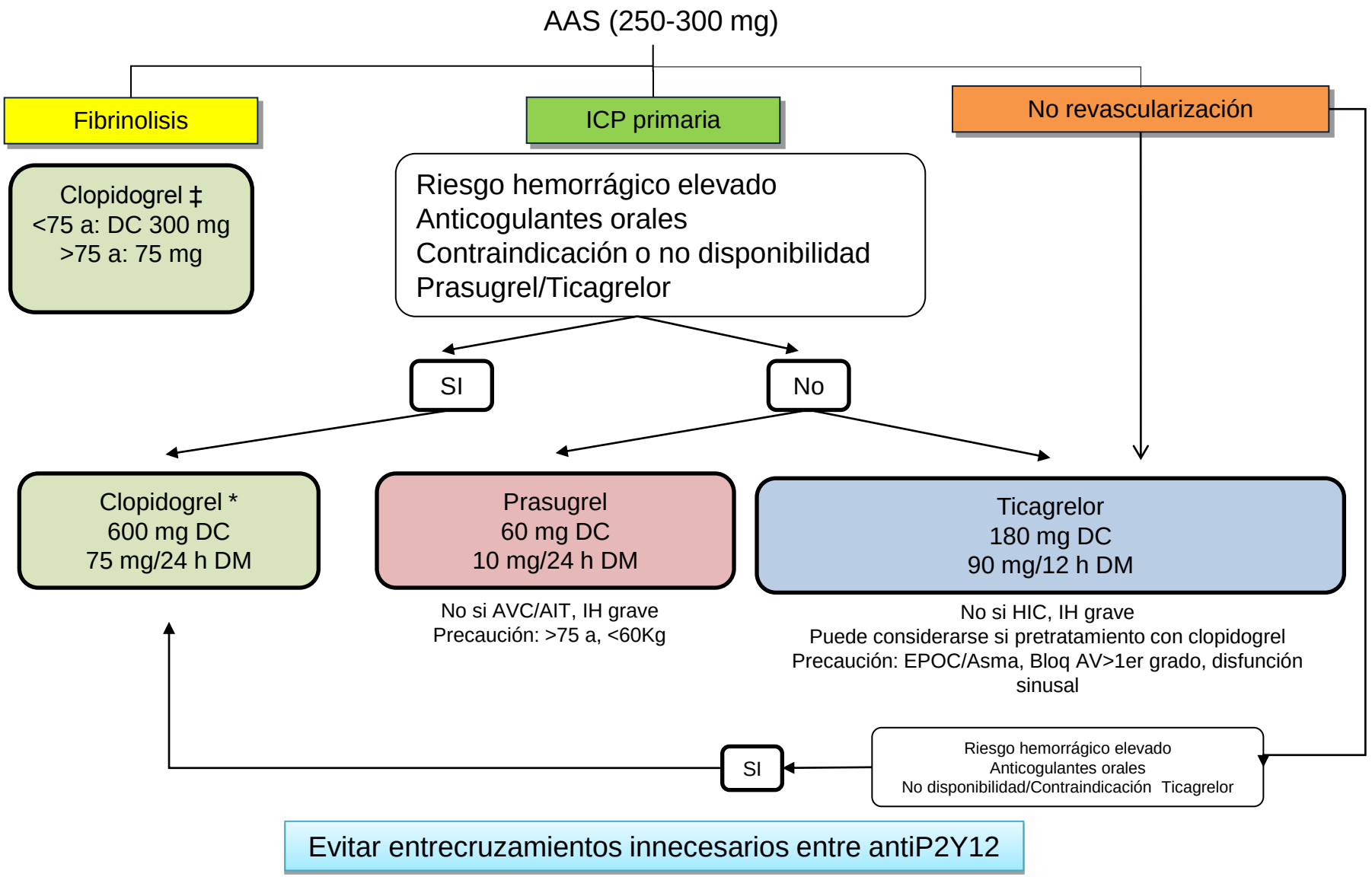
75 mg/24 h DM

Ticagrelor: 180 mg DC 90 mg/12 h
Independientemente de la estrategia terapeútica y/o pretratados con clopidogrel

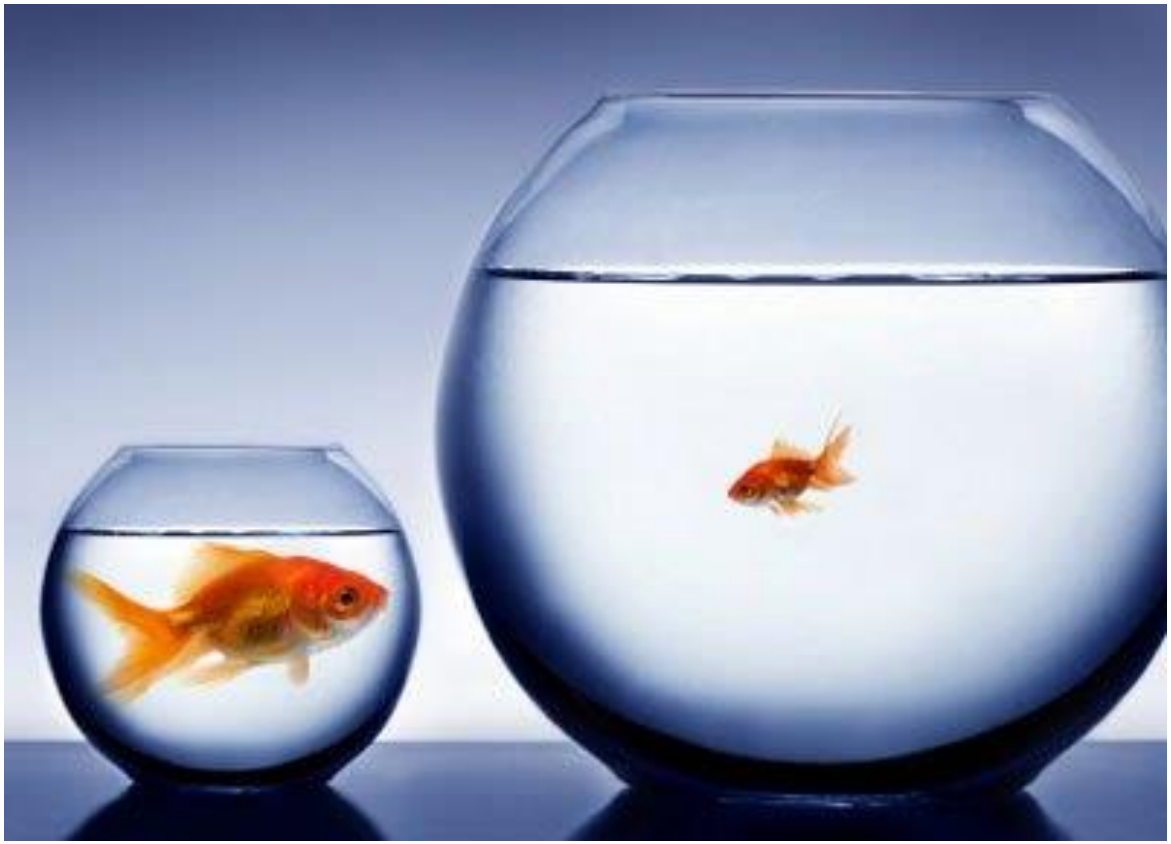
Prasugrel 60 mg DC; 10 mg/24 h
SOLO conocida anatomía coronaria y candidato a ICP

Evitar entrecruzamientos innecesarios entre antiP2Y12

SCACEST


AAS (250-300 mg)
Fibrinolisis
ICP primaria
No revascularización
Clopidogrel ‡
<75 a: DC 300 mg
>75 a: 75 mg
Riesgo hemorrágico elevado
Anticogulantes orales
Contraindicación o no disponibilidad
Prasugrel/Ticagrelor
SI
No
Clopidogrel *
600 mg DC
75 mg/24 h DM
Prasugrel
60 mg DC
10 mg/24 h DM
No si AVC/AIT, IH grave
Precaución: >75 a, <60Kg
Ticagrelor
180 mg DC
90 mg/12 h DM
No si HIC, IH grave
Puede considerarse si pretratamiento con clopidogrel
Precaución: EPOC/Asma, Bloq AV>1er grado, disfunción sinusal
SI
Riesgo hemorrágico elevado
Anticogulantes orales
No disponibilidad/Contraindicación Ticagrelor
Evitar entrecruzamientos innecesarios entre antiP2Y12

Comparaciones odiosas…



Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome (ISAR-REACT 5)

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2014 by *Deutsches Herzzentrum Muenchen*

Sponsor:
Deutsches Herzzentrum Muenchen

Information provided by (Responsible Party):
Deutsches Herzzentrum Muenchen

ClinicalTrials.gov Identifier:
NCT01944800

First received: September 13, 2013
Last updated: June 12, 2014
Last verified: June 2014
History of Changes

Purpose

Aim of the randomized, open-label, multicenter ISAR-REACT 5 trial is to assess whether ticagrelor is superior to prasugrel in patients with acute coronary syndrome and planned invasive strategy in terms of clinical outcomes.

CONCLUSIONES

- 1. Disponemos de 2 antiagregantes más potentes, predecibles y rápidos que clopidogrel.
  - ✓ Prasugrel: solo en SCA con ICP.
  - ✓ Ticagrelor: todo tipo SCA.

    Disminuye la mortalidad CV y total.
- 2. Inicio de la DA debe ser cuanto antes.
  - Prasugrel *no preICP.*
  - *Ticagrelor menos restricciones*
- 3. Poblaciones especiales:
  - Prasugrel: uso más restringido, no en ancianos, bajo peso e Ictus/TIA.
  - Ticagrelor indicado en estos pacientes.
- 4. Infrautilizados. Deben usarse de forma preferente. Protocolo común


Muchas gracias