TERAPIA ANTIAGREGANTE EN EL SÍNDROME CORONARIO AGUDO: ***PAPEL DEL TICAGRELOR***

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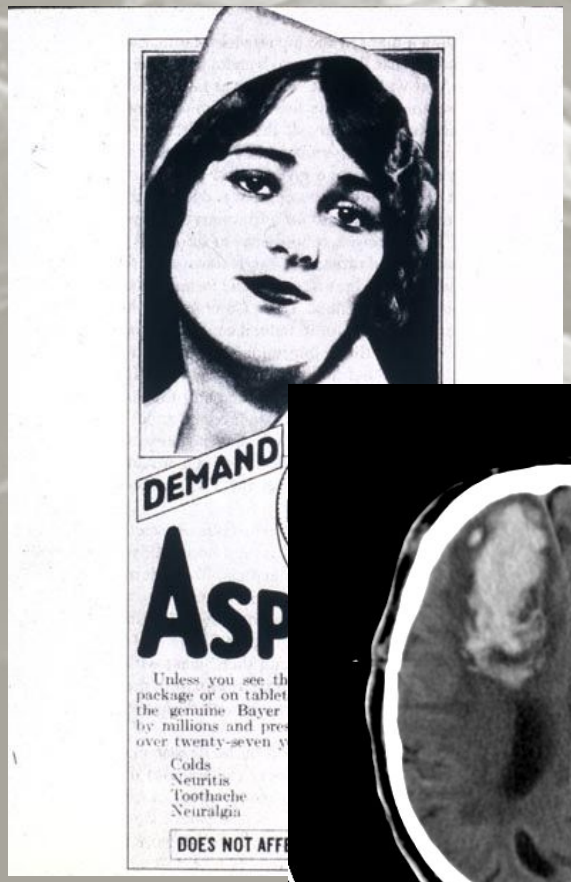
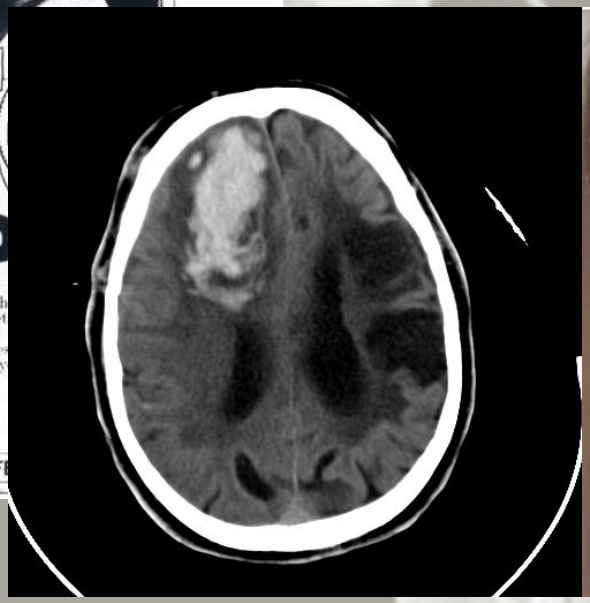
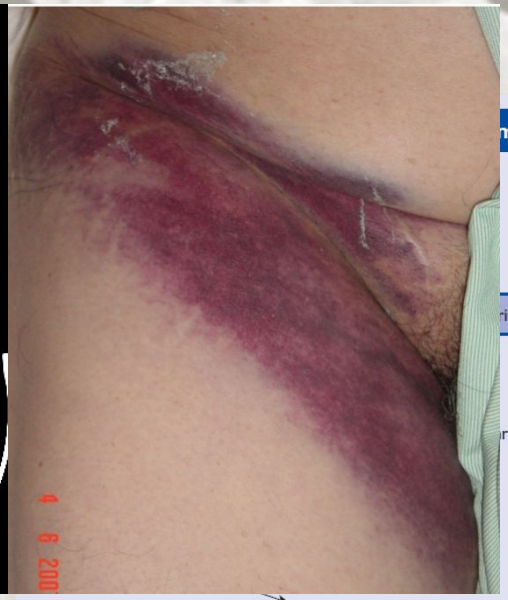
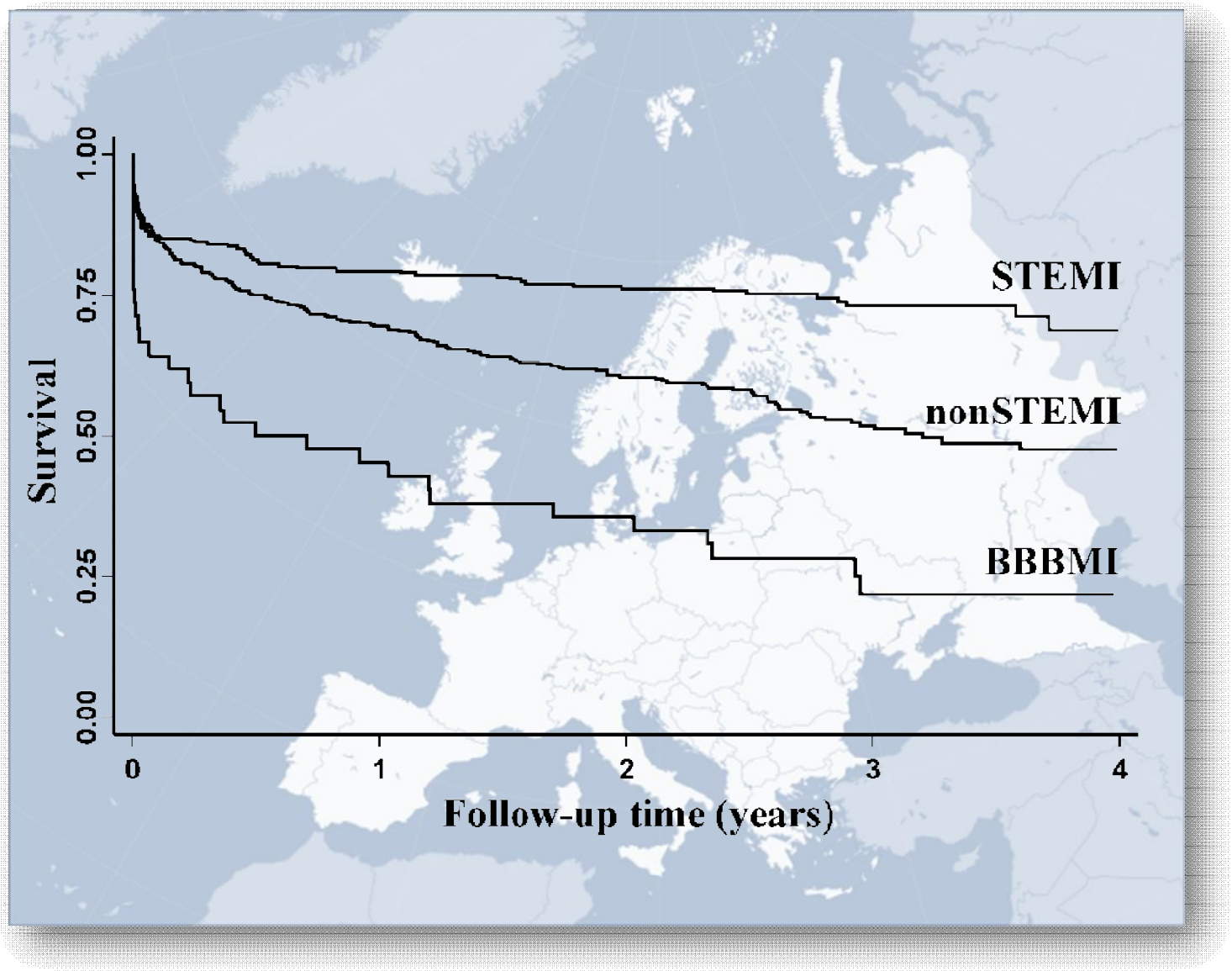
FEA CARDIOLOGÍA HVS


DEMAND
Colds
Neuritis
Toothache
Neuralgia





Antiplatelet
Collagen
ADP
Clopidogrel
Prasugrel
Ticagrelor
Conformational
activation of GPIIb/IIIa
GPIIb/IIIa
inhibitors
Platelet
aggregation
Thrombin
Bivalirudin
Fibrinogen
Fibrin
Thrombus



Bassand J-P, et al. Eur Heart J 2007;28:1598-60
Terkelsen, Eur Heart J 2005;26:18-26

LA DOBLE ANTIAGREGACIÓN CON AAS + CLOPIDOGREL HA DEMOSTRADO CLARAMENTE BENEFICIOS EN LA REDUCCIÓN DE EVENTOS EN LOS PACIENTES CON SCA

PERO…

- **Resistencia al clopidogrel (fact geneticos/no geneticos): aumento de eventos CCV: trombosis del stent, recurrencia de IAM o muerte cardiovascular.**

- El incremento de dosis de mantenimiento de clopidogrel no ha demostrado beneficio clinico (solo en portadores heterocigotos del gen CYP2C19*2, ELEVATE-TIMI 56 trial)

- PRASUGREL Y TICAGRELOR, los nuevos inhibidores del R P2Y12, una respuesta no influida por estas variantes geneticas

- Han demostrado beneficio clínico en pacientes con SCA.
Prasugrel-Estudio TRITON TIMI 38
Ticagrelor-Estudio PLATO

¿QUÉ NOS DICEN LAS GUÍAS?

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines

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

2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non –ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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

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

	COR	LOE	References
Antiplatelet therapy			
Aspirin			
• 162- to 325-mg load before procedure	I	B	(251–253)
P2Y$_{12}$ inhibitors			
Loading doses			
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B	(253,258,259)
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B	(260)
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B	(261)
Maintenance doses and duration of therapy			
DES placed: Continue therapy for 1 y with:			
• Clopidogrel: 75 mg daily	I	B	(260,262)
• Prasugrel: 10 mg daily	I	B	(262)
• Ticagrelor: 90 mg twice a day*	I	B	(261)
BMS† placed: Continue therapy for 1 y with:			
• Clopidogrel: 75 mg daily	I	B	(260,262)
• Prasugrel: 10 mg daily	I	B	(262)
• Ticagrelor: 90 mg twice a day*	I	B	(261)
DES placed:			
• Clopidogrel, prasugrel, or ticagrelor* continued beyond 1 y	IIb	C	N/A
• Patients with STEMI with prior stroke or TIA: prasugrel	III: Harm	B	(260)
• Thrombin: (high-bolus dose): 25-mcg/kg IV bolus, then 0.15 mcg/kg/min	IIa	B	(268,269)
• In patients with CrCl <30 mL/min, reduce infusion by 50%			
• Eptifibatide: (double bolus): 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus	IIa	B	(270)
• In patients with CrCl <50 mL/min, reduce infusion by 50%			
• Avoid in patients on hemodialysis			
• Pre–catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist	IIb	B	(103,268,271–277)
• Intracoronary abciximab 0.25-mg/kg bolus	IIb	B	(223,278–284)

Table 7. Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy

	COR	LOE	References
Antiplatelet therapy			
Aspirin			
• 162- to 325-mg loading dose	I	A	(308,330,331)
• 81- to 325-mg daily maintenance dose (indefinite)	I	A	(308,330,331)
• 81 mg daily is the preferred maintenance dose	IIa	B	(254,257,263,264)
$P2Y_{12}$ receptor inhibitors			
• Clopidogrel:	I	A	(330,331)
• Age ≤75 y: 300-mg loading dose			
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)	(330,331)
		C (up to 1 y)	N/A
• Age >75 y: no loading dose, give 75 mg	I	A	(330,331)
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)	(330,331)
		C (up to 1 y)	N/A
$P2Y_{12}$ receptor inhibitors			
Loading doses			
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:			
• Continue clopidogrel 75 mg daily without an additional loading dose	I	C	(260,262,330,331)
For patients who have not received a loading dose of clopidogrel:			
• If PCI is performed ≤24 h after fibrinolytic therapy: clopidogrel 300-mg loading dose before or at the time of PCI	I	C	N/A
• If PCI is performed >24 h after fibrinolytic therapy: clopidogrel 600-mg loading dose before or at the time of PCI	I	C	N/A
• If PCI is performed >24 h after treatment with a fibrin-specific agent or >48 h after a non–fibrin-specific agent: prasugrel 60 mg at the time of PCI	IIa	B	(260,262)
For patients with prior stroke/TIA: prasugrel	III: Harm	B	(260)

MEDICACIÓN ANTITROMBÓTICA EN PCI PRIMARIA

Recommendations	Class [a]	Level [b]	Ref [c]
Antiplatelet therapy			
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B	133, 134
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A	135, 136
• 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	
Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.	IIb	B	137–141
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI	IIb	B	127, 128, 137, 142

Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day. In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended. In patients >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d.

ESC Guidelines

MEDICACIÓN ANTITROMBÓTICA A LARGO PLAZO

Antiplatelet therapy with low dose aspirin (75–100 mg) is indicated indefinitely after STEMI.	I	A
In patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin.	I	B
DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI.	I	A
DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:	I	C
• 1 month for patients receiving BMS	I	C
• 6 months for patients receiving DES	IIb	B

Table 2. Recommendations for Antiplatelet Therapy

3. Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected (Appendix 6) should receive dual antiplatelet therapy on presentation.[13,16,45,69] *(Level of Evidence: A)* Aspirin should be initiated on presentation.[59,61–66] *(Level of Evidence: A)* The choice of a second antiplatelet therapy to be added to aspirin on presentation includes 1 of the following (note that there are no data for therapy with 2 concurrent $P2Y_{12}$ receptor inhibitors, and this is not recommended in the case of aspirin allergy):

   Before PCI:

   - Clopidogrel[13,16] *(Level of Evidence: B)*; or
   - Ticagrelor†[9] *(Level of Evidence: B)*; or
   - An IV GP IIb/IIIa inhibitor.[45,50,51,70,71] *(Level of Evidence: A)* IV eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors.[50,51] *(Level of Evidence: B)*

   At the time of PCI:

   - Clopidogrel if not started before PCI[13,16] *(Level of Evidence: A)*; or
   - Prasugrel*[7] *(Level of Evidence: B)*; or
   - Ticagrelor†[9] *(Level of Evidence: B)*; or

4. For UA/NSTEMI patients in whom an initial conservative (ie, noninvasive) strategy is selected, clopidogrel or ticagrelor† (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as
5. For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed.[55,72] *(Level of Evidence: A)* Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban[46,50,51] [*Level of Evidence: A*]), clopidogrel (loading dose followed by daily maintenance dose[13] [*Level of Evidence: B*]), or ticagrelor† (loading dose followed by daily maintenance dose[9] [*Level of Evidence: B*]) should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream). *(Level of Evidence: C)*

b. Prasugrel* 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI[7] *(Level of Evidence: B)* or

c. Ticagrelor† 180 mg should be given as early as possible before or at the time of PCI.[9] *(Level of Evidence: B)*

Class I

1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, heart failure, or serious arrhythmias), a stress test should be performed.[72] *(Level of Evidence: B)*
   a. If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed.[55,72] *(Level of Evidence: A)*
   b. If, after stress testing, the patient is classified as being at low risk, the instructions noted below should be followed in preparation for discharge[55,72]:
      1. Continue aspirin indefinitely.[61,63,64] *(Level of Evidence: A)*
      2. Continue clopidogrel or ticagrelor* for up to 12 months.[9,10,13] *(Level of Evidence: B)*
      3. Discontinue IV GP IIb/IIIa inhibitor if started previously.[50,51] *(Level of Evidence: A)*
      4. Continue UFH for 48 hours[66,79] *(Level of Evidence: A)* or administer enoxaparin[80–82] *(Level of Evidence: A)* or

3. In patients taking a $P2Y_{12}$ receptor inhibitor in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect[13] *(Level of Evidence: B)*. The period of withdrawal should be at least 5 days in patients receiving clopidogrel[13,45,99] *(Level of Evidence: B)* or ticagrelor*[12] *(Level of Evidence: C)* and at least 7 days in patients receiving prasugrel†[8] *(Level of Evidence: C)* unless the need for revascularization and/or the net benefit of the $P2Y_{12}$ receptor inhibitor therapy outweighs the potential risks of excess

6. For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom coronary artery disease was found on angiography, the following approach is recommended:
   a. Continue aspirin.[61,63,64] *(Level of Evidence: A)*
   b. Administer a loading dose of clopidogrel or ticagrelor* if not given before diagnostic angiography.[9,13] *(Level of Evidence: B)*
   c. Discontinue IV GP IIb/IIIa inhibitor if started previously.[50,51,57,107] *(Level of Evidence: B)*

Recommendations	Class [a]	Level [b]
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
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A
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
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
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	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B
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	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

¿PODEMOS ENTENDER TODO ESTO SIN CONOCER LA EVIDENCIA CIENTÍFICA RESPECTO TICAGRELOR Y PRASUGREL?

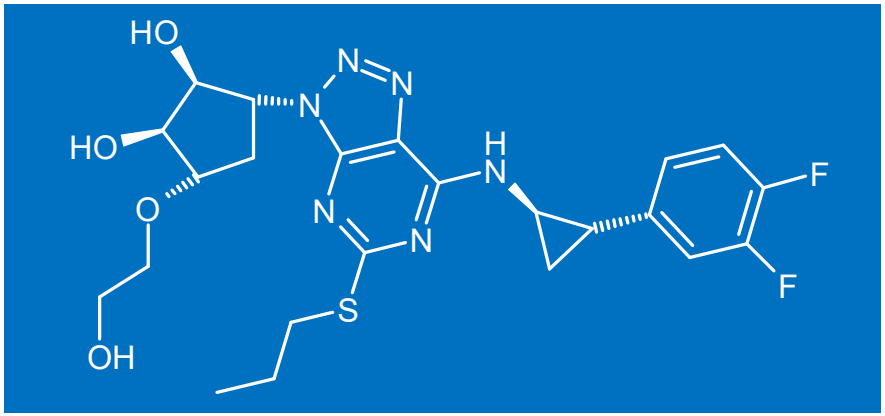
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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., Sven Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Ph.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*

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

..., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., ...abina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., ...on, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

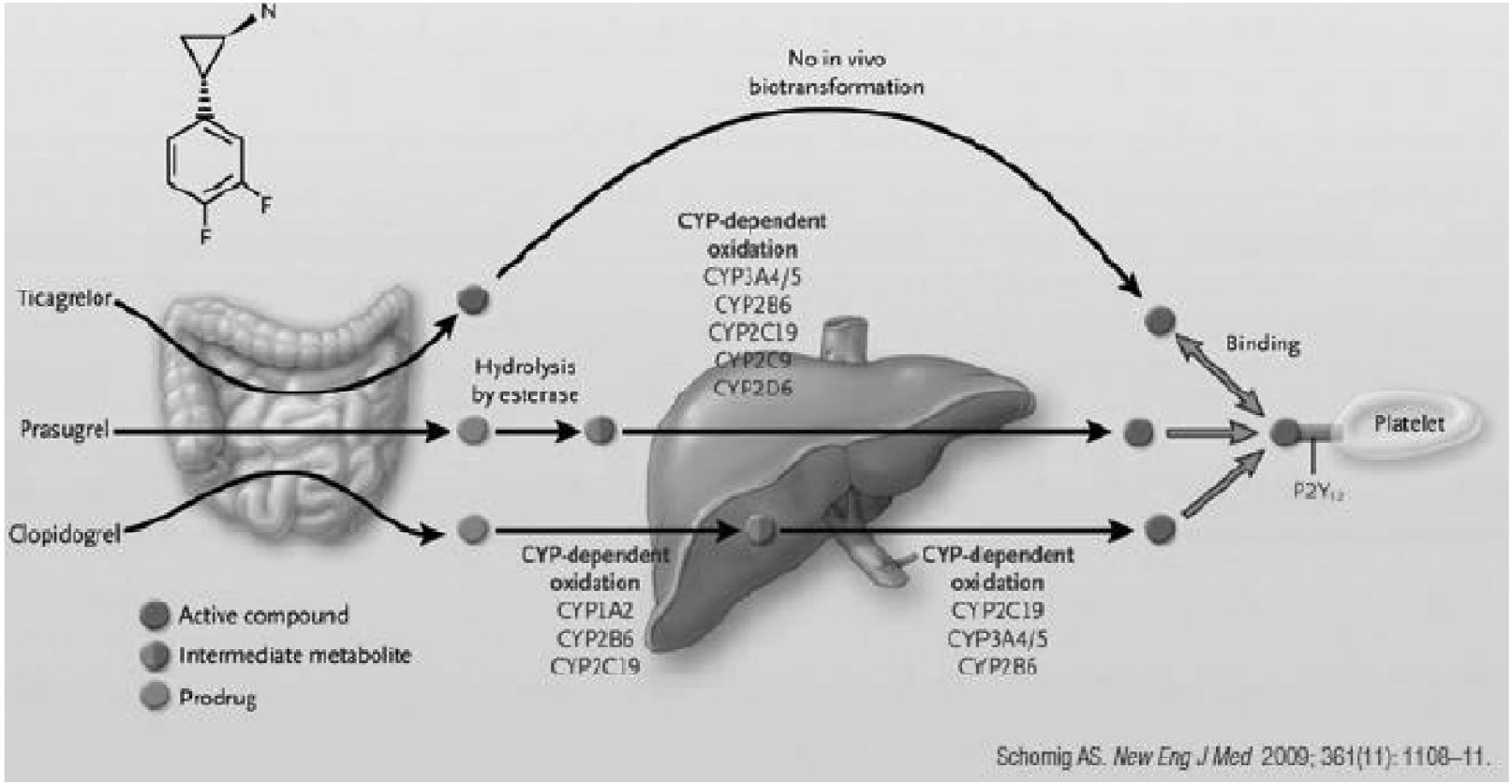
Ticagrelor (AZD 6140): es un antagonista oral reversible de $P2Y_{12}$



Ticagrelor es una cyclo-pentyl-triazolo-pyrimidine (CPTP)

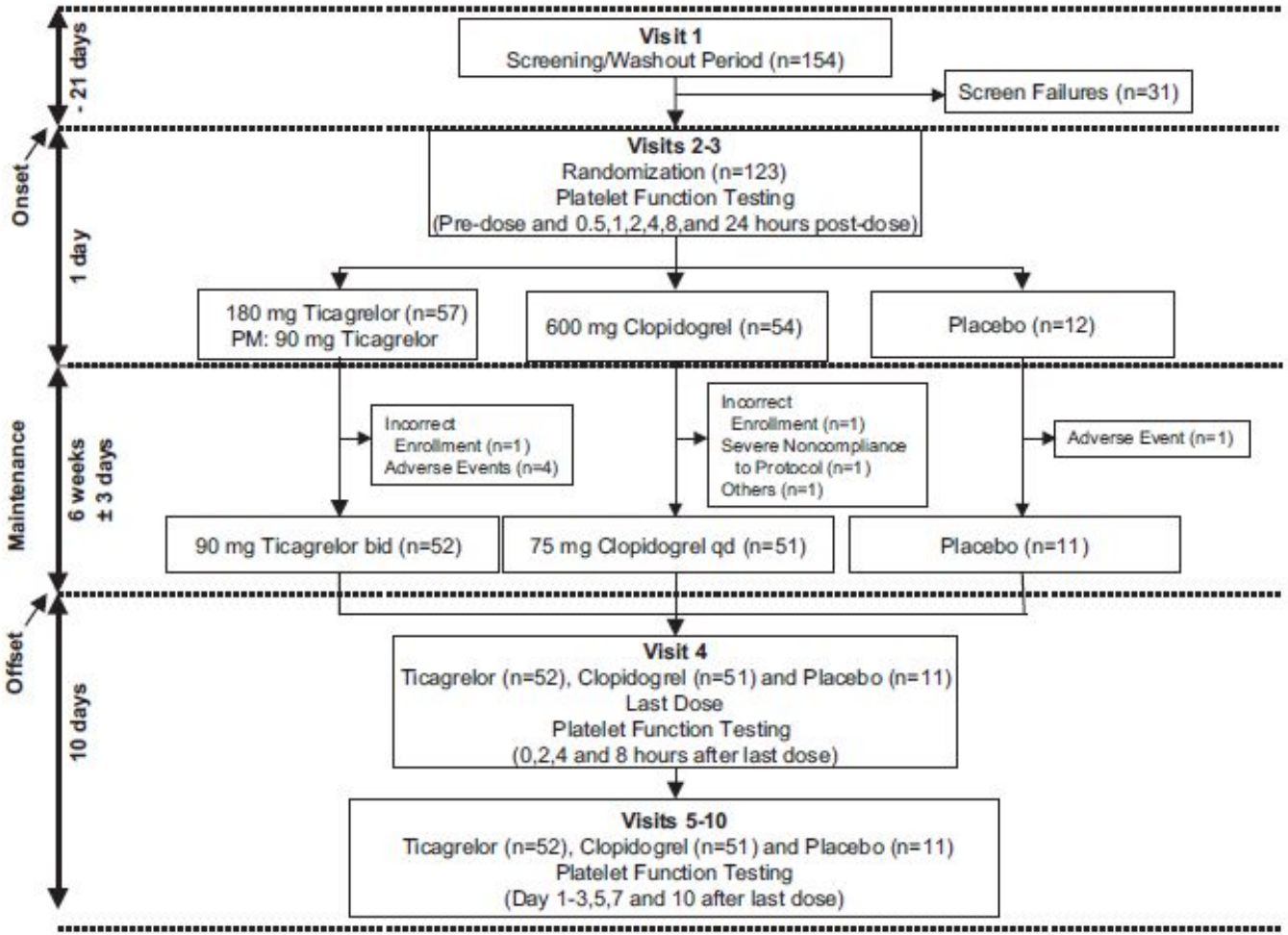
- **Acción directa**
  - No es un profármaco, no necesita activación metabólica
  - Rápido inicio de la inhibión del recptor $P2Y_{12}$
  - Mayor inhibición de la agregación plaquetaria que clopidogrel
- **Efecto reversible**
  - El grado de inhibición refleja la concentración plasmática
  - Finalización del efecto más rápido que clopidogrel
  - Recuperación de la funcionalidad plaquetaria a las 48 horas

METABOLISMO DE LOS ANTAGONISTAS DE LOS RECEPTORES P2Y12

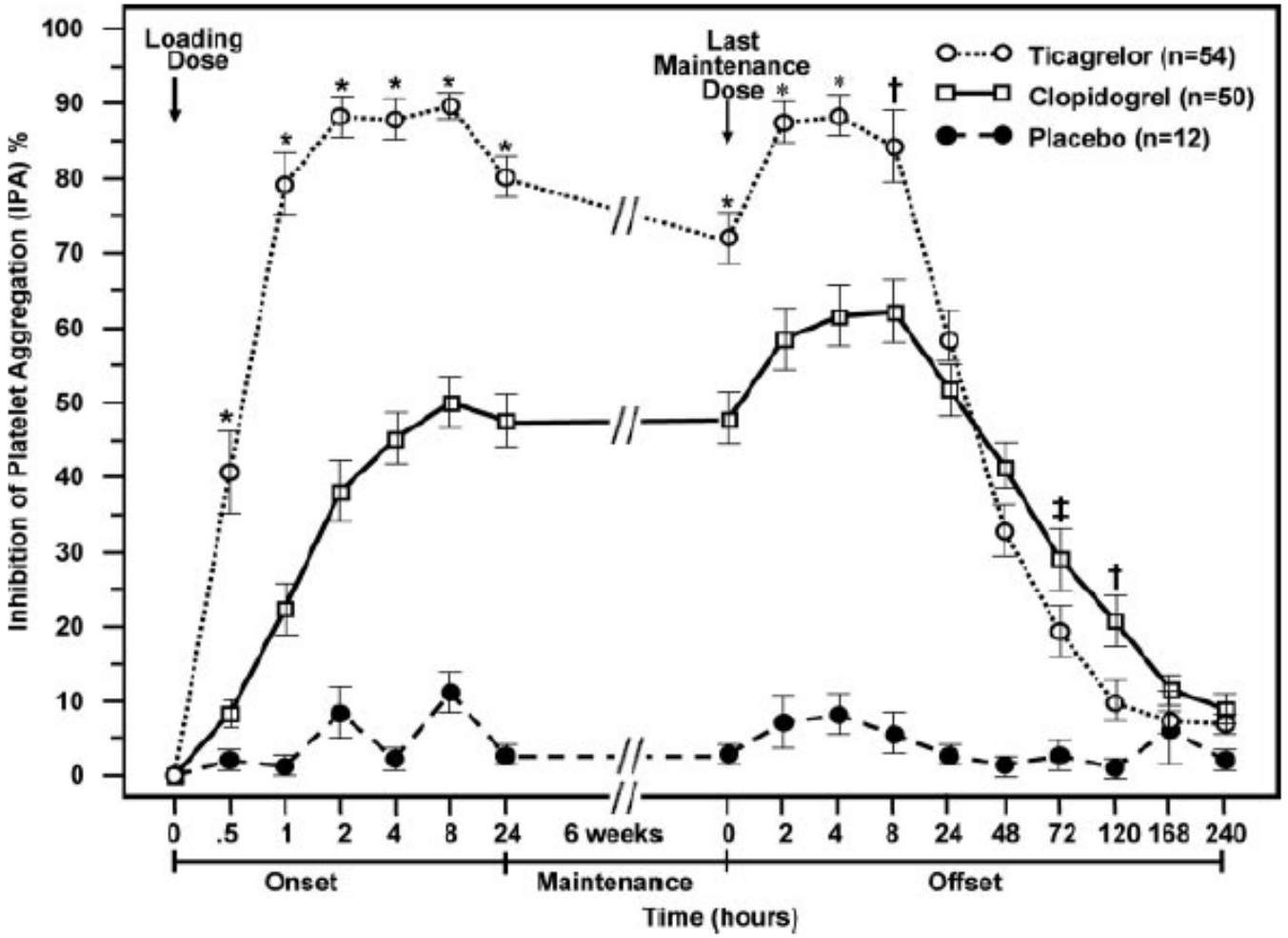


Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease

The ONSET/OFFSET Study

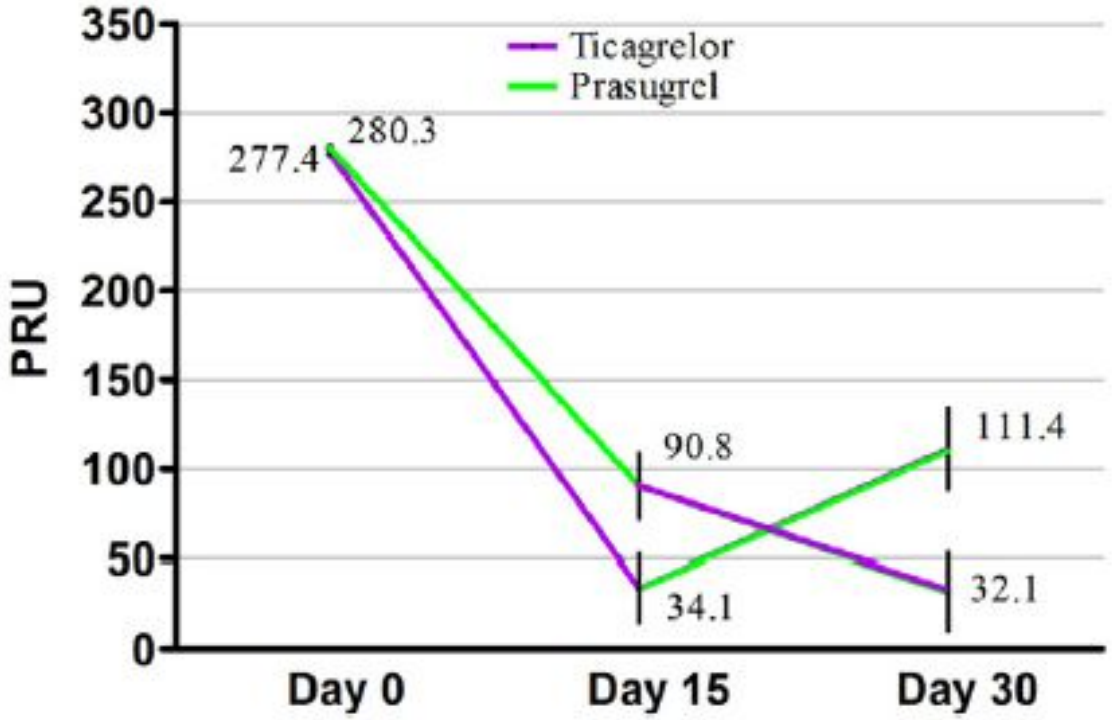


(*Circulation*. 2009;120:2577-2585.)



(*Circulation*. 2009;120:2577-2585.)

Ticagrelor Versus Prasugrel in Acute Coronary Syndrome Patients With High On-Clopidogrel Platelet Reactivity Following Percutaneous Coronary Intervention

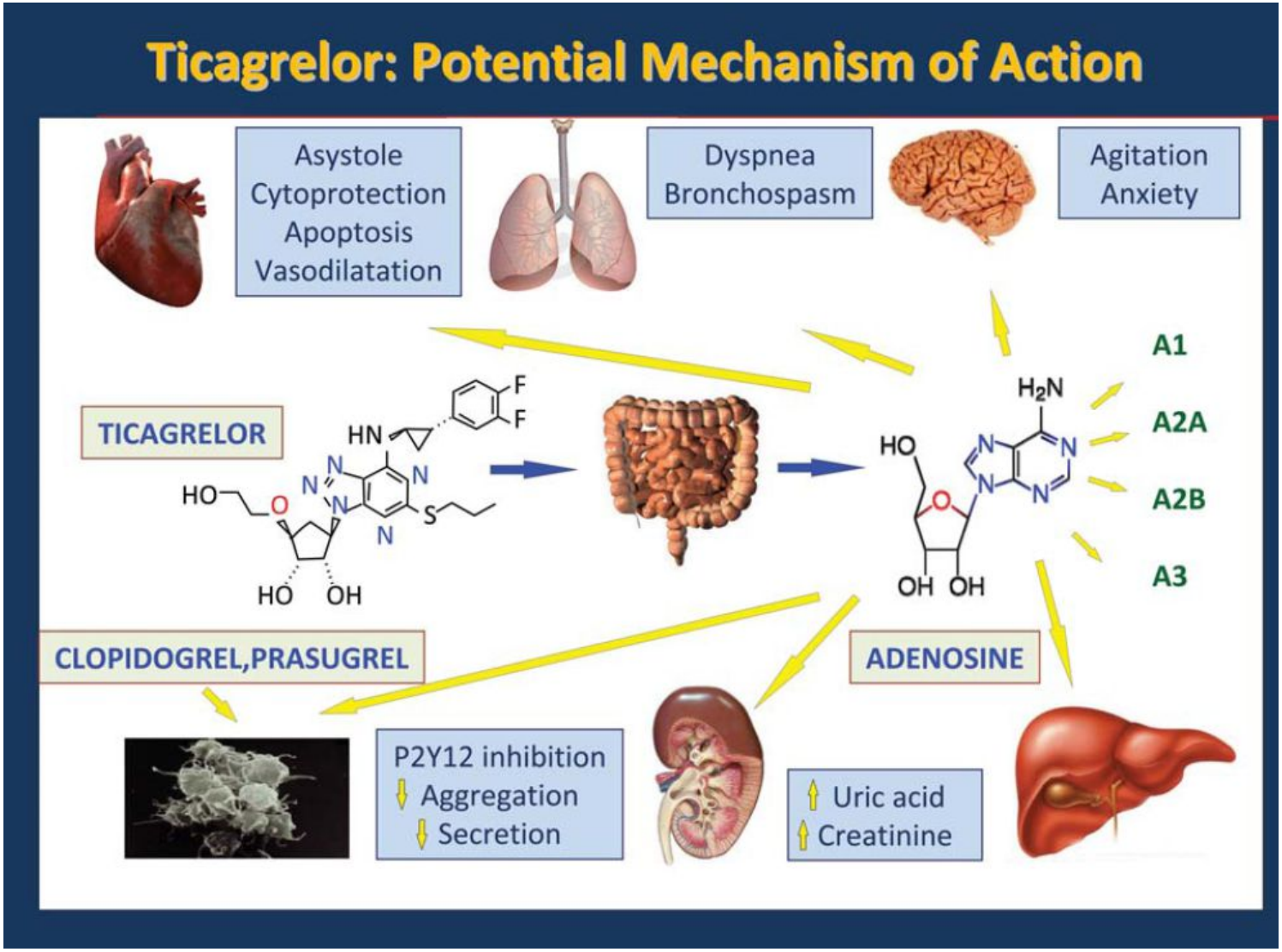


Lost to follow-up N=1

Patients with complete Day 30 data N=20

Patients with complete Day 30 data N=22

JACC Vol. 60, No. 3, 2012


Ticagrelor: Potential Mechanism of Action
Asystole
Cytoprotection
Apoptosis
Vasodilatation
Dyspnea
Bronchospasm
Agitation
Anxiety
TICAGRELOR
A1
A2A
A2B
A3
CLOPIDOGREL,PRASUGREL
ADENOSINE
P2Y12 inhibition
Aggregation
Secretion
Uric acid
Creatinine

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect	2-4 h	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

TRITON – TIMI 38

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*

catheterization laboratory. Since the protocol was designed as a trial of patients with acute coronary syndromes who were undergoing PCI, the coronary anatomy had to be known to be suitable for PCI before randomization in all patients with unstable angina or non–ST-elevation myocardial infarction, or in those enrolled after medical treat-

ASEST 10047
ACEST 3534

Carga 3 ... o 10 mg

- **Objetivo principal:** MUERTE CARDIOVASCULAR, INFARTO, ACV
- **Objetivos secundarios:** MUERTE CARDIOVASCULAR, INFARTO, REHOSPITALIZACIÓN, NECESIDAD DE NUEVA REVASCULARIZACIÓN, TROMBOSIS DEL STENT
- **Objetivos de seguridad:** sangrados mayores TIMI, sangrados potencialmente mortales

TRITON – TIMI 38

Characteristic	Prasugrel (N=6813)	Clopidogrel (N=6795)
Index procedure (%)		
PCI	99	99
CABG	1	1
Stent	94	95
Bare-metal stent only	48	47
≥1 Drug-eluting stent	47	47
Multivessel PCI	14	14
Antithrombin use to support PCI (%)		
Heparin	66	65
LMWH	9	8
Bivalirudin	3	3
Other or multiple therapies	22	23
Glycoprotein IIb/IIIa–receptor antagonist use during index hospitalization (%)	54	55
Timing of study-drug administration (%)¶		
Before PCI	26	25
During PCI	73	74
After PCI	1	1

TRITON – TIMI 38

OBJETIVOS DE EFICACIA

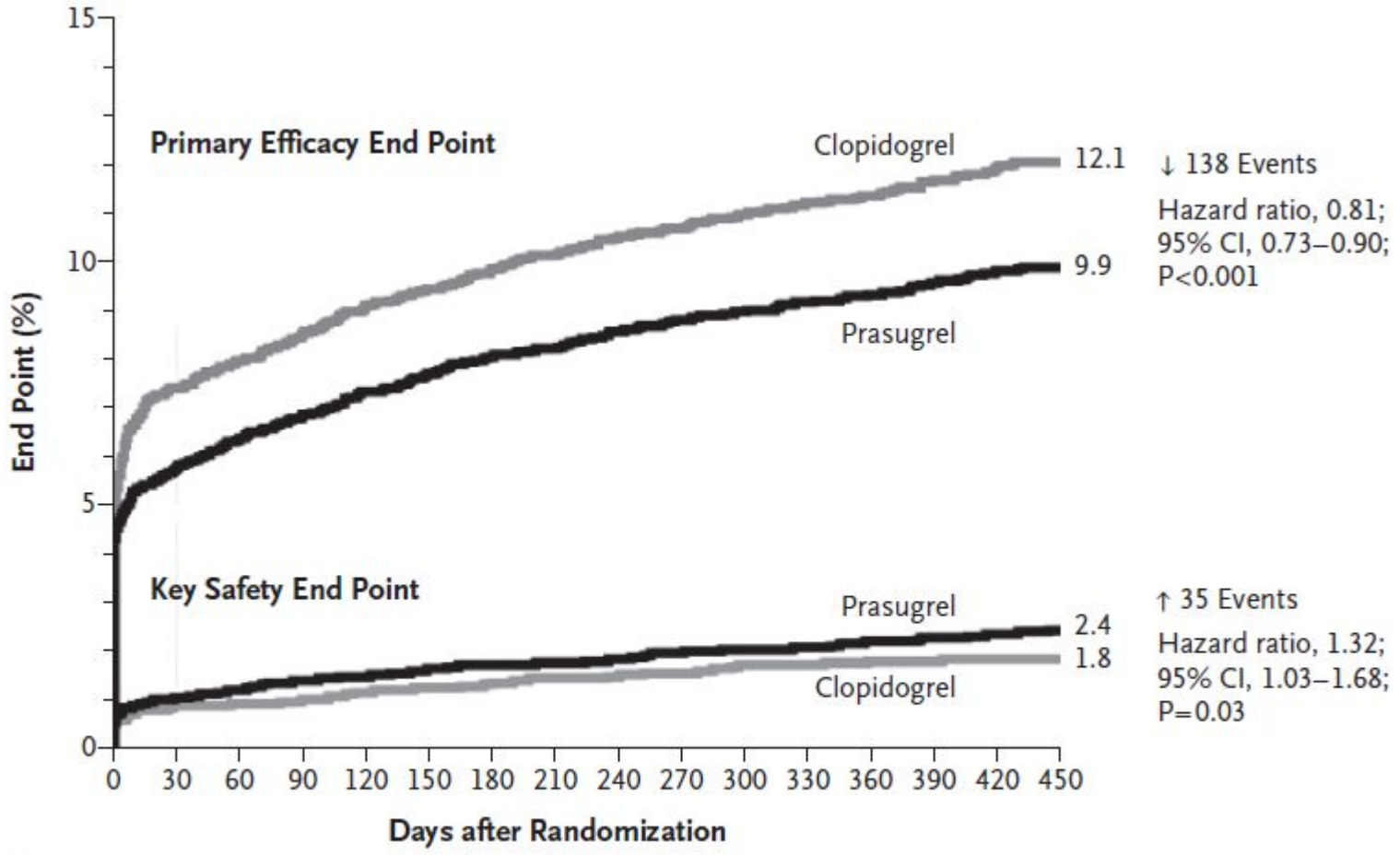
End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	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 any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
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

TRITON – TIMI 38

OBJETIVOS DE SEGURIDAD

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

TRITON – TIMI 38



No. at Risk						
Clopidogrel	6795 6169	6036	5835	5043	4369	3017
Prasugrel	6813 6305	6177	5951	5119	4445	3085

TRITON – TIMI 38

Baseline Characteristics	Total No. of Patients	Prasugrel (%)	Clopidogrel (%)	Reduction in Risk (%)
Overall	13,608	9.9	12.1	19
Unstable angina or non–ST-elevation MI	10,074	9.9	12.1	18
ST-elevation MI	3,534	10.0	12.4	21
Sex				
Male				
Female				
Age				
<65 yr				
65–74 yr				
≥75 yr				
Diabetes mellitus				
No				
Yes				
Stent placement during inde				
Bare-metal stent only				
≥1 Drug-eluting stent				
Glycoprotein IIb/IIIa recepto				
Yes				
No				
Creatinine clearance				
<60 ml/min	1,490	15.1	17.5	14
≥60 ml/min	11,890	9.0	11.1	20

Hazard Ratio for Prasugrel Efficacy (95% CI)

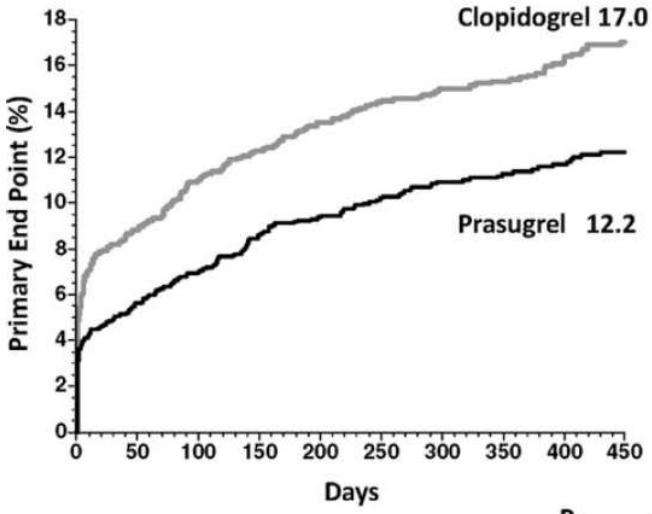
0.50 0.60 0.70 0.80 0.90 1.00 2.00

Prasugrel Better — Clopidogrel Better

A

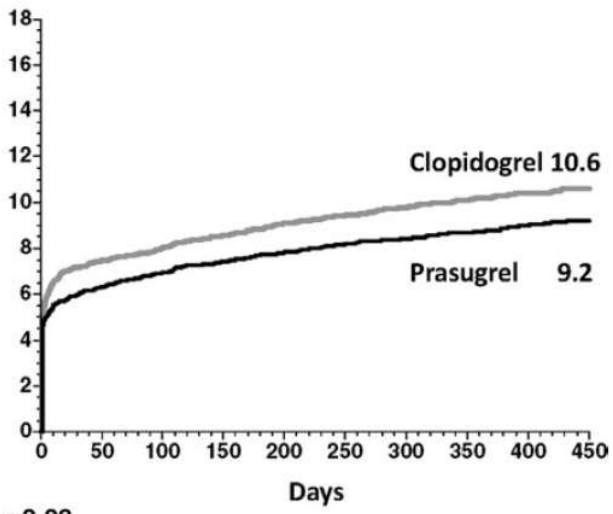
DM

HR 0.70 (0.58-0.85), P<0.001



No DM

HR 0.86 (0.76-0.98), P = 0.02



$P_{interaction} = 0.09$

TRITON – TIMI 38

End Point	Prasugrel	Clopidogrel	Hazard Ratio for Prasugrel (95% CI)	P Value	P Value for Interaction†
	no. of patients/total no. (%)				
History of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	47/262 (19.1)	35/256 (14.4)	1.37 (0.89–2.13)	0.15	
Non–CABG-related TIMI major bleeding	14/257 (5.0)	6/252 (2.9)	2.46 (0.94–6.42)	0.06	
Death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding	57/262 (23.0)	39/256 (16.0)	1.54 (1.02–2.32)	0.04	
No history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	596/6551 (9.5)	746/6539 (12.0)	0.79 (0.71–0.88)	<0.001	0.02
Non–CABG-related TIMI major bleeding	132/6484 (2.3)	105/6464 (1.8)	1.26 (0.97–1.62)	0.08	0.22
Death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding	727/6551 (11.8)	854/6539 (13.8)	0.84 (0.76–0.93)	<0.001	0.006
Age ≥75 yr, body weight <60 kg, or history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	198/1320 (16.1)	199/1347 (16.0)	1.02 (0.84–1.24)	0.83	
Non–CABG-related TIMI major bleeding	52/1305 (4.3)	38/1328 (3.3)	1.42 (0.93–2.15)	0.10	
Death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding	249/1320 (20.2)	239/1347 (19.0)	1.07 (0.90–1.28)	0.43	
Age <75 yr, body weight ≥60 kg, and no history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	433/5421 (8.3)	569/5383 (11.0)	0.74 (0.66–0.84)	<0.001	0.008
Non–CABG-related TIMI major bleeding	91/5390 (2.0)	73/5337 (1.5)	1.24 (0.91–1.69)	0.17	0.64
Death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding	522/5421 (10.2)	641/5383 (12.5)	0.80 (0.71–0.89)	<0.001	0.006

PLATO

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*

SCASEST DE ALTO – MODERADO RIESGO
SCACEST SI PCI PRIMARIA
(pretratados con clopidogrel o pacientes naive)

DOBLE CIEGO

N = 18624

SCASEST 11080
SCACEST 7544

CLOPIDOGREL
Carga 300 mg / mantenimiento 75 mg
Si pretratados, no dosis adicional

TICAGRELOR
Carga 180 mg / mantenimiento 90 mg / 12 h

Duración del tratamiento: 6 - 12 meses

- **Objetivo principal:** MUERTE CARDIOVASCULAR, INFARTO, ACV
- **Objetivos de seguridad:** sangrados mayores

PLATO

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value†
Start of randomized treatment			
Patients receiving treatment — no. (%)	9235 (98.9)	9186 (98.9)	
Time after start of chest pain — hr			0.89
Median	11.3	11.3	
IQR	4.8–19.8	4.8–19.8	
Time after start of hospitalization — hr			0.75
Median	4.9	5.3	
IQR	1.3–18.8	1.4–15.8	
Premature discontinuation of study drug — no. (%)	2186 (23.4)	1999 (21.5)	0.002
Because of adverse event	690 (7.4)	556 (6.0)	<0.001
Because of patient's unwillingness to continue	946 (10.1)	859 (9.2)	0.04
Other reason	550 (5.9)	584 (6.3)	0.27
Adherence to study drug — no. (%)‡	7724 (82.8)	7697 (82.8)	0.89
Exposure to study drug — days			0.11
Median	277	277	
IQR	177–365	181–365	

PLATO

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value†
Clopidogrel administered in hospital before randomization — no. (%)	4293 (46.0)	4282 (46.1)	0.91
Clopidogrel dose given (as study drug or not) within 24 hours before or after randomization — no. (%)			0.65
No loading dose, or missing information	4937 (52.9)	94 (1.0)	
300–375 mg	1921 (20.6)	5528 (59.5)	
600–675 mg	1282 (13.7)	1822 (19.6)	
Other dose	697 (7.5)	1339 (14.4)	
Same dose as that given before index event§	496 (5.3)	508 (5.5)	
Antithrombotic treatment in hospital — no. (%)			
Aspirin			
Before randomization	8827 (94.6)	8755 (94.2)	0.31
After randomization	9092 (97.4)	9056 (97.5)	0.85
Unfractionated heparin	5304 (56.8)	5233 (56.3)	0.49
Low-molecular-weight heparin	4813 (51.6)	4706 (50.7)	0.21
Fondaparinux	251 (2.7)	246 (2.6)	0.89
Bivalirudin	188 (2.0)	183 (2.0)	0.83
Glycoprotein IIb/IIIa inhibitor	2468 (26.4)	2487 (26.8)	0.62

PLATO

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value†
Invasive procedure performed during index hospitalization — no. (%)			
Planned invasive treatment	6732 (72.1)	6676 (71.9)	0.68
Coronary angiography	7599 (81.4)	7571 (81.5)	0.91
PCI			
During index hospitalization	5687 (60.9)	5676 (61.1)	0.83
Within 24 hours after randomization	4560 (48.9)	4546 (48.9)	0.93
Cardiac surgery	398 (4.3)	434 (4.7)	0.19
Invasive procedure performed during study — no. (%)			
PCI	5978 (64.1)	5999 (64.6)	0.46
Stenting	5640 (60.4)	5649 (60.8)	0.61
With bare-metal stent only	3921 (42.0)	3892 (41.9)	0.87
With ≥1 drug-eluting stent	1719 (18.4)	1757 (18.9)	0.40
CABG	931 (10.0)	968 (10.4)	0.32
Time from first dose of study drug to PCI — hr			0.78
Patients with ST-elevation MI			
Median	0.25	0.25	
IQR	0.05–0.75	0.05–0.72	
Patients with non–ST-elevation MI			
Median	3.93	3.65	
IQR	0.48–46.9	0.45–50.8	

OBJETIVOS DE EFICACIA

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
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
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04

OBJETIVOS DE EFICACIA

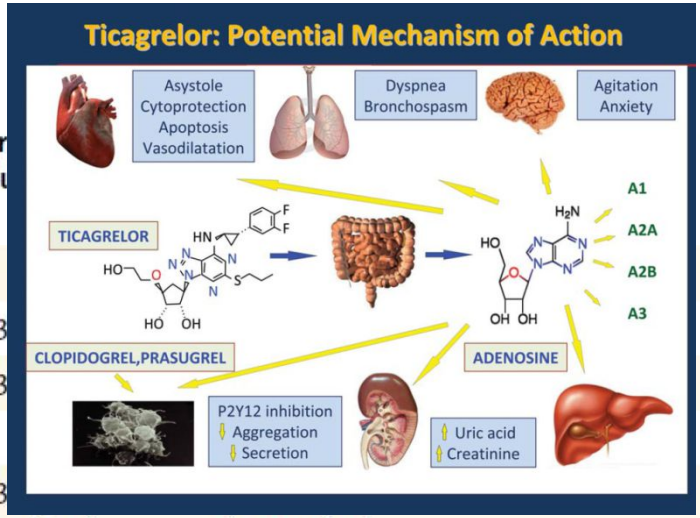
End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09
Death from vascular causes, MI, stroke — no./total no. (%)				
Invasive treatment planned§	569/6732 (8.9)	668/6676 (10.6)	0.84 (0.75–0.94)	0.003‡
Event rate, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Event rate, days 31–360¶	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Stent thrombosis — no. of patients who received a stent/ total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

OBJETIVOS DE SEGURIDAD

Definición de sangrado mayor según estudio:
- Sangrado fatal
- Sangrado intracraneal
- Hemopericardio con taponamiento
- Shock hipovolémico o hipotensión severa
- Descenso en hemoglobina de > 3 g/dl
- Sangrado en órgano crítico

End Point				P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria				0.43
Major bleeding, TIMI criteria‡				0.57
Bleeding requiring red-cell transfusion				0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33

OBJETIVOS DE SEGURIDAD



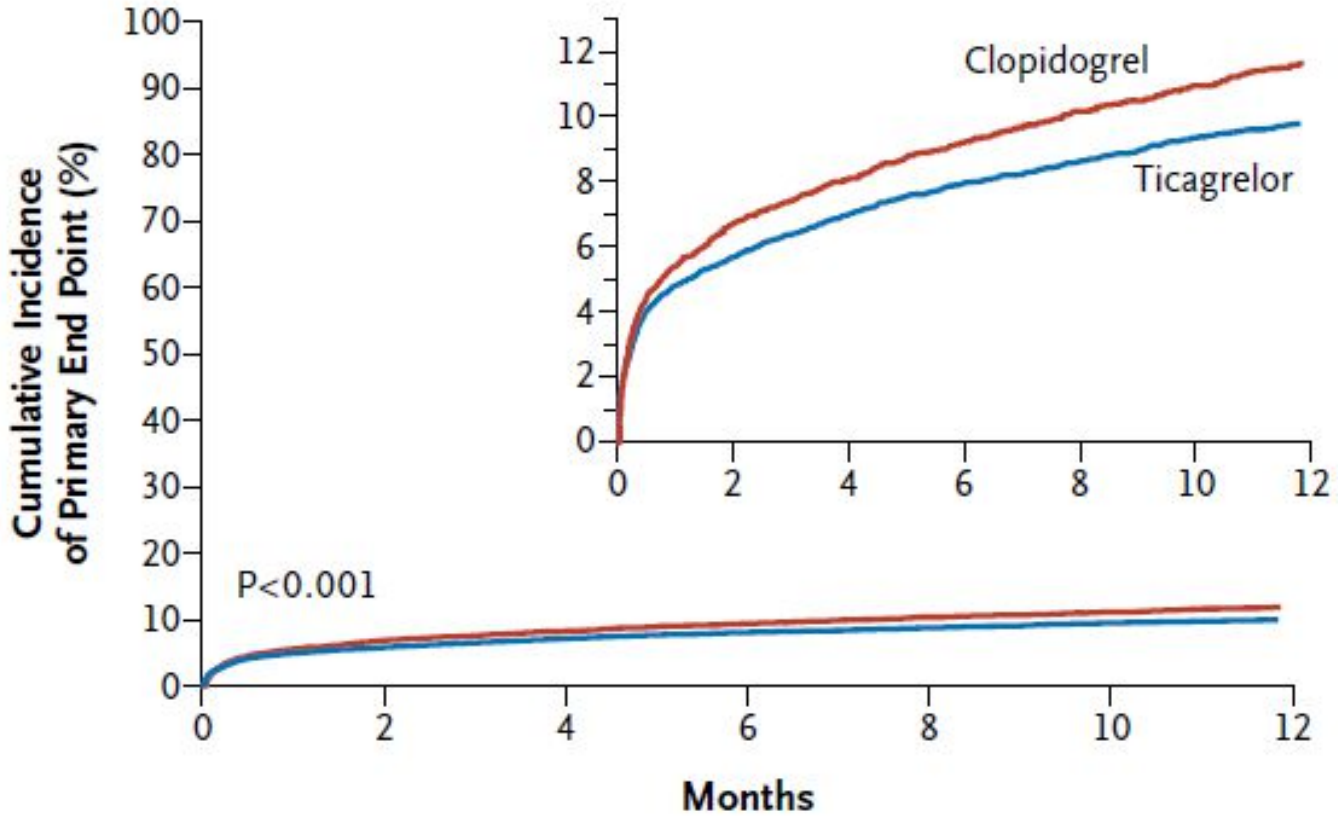
End Point	Ticagr... Grou...		P Value
Dyspnea — no./total no. (%)			
Any	1270/923...		<0.001
Requiring discontinuation of study treatment	79/923...		<0.001
Bradycardia — no./total no. (%)			
Pacemaker insertion	82/923...		0.87
Syncope	100/9235 (1.1)	76/9186 (0.8)	0.08
Bradycardia	409/9235 (4.4)	372/9186 (4.0)	0.21
Heart block	67/9235 (0.7)	66/9186 (0.7)	1.00
Holter monitoring — no./total no. (%)			
First week			
Ventricular pauses ≥3 sec	84/1451 (5.8)	51/1415 (3.6)	0.01
Ventricular pauses ≥5 sec	29/1451 (2.0)	17/1415 (1.2)	0.10
At 30 days			
Ventricular pauses ≥3 sec	21/985 (2.1)	17/1006 (1.7)	0.52
Ventricular pauses ≥5 sec	8/985 (0.8)	6/1006 (0.6)	0.60

OBJETIVOS DE SEGURIDAD

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Increase in serum uric acid from baseline value — %				
At 1 mo	14±46	7±44		<0.001
At 12 mo	15±52	7±31		<0.001
1 Mo after end of treatment	7±43	8±48		0.56
Increase in serum creatinine from baseline value — %				
At 1 mo	10±22	8±21		<0.001
At 12 mo	11±22	9±22		<0.001
1 Mo after end of treatment	10±22	10±22		0.59

PLATO

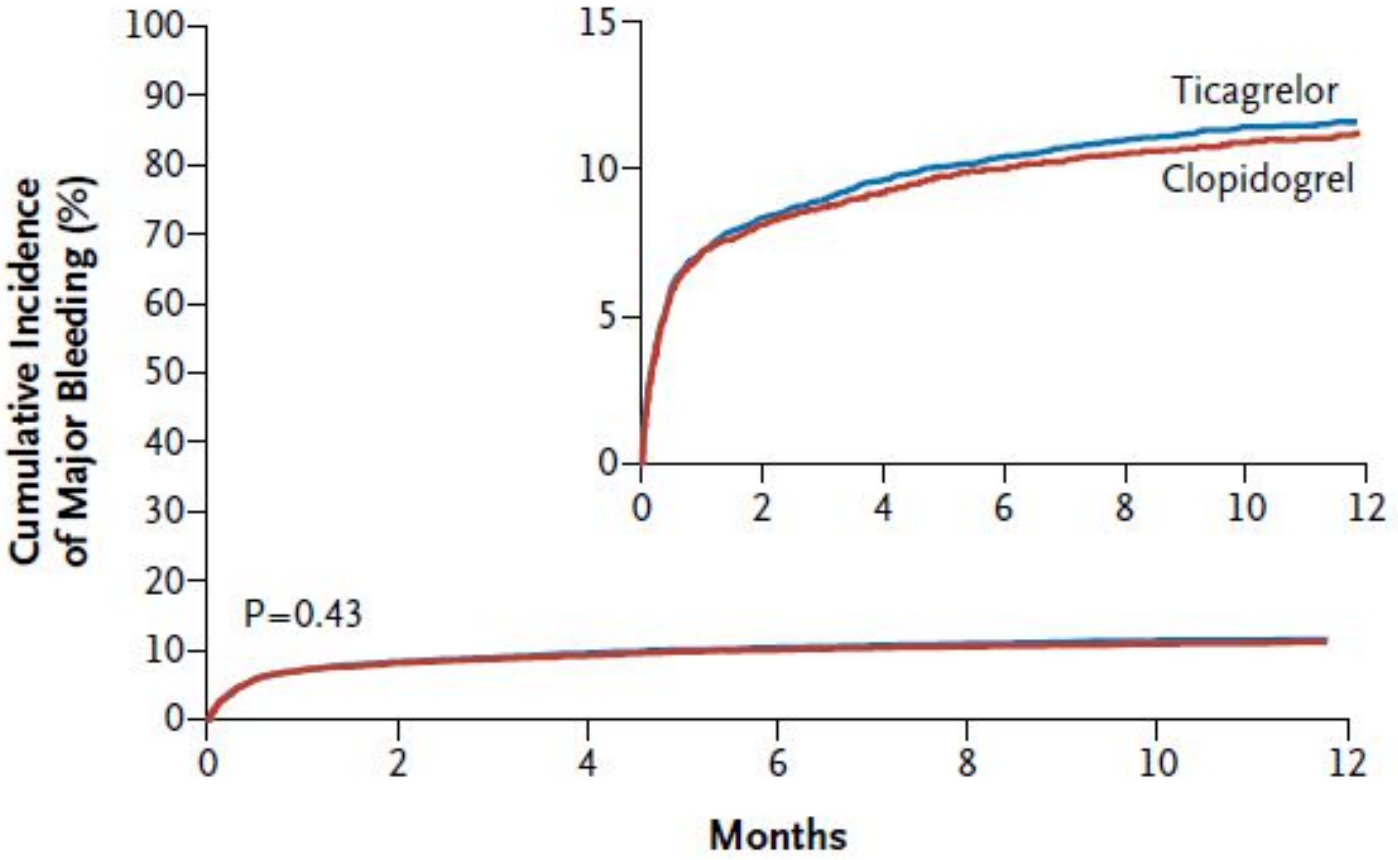
OBJETIVOS DE EFICACIA



No. at Risk

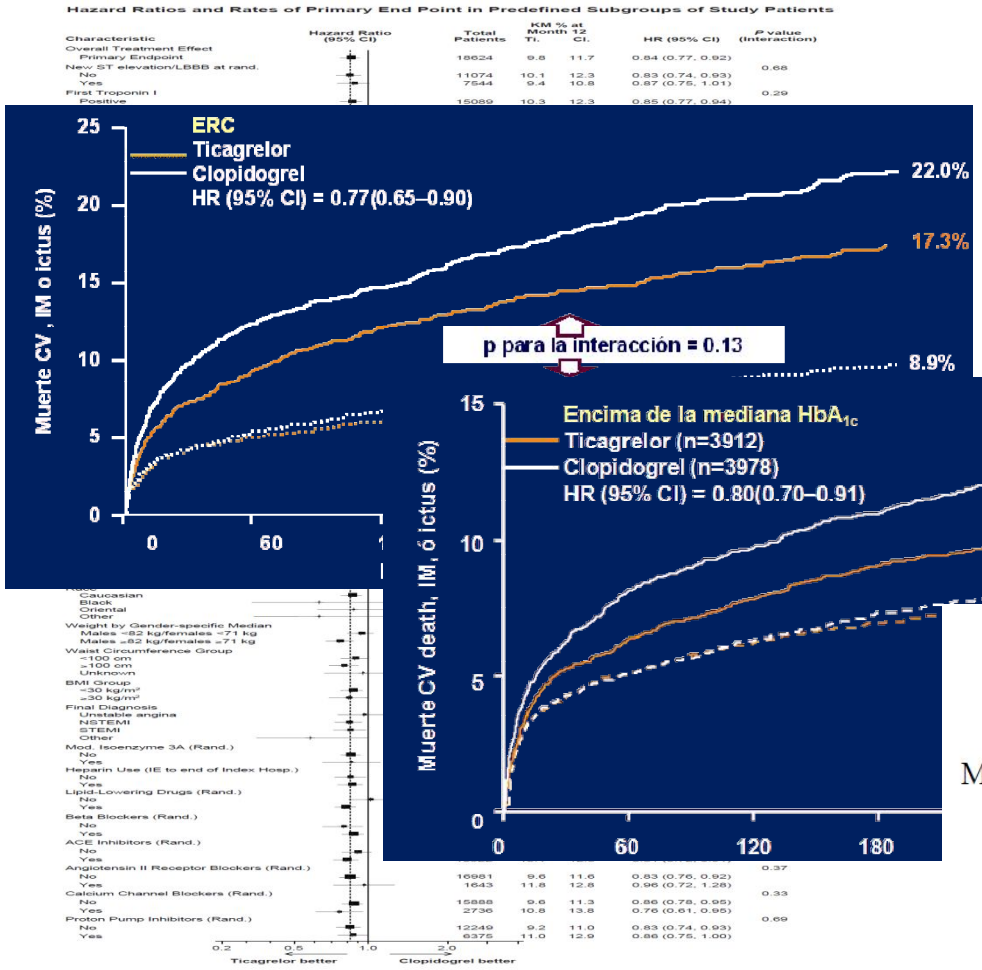
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

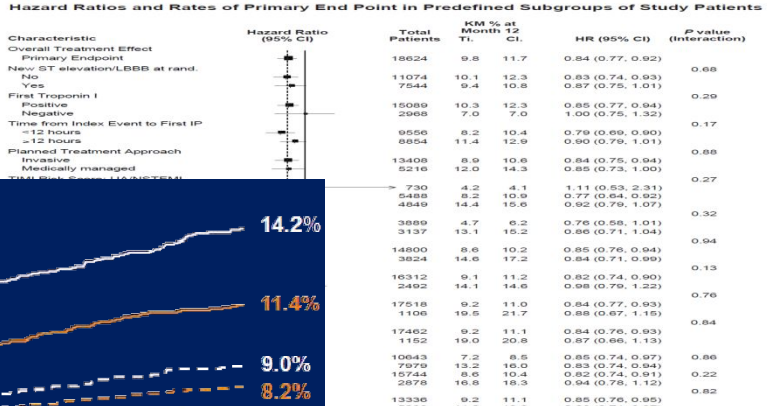
OBJETIVOS DE SEGURIDAD



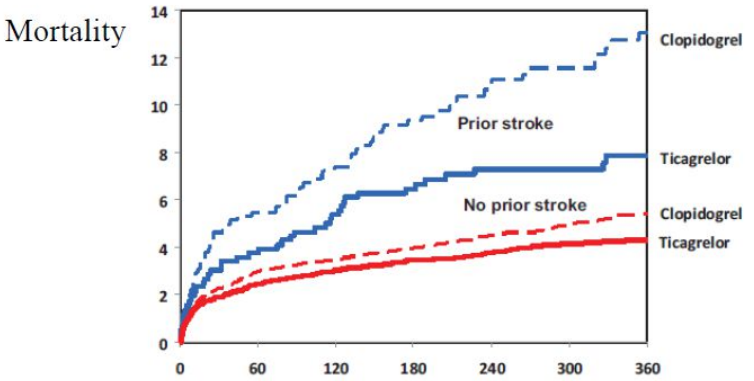
No. at Risk							
Ticagrelor	9235	7246	6826	6545	5129	3783	3433
Clopidogrel	9186	7305	6930	6670	5209	3841	3479

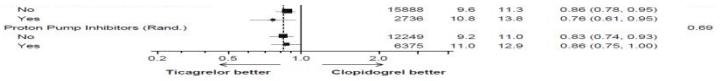
PLATO





Beneficio con ACVA previo





ORIGINAL ARTICLE

ESTUDIO ACCOAST

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

SCASEST SUSCEPTIBLES DE PCI

2037 pacientes

DOBLE CIEGO

1996 pacientes

PRETRATAMIENTO
30 mg en la randomización
30 mg más si PCI se realizaba

NO PRETRATAMIENTO
60 mg si PCI se realizaba

BACKGROUND

...effective in patien... ...vation ...omes, the effect of ...on — ...graphy — is not k... ...ect of ...nist prasugrel at the time of diagnosis versus admin-istering it after the coronary angiography if percutaneous coronary intervention (PCI) was indicated.

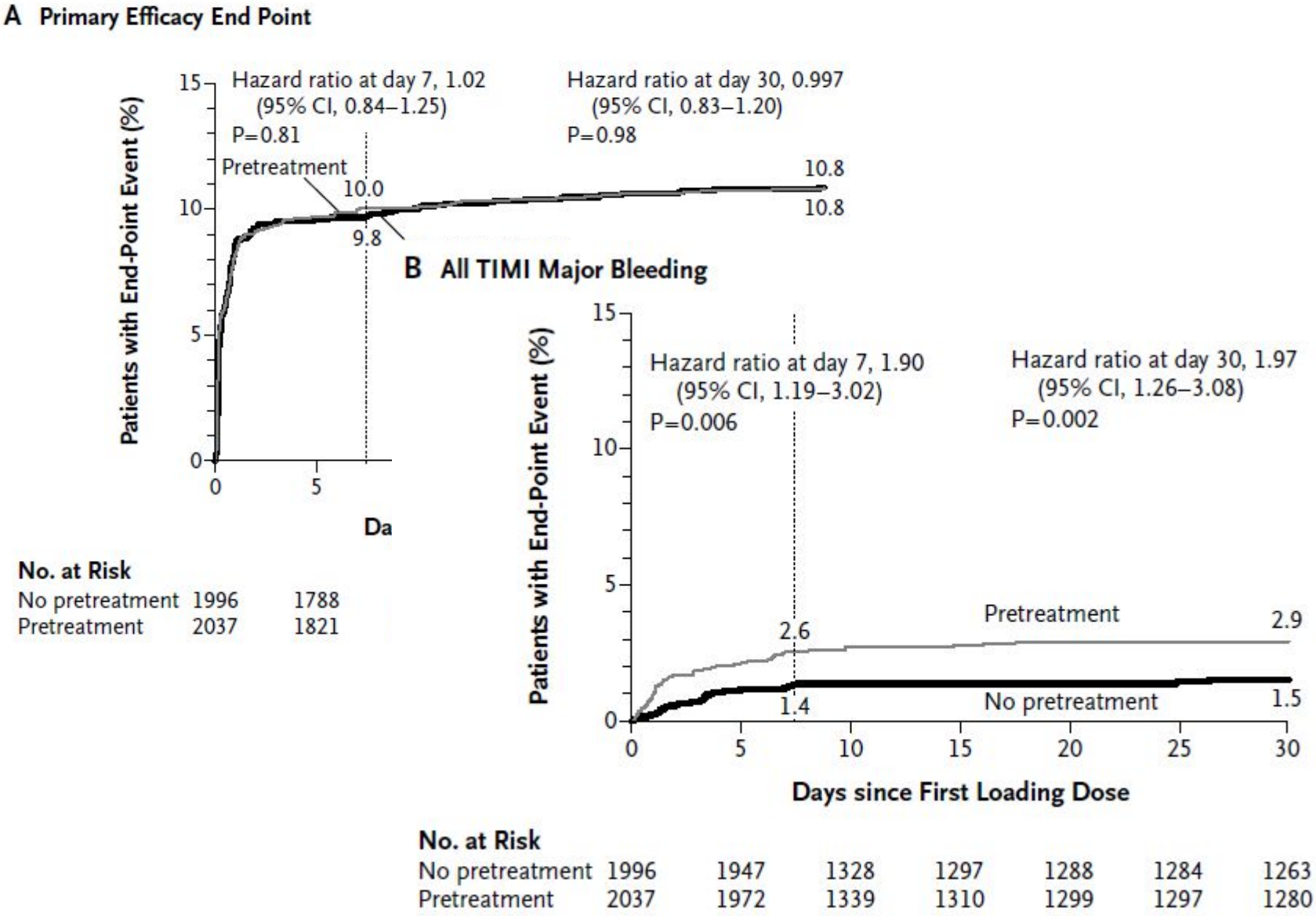
SEGUIMIENTO A LOS 7 Y 30 DÍAS

PCI 68.7 %
Tto médico 25.1 %
Cirugía 6.2 %

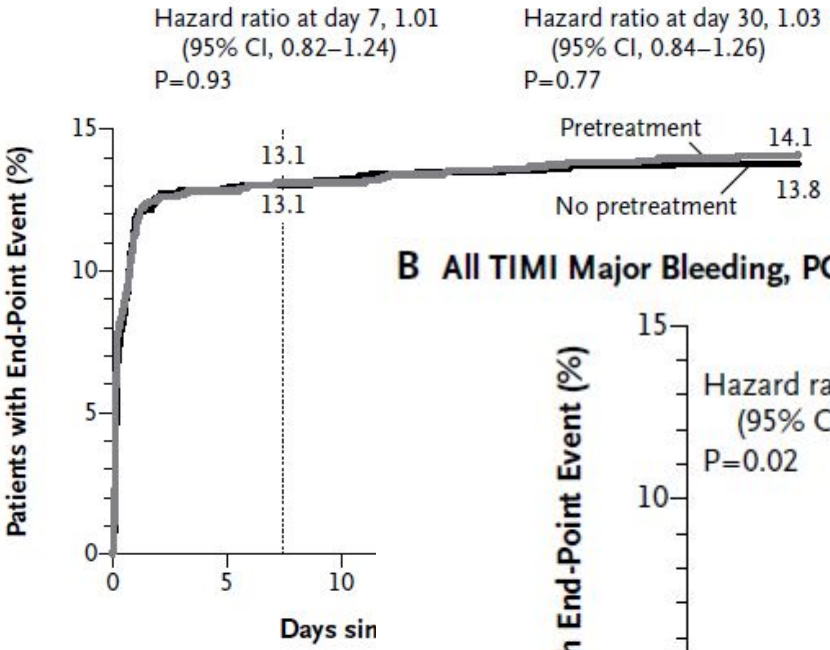
- **Objetivo principal:** MUERTE CARDIOVASCULAR, INFARTO, ACV, REVASCULARIZACIÓN URGENTE Y USO DE INHIBIDORES DE GP IIb-IIIa DE RESCATE
- **Objetivos secundarios:** MUERTE CARDIOVASCULAR + IAM + ACV, MUERTE DE CUALQUIER CAUSA, TROMBOSIS DE STENT
- **Objetivos de seguridad:** sangrados mayores y menores TIMI

End Point	Pretreatment (N = 2037)	No Pretreatment (N = 1996)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
7 Days				
Death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout: primary end point	203 (10.0)	195 (9.8)	1.02 (0.84–1.25)	0.81
Death				
From any cause	8 (0.4)	10 (0.5)	0.78 (0.31–1.98)	0.61
From cardiovascular cause	7 (0.3)	10 (0.5)	0.69 (0.26–1.80)	0.44
Myocardial infarction	119 (5.8)	109 (5.5)	1.07 (0.83–1.39)	0.60
Stroke	8 (0.4)	10 (0.5)	0.78 (0.31–1.98)	0.60
Urgent revascularization	22 (1.1)	26 (1.3)	0.83 (0.47–1.46)	0.52
Glycoprotein IIb/IIIa bailout	76 (3.7)	78 (3.9)	0.96 (0.70–1.31)	0.79

End Point	Pretreatment (N = 2037)	No Pretreatment (N = 1996)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
30 Days				
Death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout	219 (10.8)	216 (10.8)	0.997 (0.83–1.20)	0.98
Death from cardiovascular causes, myocardial infarction, or stroke	144 (7.1)	144 (7.2)	0.98 (0.78–1.23)	0.86
Death from cardiovascular causes or myocardial infarction	135 (6.6)	130 (6.5)	1.02 (0.80–1.30)	0.88
Death from cardiovascular causes, myocardial infarction, or urgent revascularization	157 (7.7)	146 (7.3)	1.06 (0.85–1.33)	0.62
Death from cardiovascular causes	14 (0.7)	22 (1.1)	0.62 (0.32–1.22)	0.16
Myocardial infarction	126 (6.2)	116 (5.8)	1.07 (0.83–1.37)	0.62


A Primary Efficacy End Point
Patients with End-Point Event (%)
15
10
5
0
Hazard ratio at day 7, 1.02
(95% CI, 0.84–1.25)
P=0.81
Hazard ratio at day 30, 0.997
(95% CI, 0.83–1.20)
P=0.98
Pretreatment
10.0
9.8
10.8
10.8
0
5
Da
No. at Risk
No pretreatment 1996 1788
Pretreatment 2037 1821
B All TIMI Major Bleeding
Patients with End-Point Event (%)
15
10
5
0
Hazard ratio at day 7, 1.90
(95% CI, 1.19–3.02)
P=0.006
Hazard ratio at day 30, 1.97
(95% CI, 1.26–3.08)
P=0.002
Pretreatment
2.6
2.9
No pretreatment
1.4
1.5
0
5
10
15
20
25
30
Days since First Loading Dose
No. at Risk
No pretreatment 1996 1947 1328 1297 1288 1284 1263
Pretreatment 2037 1972 1339 1310 1299 1297 1280

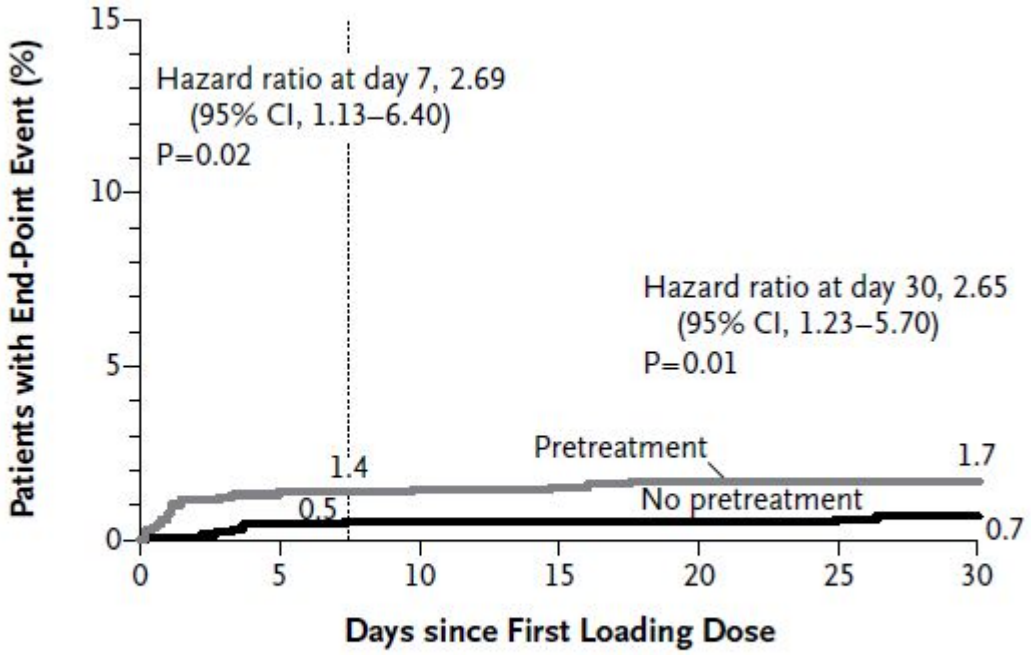
A Primary Efficacy End Point, PCI Group



No. at Risk

No pretreatment	1372	1191	1187
Pretreatment	1389	1206	1202

B All TIMI Major Bleeding, PCI Group



No. at Risk

No pretreatment	1372	1356	1302	1280	1272	1268	1249
Pretreatment	1389	1364	1314	1293	1282	1280	1269

Resultados en pacientes con SCACEST y PCI planeada

- La angioplastia primaria es la MEJOR opcion para pacientes con SCACEST.
- Los pacientes con SCACEST sometidos a angioplastia primaria requieren una rápida y efectiva inhibición plaquetaria.
- El objetivo predefinido en el subanálisis del estudio PLATO fue investigar la eficacia y seguridad de TICAGRELOR vs. CLOPIDOGREL en paciente con SCACEST sometidos a angioplastia primaria.

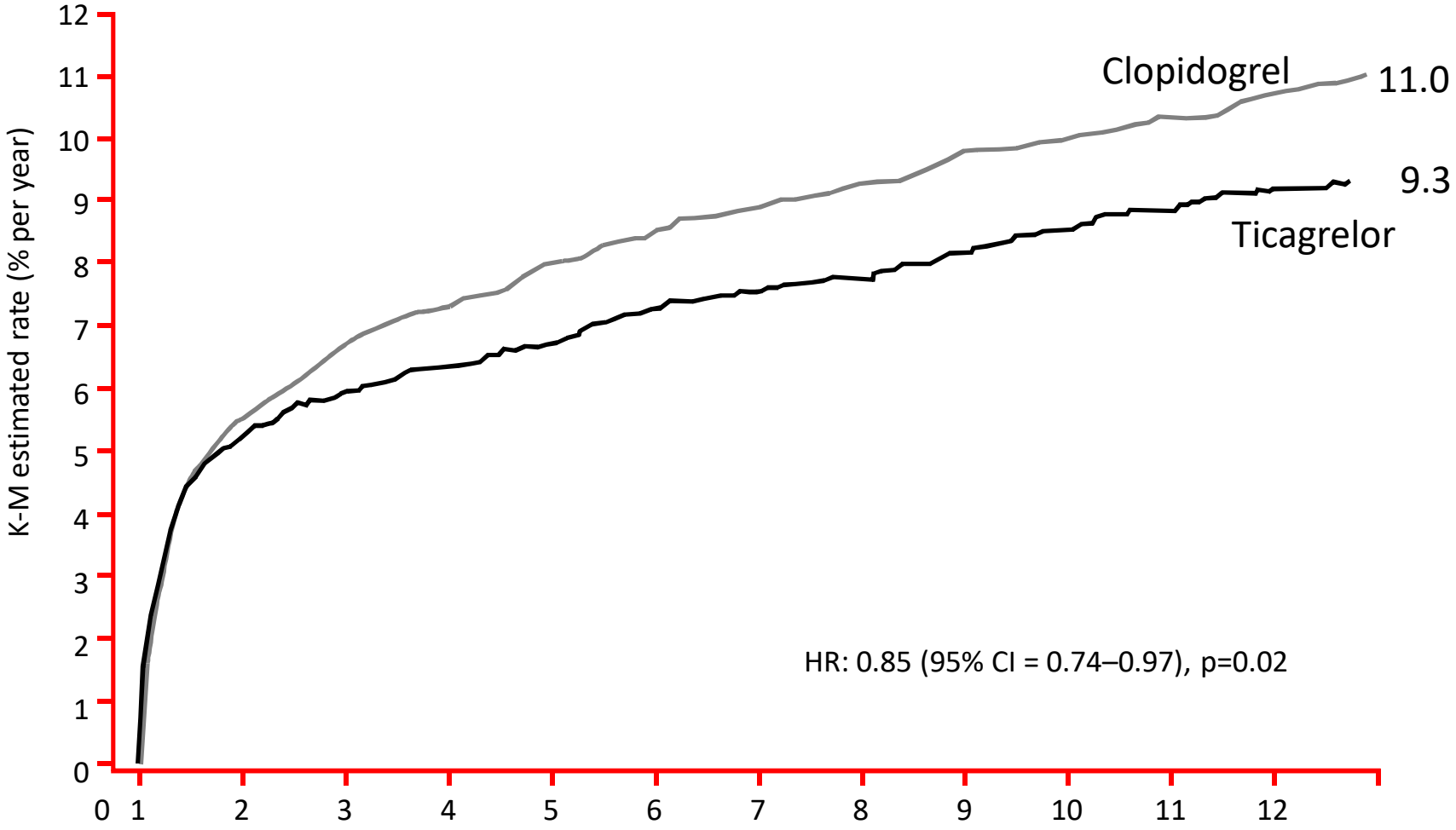
PLATO SCACEST

	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Start of randomized treatment		
Median time after start of chest pain, hours	5.6	5.8
Premature discontinuation of study drug, %	19.5	18.9
Invasive procedures at index hospitalization, %		
Coronary angiography	92.6	92.8
PCI during index hospitalization	80.6	80.0
CABG during index hospitalization	2.2	2.9
Received at least one stent, %	74.3	74.2
Bare metal stent only	57.9	57.6
Drug-eluting stent (at least one)	16.1	16.3
Open-label clopidogrel pre-randomization, %		
None	56.5	55.5
75 mg	4.8	5.1
300 mg	18.1	18.6
600 mg	20.7	20.8
Total clopidogrel (OL + IP)* pre-randomization to 24 h, %		
300 mg	65.2	65.4
600 mg	34.8	34.6

COTRATAMIENTOS

Medication	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Anti-thrombotic treatment in hospital, %		
Aspirin prior to index event	21.4	20.7
Aspirin from index event to discharge	99.0	98.8
Unfractionated heparin	66.3	65.8
Low molecular weight heparin	45.8	46.1
Fondaparinux	1.8	1.7
Bivalirudin	1.3	1.4
GPIIb/IIIa inhibitor from index event to randomization	34.7	35.2
Other medication in hospital or at discharge, %		
Beta-blockade	85.8	86.2
ACE inhibition and/or angiotensin-II receptor blocker	86.0	85.9
Cholesterol lowering (statin)	94.8	95.1
Calcium-channel blocker	17.1	17.1
Diuretic	36.2	35.4
Proton pump inhibitor	49.1	49.1

Primary endpoint: CV death, MI or stroke



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

PLATO SCACEST

Endpoint*	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Primary endpoint, %				
CV death + MI + stroke	9.3	11.0	0.85 (0.74–0.97)	0.02
Secondary endpoints, %				
Total death + MI + stroke	9.7	11.5	0.84 (0.73–0.96)	0.01
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	13.4	15.4	0.86 (0.76–0.96)	0.01
MI	4.7	6.1	0.77 (0.63–0.93)	0.01
CV death	4.5	5.4	0.84 (0.69–1.03)	0.09
Stroke	1.6	1.0	1.45 (0.98–2.17)	0.07
All-cause mortality	4.9	6.0	0.82 (0.68–0.99)	0.04

The percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than one type of endpoint.

†By univariate Cox model

TROMBOSIS DEL STENT

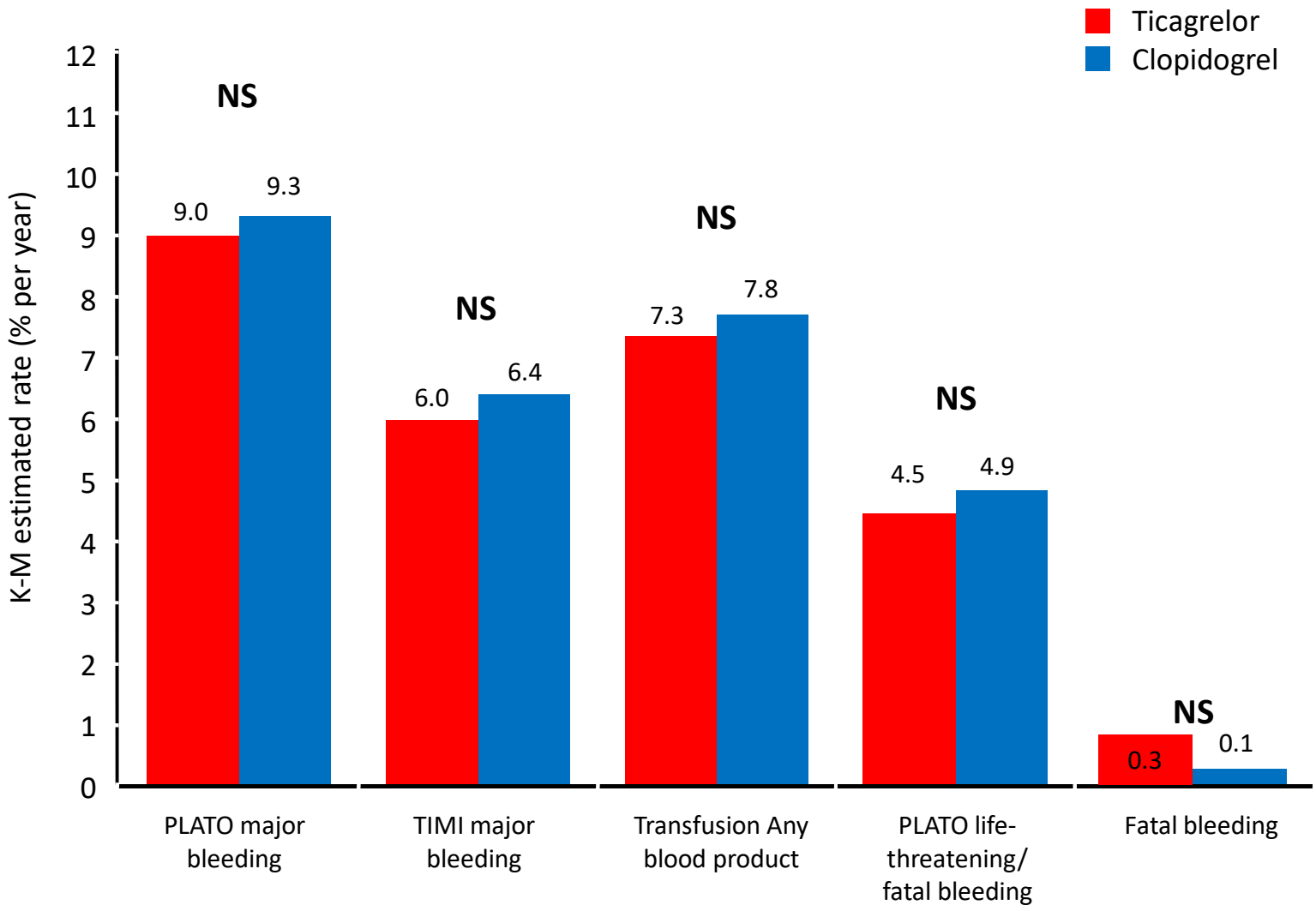
	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Definite	1.6	2.5	0.61 (0.42–0.87)	0.01
Probable or definite	2.5	3.6	0.69 (0.52–0.92)	0.01
Possible, probable, or definite	3.2	4.4	0.73 (0.56–0.94)	0.02

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

*Cutlip et. al., Circulation. 2007;115:2344–2351

†By univariate Cox model

SANGRADO MAYOR



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. New Eng J Med. 2007;357:2001–15;
NS = not significant

TRITON TIMI 38 SCACEST

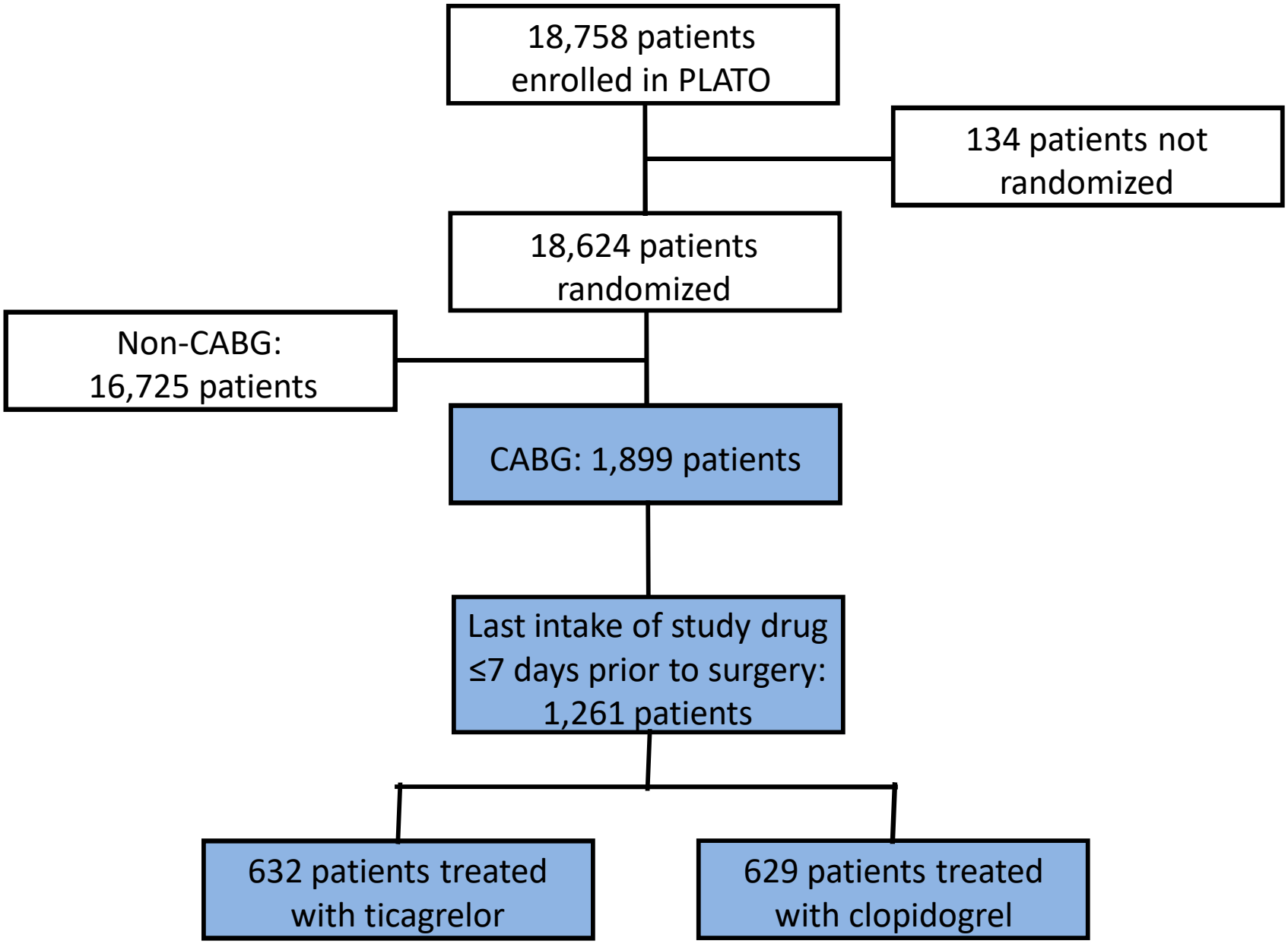
	Clopidogrel	Prasugrel	Hazard ratio (95% CI)	p	Number needed to treat (95% CI)*
Efficacy endpoints					
Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)					
All STEMI cohort	216 (12·4%)	174 (10·0%)	0·79 (0·65–0·97)	0·0221	41 (24–266)
Primary PCI	142 (11·6%)	121 (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	..

PLATO CABG

TICAGRELOR VERSUS CLOPIDOGREL EN PACIENTES CON SCA DERIVADOS A CIRUGÍA DE REVASCULARIZACIÓN CORONARIA.

- La recuperación de la funcionalidad plaquetaria ocurre después de 5 – 7 días tras la inhibición irreversible de aspirina y clopidogrel.
  - Esto puede incrementar el riesgo de complicaciones en pacientes que necesitan cirugía mayor de forma urgente como la cirugía de revascularización coronaria.
- La inhibición reversible de $P2Y_{12}$ por parte de ticagrelor puede acortar este tiempo a 2 – 3 días.
- El objetivo PREDEFINIDO en el subanálisis del estudio PLATO fue evaluar la eficacia y la seguridad después de la cirugía de revascularización coronaria en pacientes con toma de la medicación dentro de los siete dias previos a la cirugía.

PLATO CABG


18,758 patients enrolled in PLATO
134 patients not randomized
18,624 patients randomized
Non-CABG: 16,725 patients
CABG: 1,899 patients
Last intake of study drug ≤7 days prior to surgery: 1,261 patients
632 patients treated with ticagrelor
629 patients treated with clopidogrel

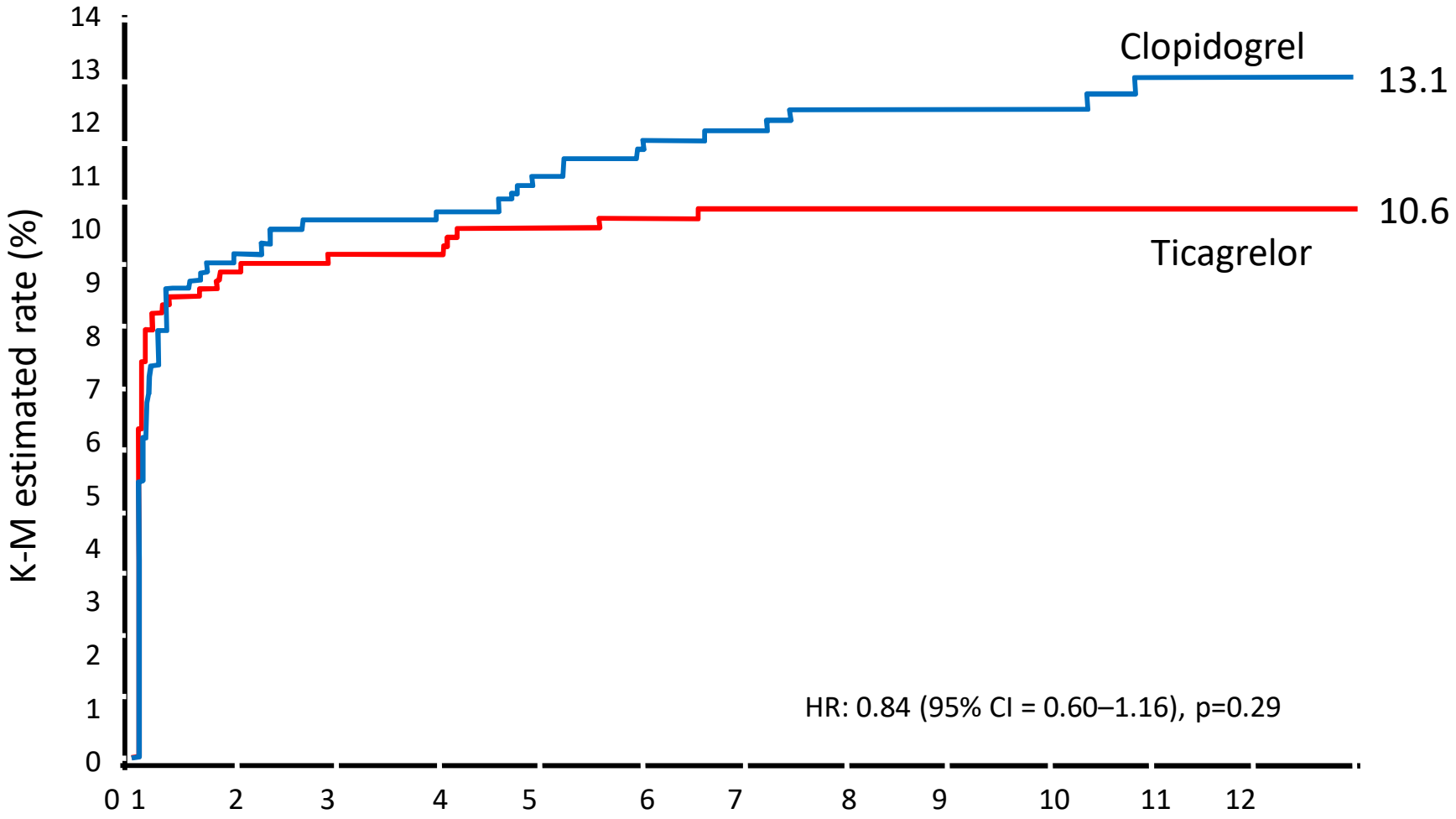
PLATO CABG

	Ticagrelor (n=632)	Clopidogrel (n=629)
Days study drug stopped before CABG, %		
1 day	13.3	14.0
2 days	16.8	13.7
3 days	18.0	11.6
4 days	13.3	11.0
5 days	12.5	15.3
6 days	14.4	17.5
7 days	11.7	17.0
Patients not restarted on study drug/unknown	n=234	n=238
Time study drug restarted after CABG, %*	(n=398)	(n=391)
<7 days	57.0	57.5
7–14 days	27.9	25.6
>14 days	15.1	16.9

*Percentages calculated based on number of patients with available data

PLATO CABG

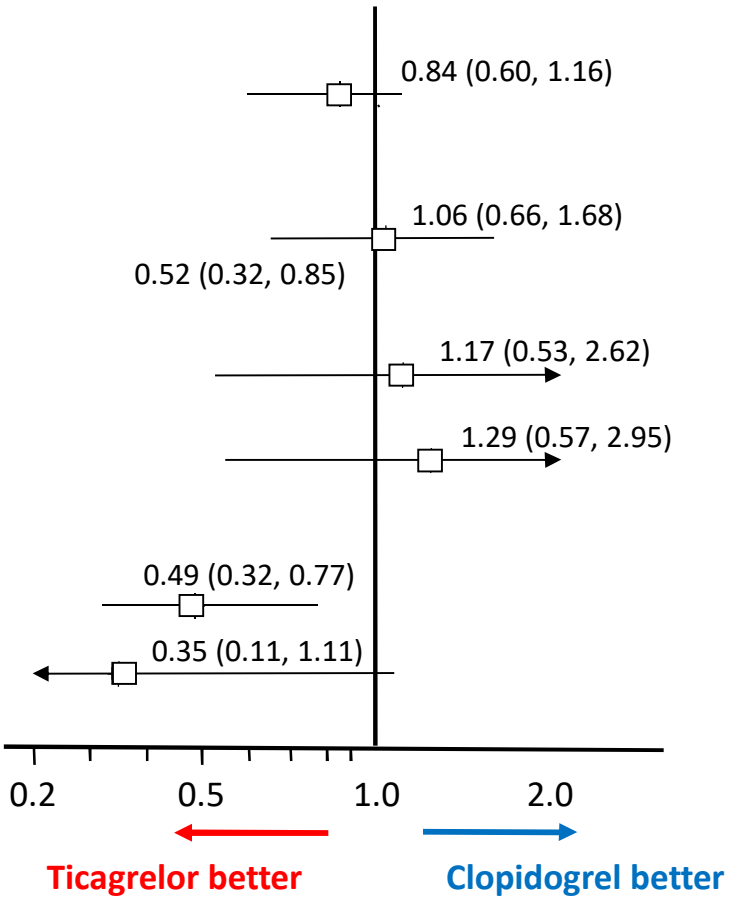
Primary endpoint: CV death, MI or stroke



No. at risk							
Ticagrelor	629	543	519	458	386	268	108
Clopidogrel	629	541	516	448	386	255	125

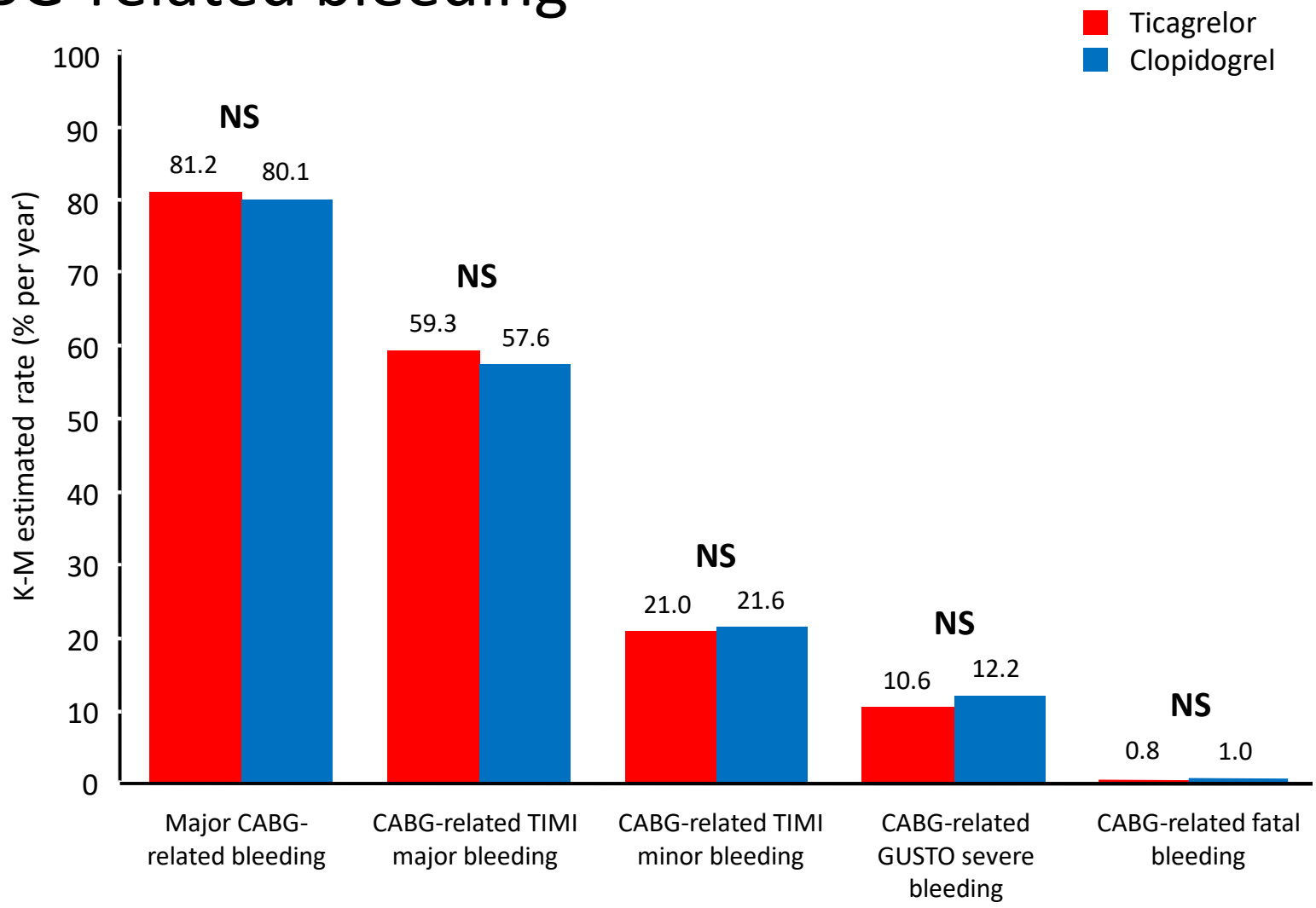
Primary and secondary efficacy endpoints post-CABG

Characteristic	Ticagrelor (n=631)	Clopidogrel (n=629)	p-value
Primary endpoint			
CV death + MI + stroke	10.5	12.6	0.29
Secondary endpoints			
MI	5.9	5.6	0.82
CV death	4.0	7.5	0.009
Stroke	2.1	1.7	0.70
Non-hemorrhagic/ unknown stroke	2.1	1.6	0.54
Hemorrhagic stroke	0.0	0.2	
All-cause mortality	4.6	9.2	0.002
Non-CV death	0.6	1.7	0.07



Patients could have had more than one type of endpoint. Event rate is number of events divided by n

CABG-related bleeding



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. New Eng J Med. 2007;357:2001–15;
NS = not significant

ESTRATEGIA CONSERVADORA

- Comparado con pacientes que se revascularizan, los pacientes sometidos a tratamiento conservador o no invasivo:
  - Presentan elevada comorbilidad y caractériticas clínicas de alto riesgo
  - Reciben de forma menos frecuente las recomendaciones clínicas actuales
  - Tiene mayor riesgo de eventos a corto y largo plazo

- El tratamiento médico conservador en el SCA representa un porcentaje no desdeñable de pacientes
  - 27–48% de pacientes con SCASEST no se someten a cateterismo diagnóstico
  - 45–69% de pacientes con SCASEST no reciben tratamiento revascularizador

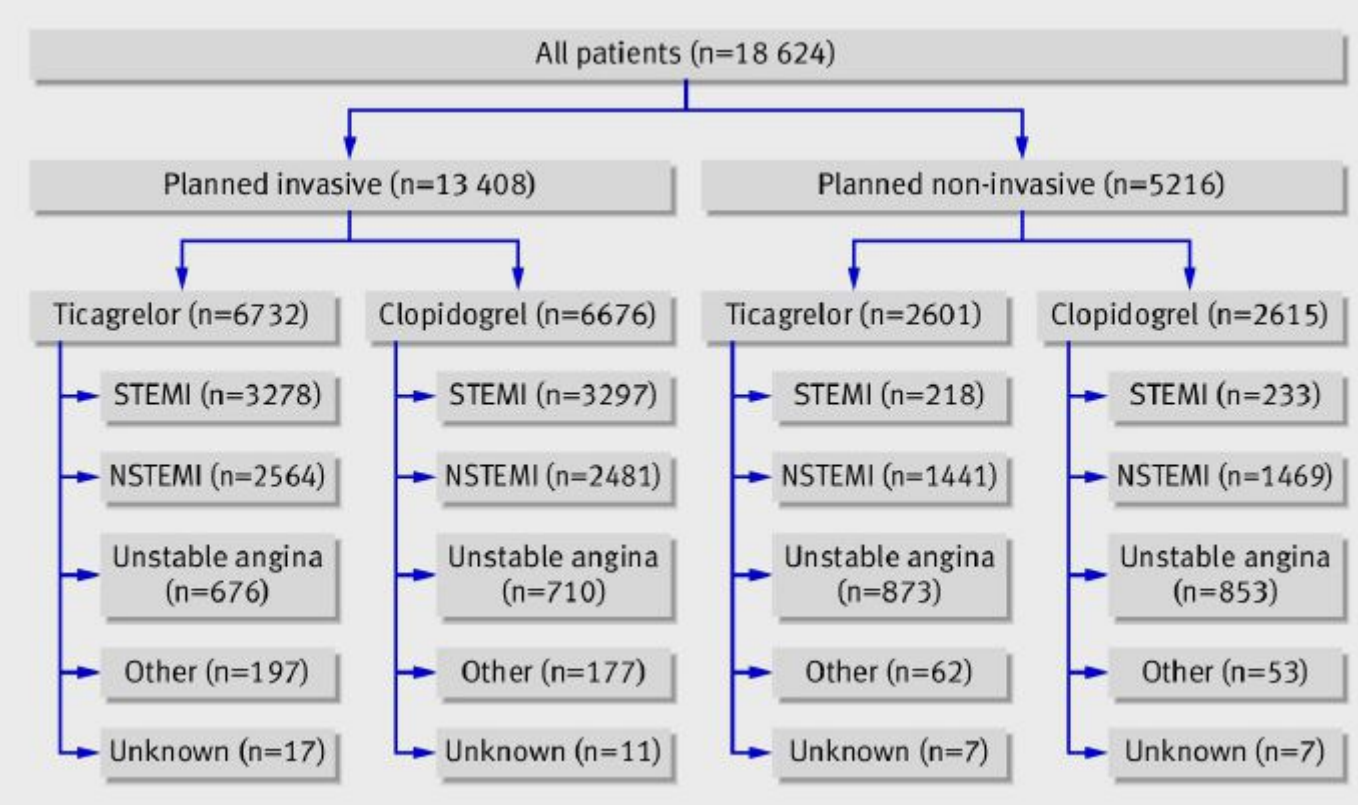
- Sin embargo, y a pesar del importante número de pacientes a los que se maneja de forma conservadora; éstos están infrarrepresentados en los estudios randomizados.

ACS, acute coronary syndrome; NSTE-ACS, non-ST-segment elevation acute coronary syndromes.

Chan MY, et al. *Am Heart J* 2008;155:397–407;
Roe MT, et al. *N Engl J Med* 2012;367:1297–1309.

PLATO no invasivo

Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial

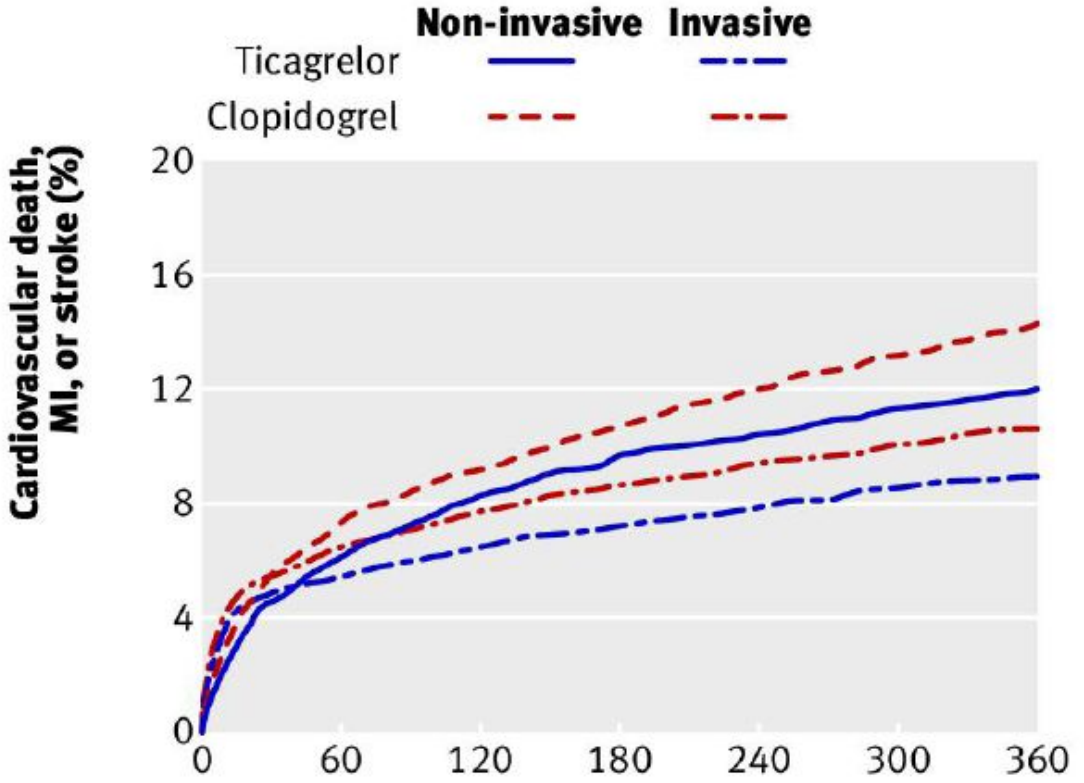


BMJ 2011;342:d3527 doi: 10.1136/bmj.d3527

PLATO no invasivo

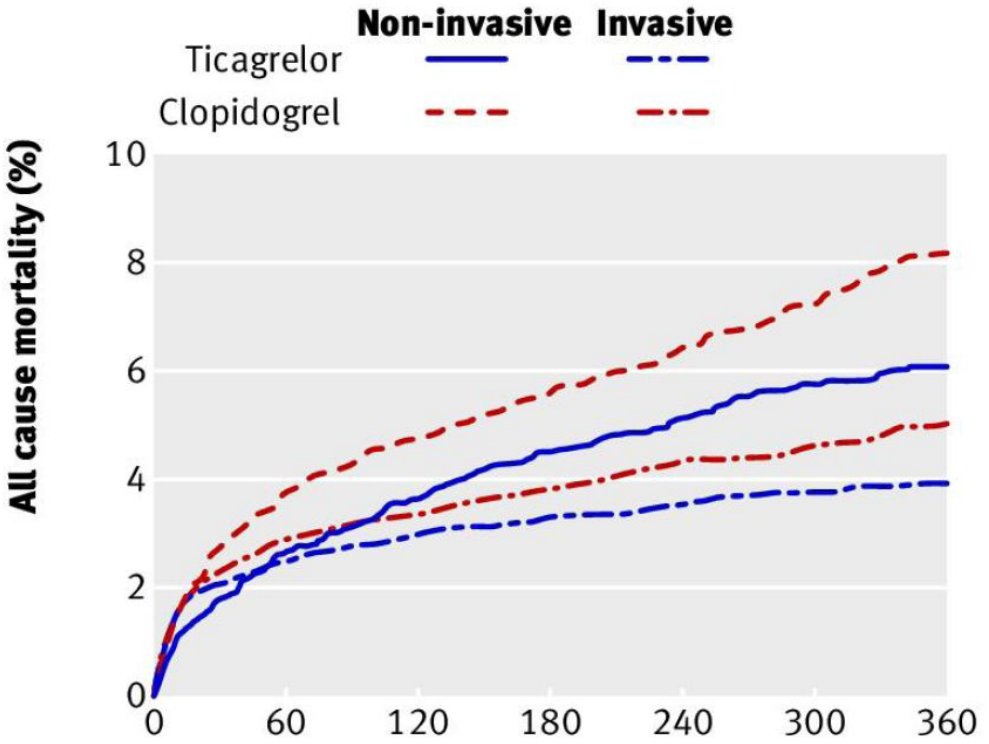
	Planned non-invasive			Planned invasive (n=13 408)
	Ticagrelor (n=2601)	Clopidogrel (n=2615)	Total (n=5216)	
Invasive procedures				
Coronary angiography:				
Before discharge	41.8 (1088)	41.9 (1095)	41.9 (2183)	96.9 (12 987)
Any time during follow-up	55.6 (1447)	55.4 (1448)	55.5 (2895)	97.6 (13 085)
Median (IQR) time to angiography (hours)	89 (26-266) (n=1445)	92 (26-235) (n=1446)	91 (26-240) (n=2891)	0.6 (0.1-3.8) (n=13 083)
Percutaneous coronary intervention (PCI):				
Before discharge	20.3 (528)	20.5 (537)	20.4 (1065)	76.8 (10 298)
Any time during follow-up	28.4 (738)	29.7 (776)	29.0 (1514)	78.0 (10 463)
Median (IQR) time to PCI (hours)	136 (40-379) (n=738)	144 (42-391) (n=776)	141 (41-383) (n=1514)	0.8 (0.3-3.0) (n=10 462)
Coronary artery bypass grafting (CABG):				
Before discharge	4.2 (108)	3.8 (100)	4.0 (208)	5.7 (762)
Any time during follow-up	11.0 (287)	10.4 (272)	10.7 (559)	10.0 (1340)
Median (IQR) time to CABG (hours)	609 (306-1682) (n=287)	642 (308-1852) (n=272)	623 (307-1742) (n=559)	240 (92-1145) (n=1340)

PLATO no invasivo



No at risk							
Invasive							
Ticagrelor	6732	6236	6134	5972	4889	3735	3048
Clopidogrel	6676	6129	6034	5881	4815	3680	2965
Non-invasive							
Ticagrelor	2601	2392	2326	2247	1854	1426	1099
Clopidogrel	2615	2392	2328	2243	1835	1416	1109

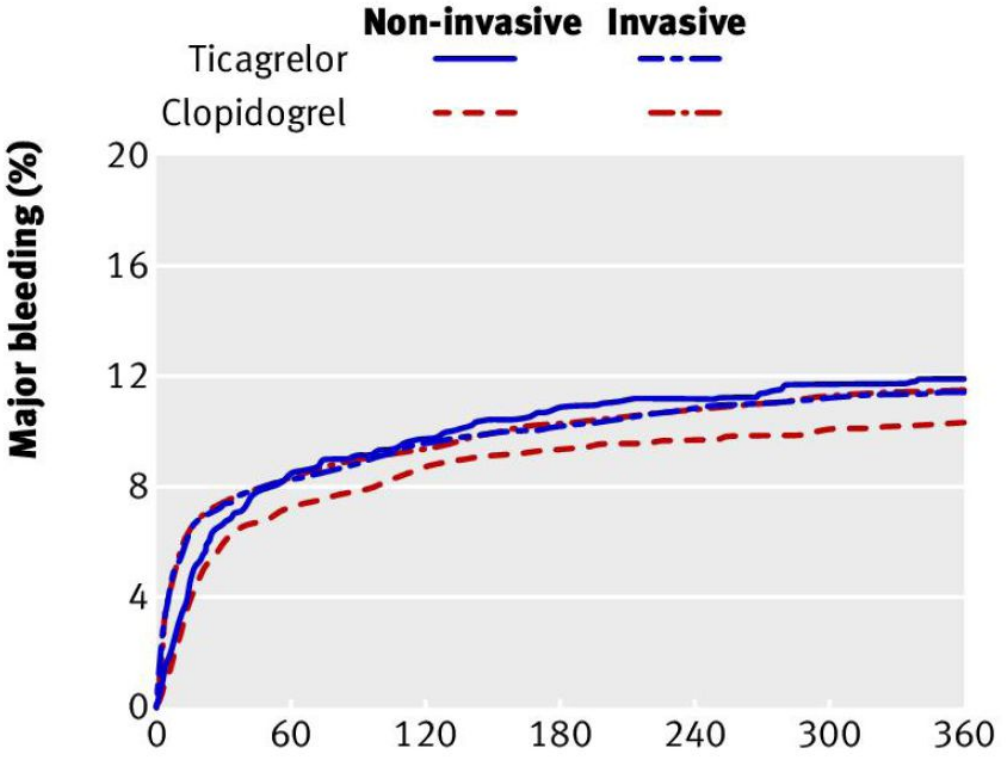
PLATO no invasivo



No at risk

Invasive							
Ticagrelor	6732	6439	6375	6241	5141	3951	3233
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
Ticagrelor	2601	2485	2447	2385	1978	1531	1186
Clopidogrel	2615	2488	2448	2380	1965	1524	1200

PLATO no invasivo



No at risk							
Invasive							
Ticagrelor	6651	5238	4948	4766	3730	2748	2521
Clopidogrel	6585	5220	4985	4798	3756	2760	2507
Non-invasive							
Ticagrelor	2584	2008	1878	1779	1399	1035	912
Clopidogrel	2601	2085	1945	1872	1453	1081	972

ORIGINAL ARTICLE

ESTUDIO TRILOGY

Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization

SCA MANEJO CONSERVADOR

DOBLE CIEGO

N =9326 pacientes

BACKGROUND

The effect of i[illegible]nhibition for pat[illegible]e angina or myocardial infarct[illegible]gment elevation [illegible]go revascularization has not b[illegible]

< 75 AÑOS
7243 pacientes

75 AÑOS
2083 pacientes

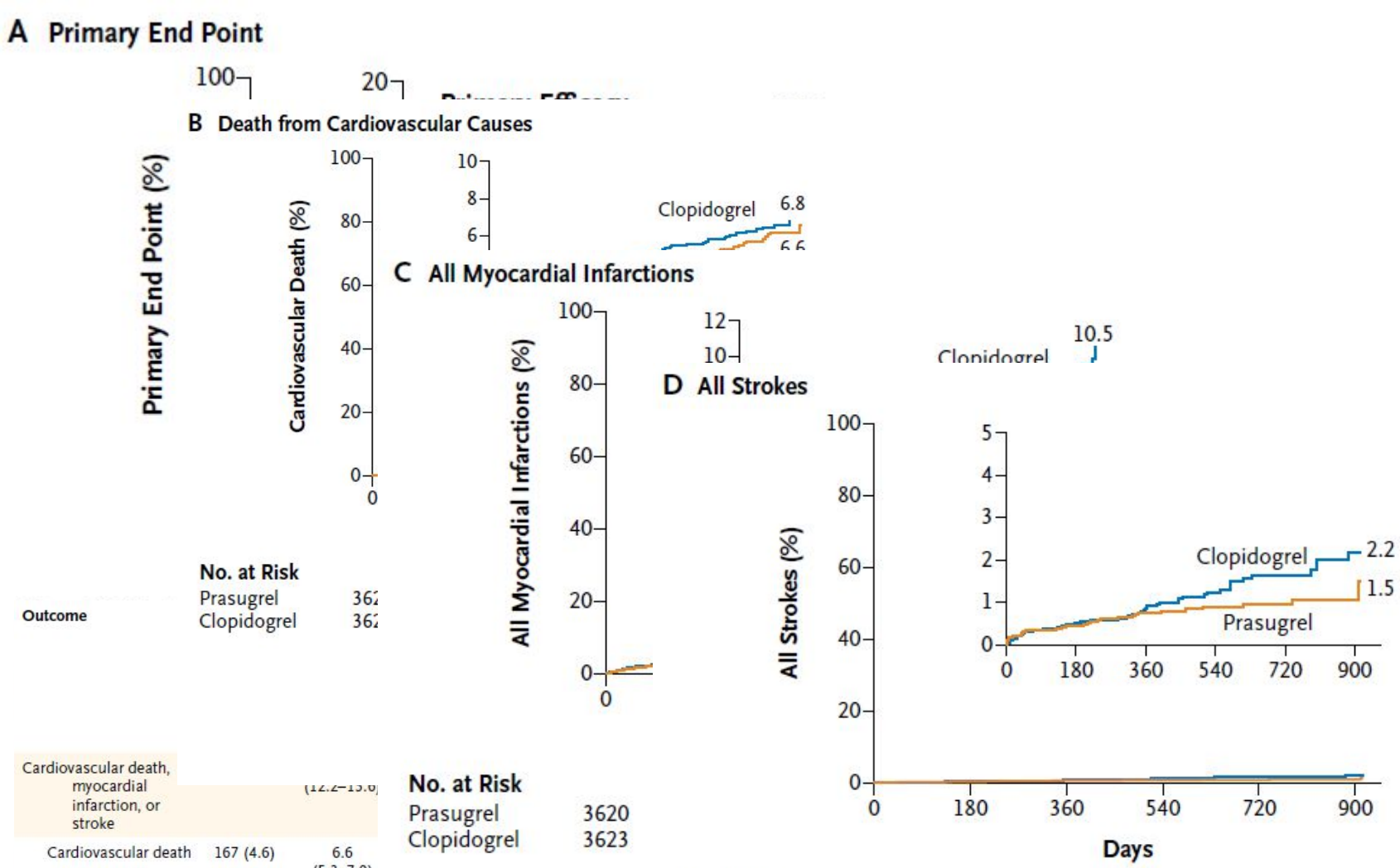
Prasugrel 10 mg/día

Clopidogrel 75 mg/día

Prasugrel 5 mg/día

Seguimiento medio 14.5 meses

- **Objetivo principal:** MUERTE CARDIOVASCULAR, INFARTO, ACV
- **Objetivos de seguridad:** sangrados mayores



Outcome												
Cardiovascular death, myocardial infarction, or stroke		(12.2–13.0)										
Cardiovascular death	167 (4.6)	6.6 (5.3–7.9)										
Myocardial infarction	217 (6.0)	8.3 (7.1–9.6)	244 (6.7)	10.5 (8.6–12.4)	0.89 (0.74–1.0							
Stroke	31 (0.9)	1.5 (0.6–2.4)	46 (1.3)	2.2 (1.4–2.9)	0.67 (0.42–1.0							
Death from any cause	208 (5.7)	7.8 (6.5–9.1)	218 (6.0)	8.1 (7.0–9.3)	0.96 (0.79–1.16)	0.63	385 (8.3)	11.6 (10.3–13.0)	409 (8.8)	12.2 (10.9–13.4)	0.94 (0.82–1.08)	0.40

Table 3. Safety Outcomes at 30 Months.*

Outcome	Age <75 years						Overall Population					
	Prasugrel (N=3590)		Clopidogrel (N=3590)		Hazard Ratio (95% CI)	P Value	Prasugrel (N=4623)		Clopidogrel (N=4617)		Hazard Ratio (95% CI)	P Value
	Patients with Event	*Event Rate at 30 Mo*	*Patients with Event*	*Event Rate at 30 Mo*			*Patients with Event*	*Event Rate at 30 Mo*	*Patients with Event*	*Event Rate at 30 Mo*		
	no. (%)	*% (95% CI)*	*no. (%)*	*% (95% CI)*			*no. (%)*	*% (95% CI)*	*no. (%)*	*% (95% CI)*		
GUSTO criteria												
Severe or life-threatening	13 (0.4)	0.9 (0.1–1.7)	14 (0.4)	0.6 (0.3–1.0)	0.94 (0.44–1.99)	0.87	22 (0.5)	1.1 (0.4–1.9)	27 (0.6)	1.0 (0.6–1.4)	0.83 (0.48–1.46)	0.53
Severe or life-threatening or moderate	52 (1.4)	2.5 (1.5–3.4)	35 (1.0)	1.7 (1.0–2.3)	1.50 (0.98–2.30)	0.06	89 (1.9)	3.6 (2.6–4.5)	69 (1.5)	2.8 (2.0–3.5)	1.31 (0.96–1.80)	0.10
TIMI criteria††												
Major	39 (1.1)	2.1 (1.1–3.0)	30 (0.8)	1.5 (0.9–2.1)	1.31 (0.81–2.11)	0.27	58 (1.3)	2.5 (1.6–3.3)	48 (1.0)	1.8 (1.2–2.4)	1.23 (0.84–1.81)	0.29
Life-threatening	16 (0.4)	0.9 (0.1–1.6)	17 (0.5)	0.8 (0.4–1.2)	0.95 (0.48–1.87)	0.88	25 (0.5)	1.1 (0.4–1.8)	27 (0.6)	1.1 (0.6–1.5)	0.95 (0.55–1.63)	0.85
Fatal	4 (0.1)	0.5 (0.0–1.2)	4 (0.1)	0.2 (0.0–0.5)	1.01 (0.25–4.05)	0.99	7 (0.2)	0.6 (0.0–1.2)	9 (0.2)	0.4 (0.1–0.6)	0.80 (0.30–2.14)	0.68
Intracranial hemorrhage	8 (0.2)	0.7 (0.0–1.5)	12 (0.3)	0.5 (0.2–0.8)	0.67 (0.28–1.65)	0.39	14 (0.3)	0.8 (0.1–1.4)	19 (0.4)	0.7 (0.4–1.0)	0.76 (0.38–1.51)	0.42
Major or minor	70 (1.9)	3.3 (2.3–4.4)	46 (1.3)	2.1 (1.4–2.8)	1.54 (1.06–2.23)	0.02	97 (2.1)	3.9 (2.9–4.9)	77 (1.7)	3.0 (2.2–3.9)	1.28 (0.95–1.73)	0.11

	ACS		Pretreatment
	Invasive management	**Medical management**	
Ticagrelor	Label (PLATO)	Label (PLATO)	Label (PLATO)
Clopidogrel	Label	Label	Label
Prasugrel	Label (TRITON)	~~Primary endpoint not met (TRILOGY)~~	~~Primary endpoint not met (ACCOAST)~~

Montalescot G, et al. *Am Heart J* 2011;161:650–656; Roe MT, et al. *N Engl J Med* 2012;367:1297–1309;
Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057;
Wiviott SD, et al. *N Engl J Med* 2007;357:2001–2015.

CONCLUSIONES

- La angioplastia primaria constituye la estrategia óptima de reperfusión en el SCACEST

- Aunque la doble antiagregación con AAS + Clopidogrel han demostrado su beneficio, la tasa de respuesta inadecuada a Clopidogrel en el momento de la ICP primaria es muy elevada a pesar de la precarga oral

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

CONCLUSIONES

- El **SCASEST** presenta un pronóstico a largo plazo peor que el del Infarto con elevación del ST.
- El manejo invasivo precoz y una terapia intensiva antiplaquetaria son claves en el manejo de estos pacientes
- Actualmente en el manejo del SCASEST los nuevos fármacos antiagregantes, Ticagrelor y Prasugrel, mejoran los resultados respecto al Clopidogrel
- El **TICAGRELOR** es el único fármaco que nos permite tratar todo el espectro de pacientes con SCASEST desde el ingreso sin necesidad de suspensión ni de switch a ningún otro fármaco e independientemente del manejo que se programe para el paciente (intervencionismo percutáneo, manejo conservador, cirugía)

CONCLUSIONES

- En el periodo actual de restricción de costos el uso de estos nuevos fármacos se podría concentrar en los grupos de más riesgo
  - Diabetes mellitus
  - Insuficiencia renal crónica
  - Enfermedad coronaria previa
  - Trombosis del stent
  - ACTP primaria de riesgo (TCI, enfermedad multivaso, bifurcaciones, multiples stents)

- El uso de TICAGRELOR estaría especificamente favorecido en presencia de alguna de las siguientes condiciones
  - > 75 años
  - < 60 Kg de peso
  - Ictus o AIT previo
  - Insuficiencia renal crónica
  - Cirugía posible a corto plazo