

IAMCEST: Manejo prehospitalario

TRATAMIENTO ANTITROMBÓTICO

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Gregorio Marañón

Management of STEMI

REPERFUSION Therapy



Primary Angioplasty

Pharmacologic Therapy

Antithrombotic Therapy

Antiplatelets

- Aspirin
- Clopidogrel
- GP IIb/IIIa Inh
- Prasugrel, Ticagrelor

Anticoagulants

- UFH
- Enoxaparin
- Bivalirudin

Antiischemic Therapy

- BB
- GTN
- Other

Other therapies

- Statins
- ACEI
- Aldosterone Inh

Mujer de 75 años que acude a un hospital rural en zona montañosa

Dolor torácico de 2 horas

Diabética. HTA.

TA: 150/110 mm Hg
Kg Sat O₂. 95%

FC: 95 lpm T: 155 cm P: 60

AC: RCR. No soplos

AP: Algunos crepitantes en bases

IAM anterior extenso

Hospital con capacidad de angioplastia primaria 24 h. a 1,5 - 2 horas

Table 8 Logistics of pre-hospital care

Recommendations	Class ^a	Level ^b	Ref ^c
Ambulance teams must be trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including thrombolysis where applicable.	I	B	43
The prehospital management of STEMI patients must be based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible.	I	B	47
Primary PCI-capable centres must deliver a 24/7 service and be able to start primary PCI as soon as possible but always within 60 min from the initial call.	I	B	6, 52, 55
All hospitals and EMSs participating in the care of patients with STEMI must record and monitor delay times and work to achieve and maintain the following quality targets: <ul style="list-style-type: none"> • first medical contact to first ECG ≤10 min; • first medical contact to reperfusion therapy; • for fibrinolysis ≤30 min; • for primary PCI ≤90 min (≤60 min if the patient presents within 120 min of symptom onset or directly to a PCI-capable hospital). 	I	B	56, 57
All EMSs, emergency departments, and coronary care units must have a written updated STEMI management protocol, preferably shared within geographic networks.	I	C	
Patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI must be attended in an appropriately monitored area.	I	C	
Patients transferred to a PCI-capable centre for primary PCI should bypass the emergency department and be transferred directly to the catheterization laboratory.	IIa	B	41, 50, 58

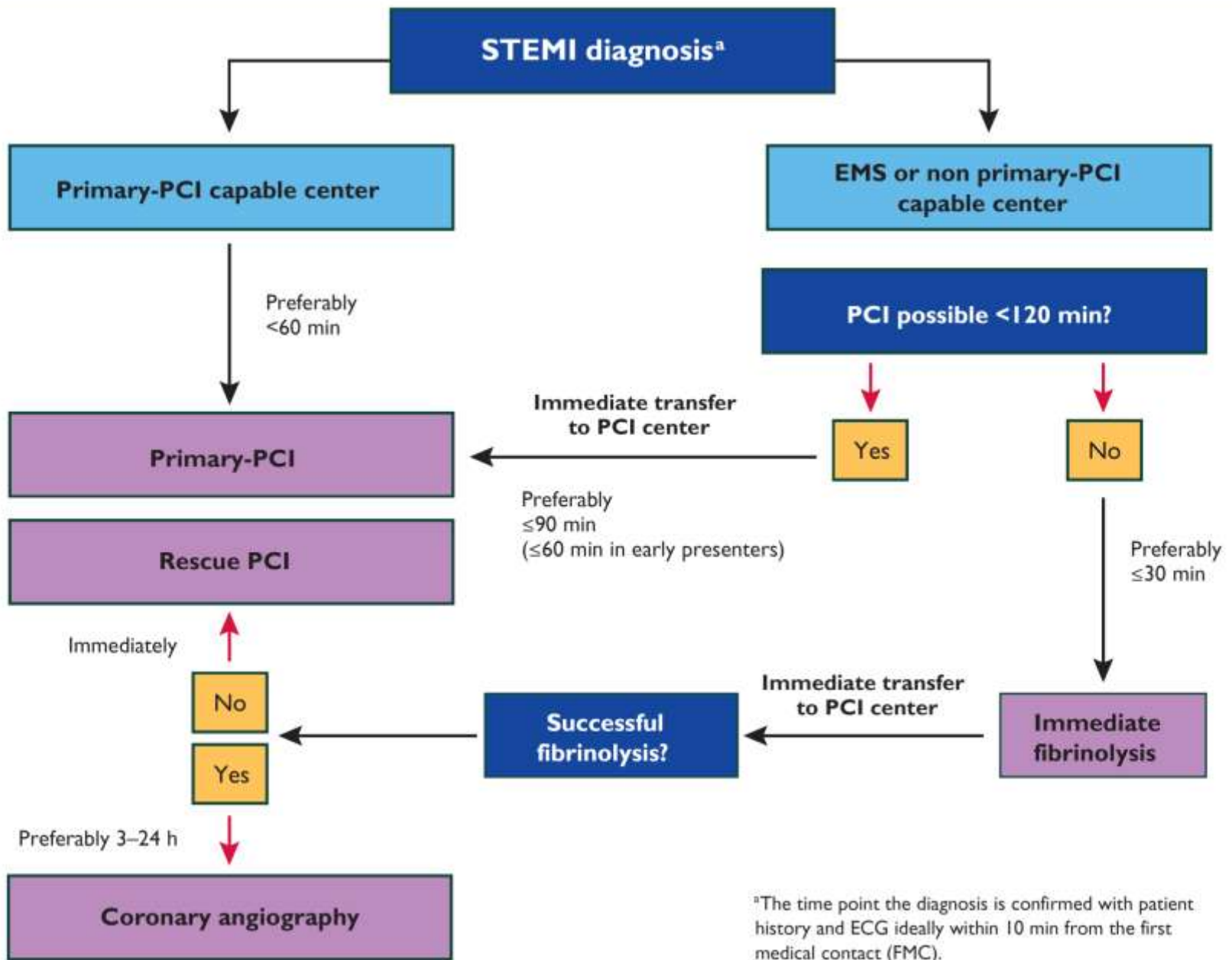
¿Qué harías ahora?

1. Fibrinólisis e ingreso en la UVI del hospital
2. Fibrinólisis y traslado a hospital con sala de hemodinámica
3. Traslado para angioplastia primaria a hospital con sala de hemodinámica
4. Llamar a Pepe Barrabés para que me diga que hacer

Table 10 A summary of important delays and treatment goals in the management of acute ST-segment elevation myocardial infarction

Delay	Target
Preferred for FMC to ECG and diagnosis	≤10 min
Preferred for FMC to fibrinolysis ('FMC to needle')	≤30 min
Preferred for FMC to primary PCI ('door to balloon') in primary PCI hospitals	≤60 min
Preferred for FMC to primary PCI	≤90 min (≤60 min if early presenter with large area at risk)
Acceptable for primary PCI rather than fibrinolysis	≤120 min (≤90 min if early presenter with large area at risk) if this target cannot be met, consider fibrinolysis.
Preferred for successful fibrinolysis to angiography	3–24 h

FMC = first medical contact; PCI = percutaneous coronary intervention.



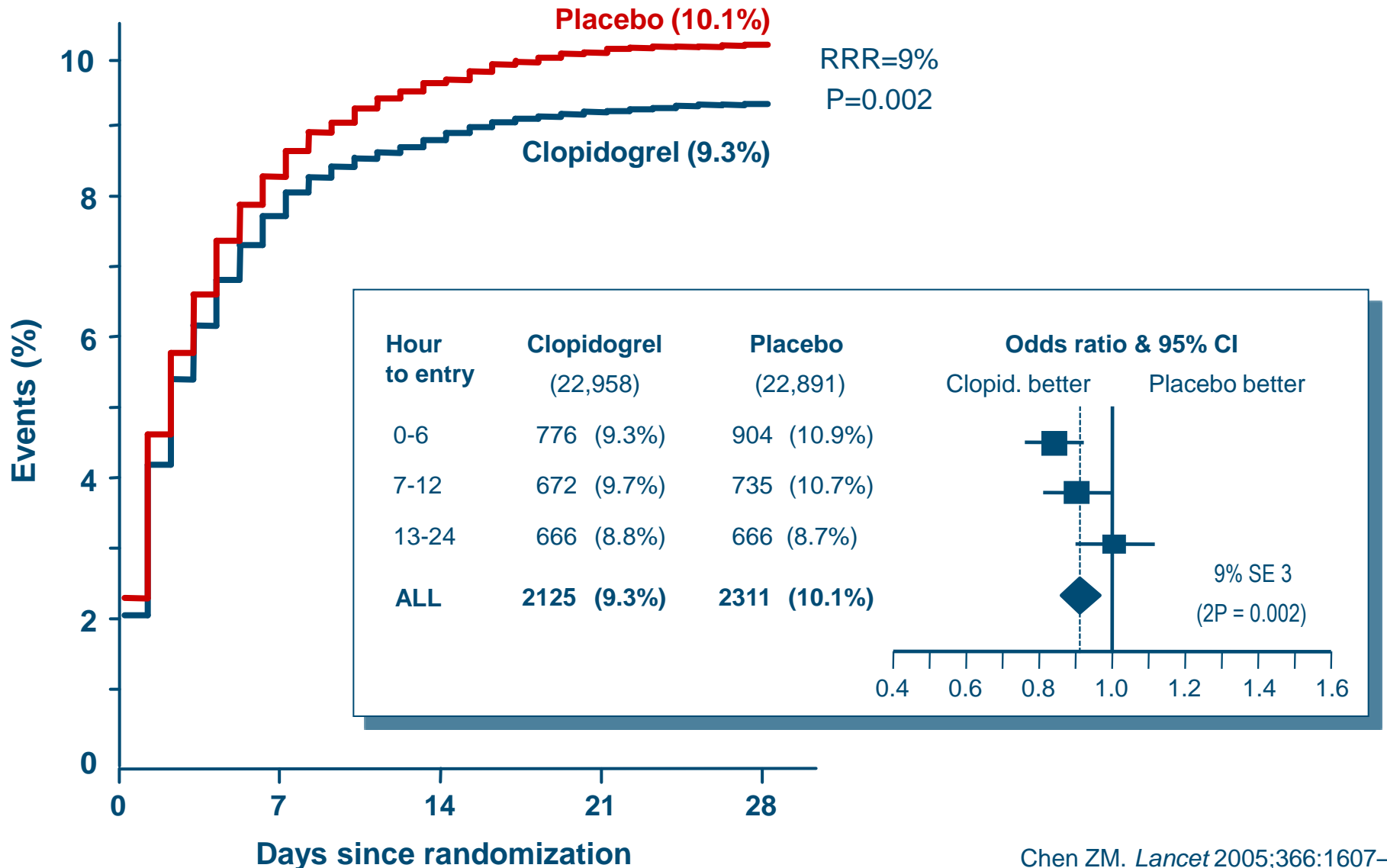
^aThe time point the diagnosis is confirmed with patient history and ECG ideally within 10 min from the first medical contact (FMC). All delays are related to FMC (first medical contact).

Si la opción fuera fibrinólisis,

¿qué tratamiento antitrombótico utilizarías?

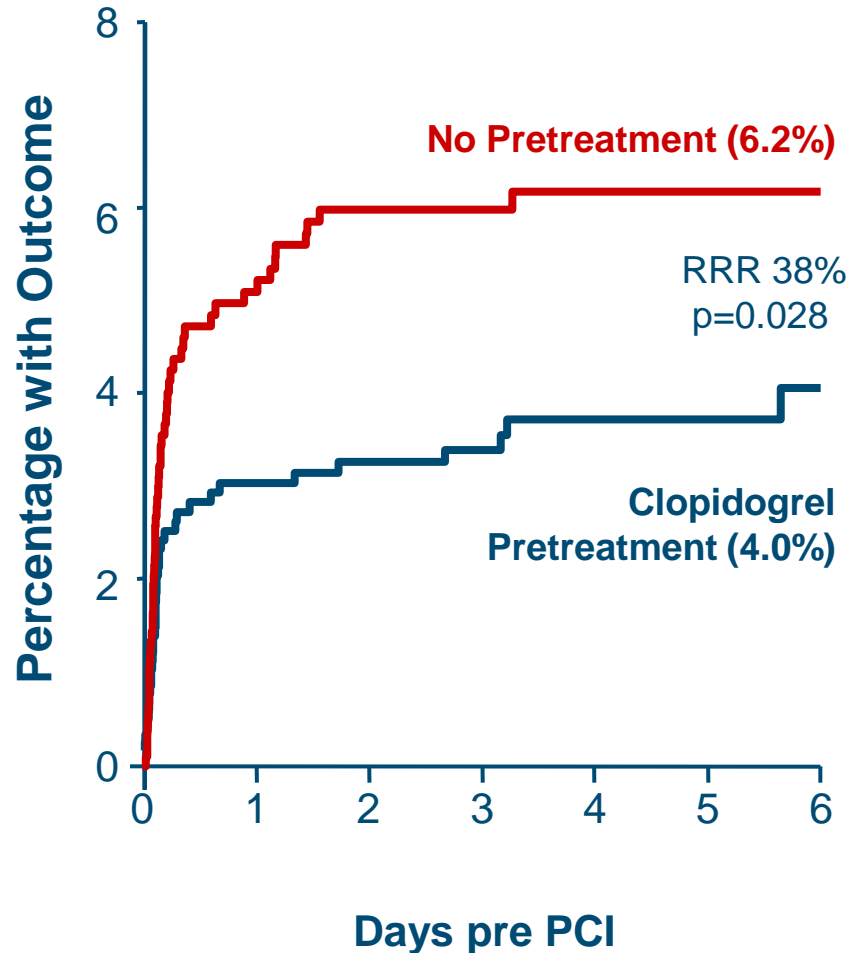
1. AAS 500 mg iv + Clopidogrel 600 mg p.o + Enoxaparina (30 mg iv + 60 mg sc.)
2. AAS 300 mg po + Clopidogrel 300 mg p.o + Enoxaparina (45mg sc.)
3. AAS 300 mg po + Prasugrel 60 mg + Fondaparinux 2,5 mg sc.
4. AAS 300 mg po + Ticagrelor 180 mg + Enoxaparina 40 mg sc.
5. Cualquiera de las anteriores sería válida

COMMIT: Effect of timing of clopidogrel treatment on STEMI outcomes (Death, re-infarction, stroke)

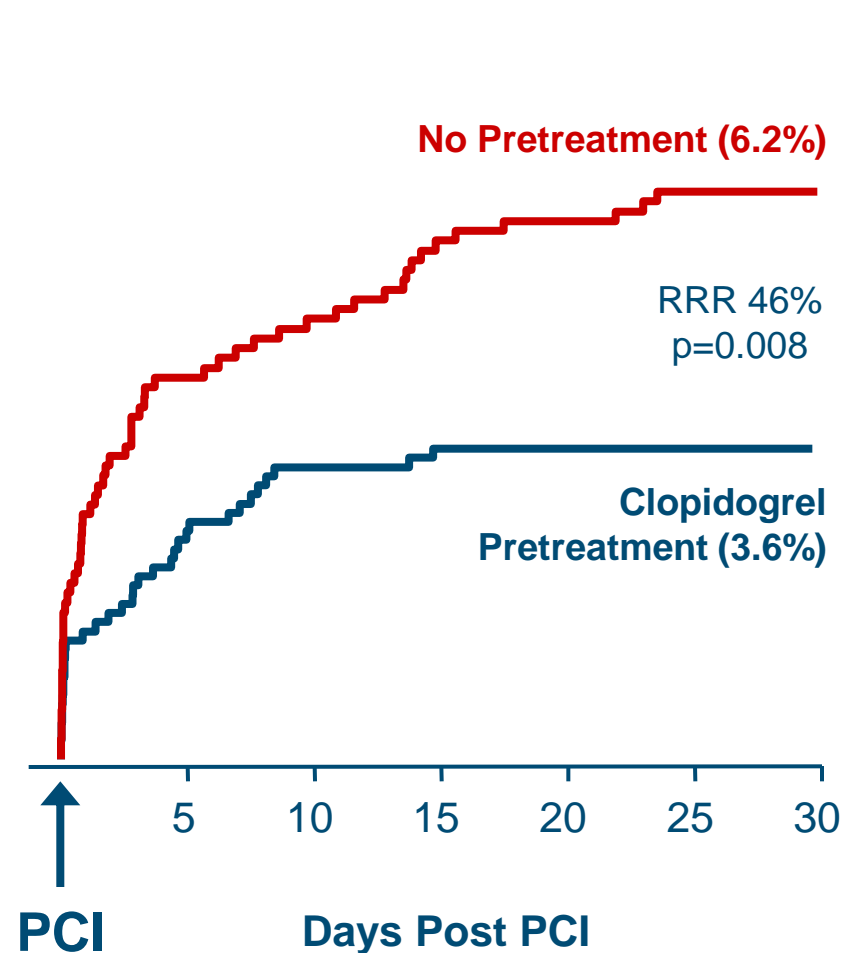


PCI-CLARITY: Effect of clopidogrel pretreatment on STEMI outcomes before and after PCI

Recurrent MI or stroke before PCI



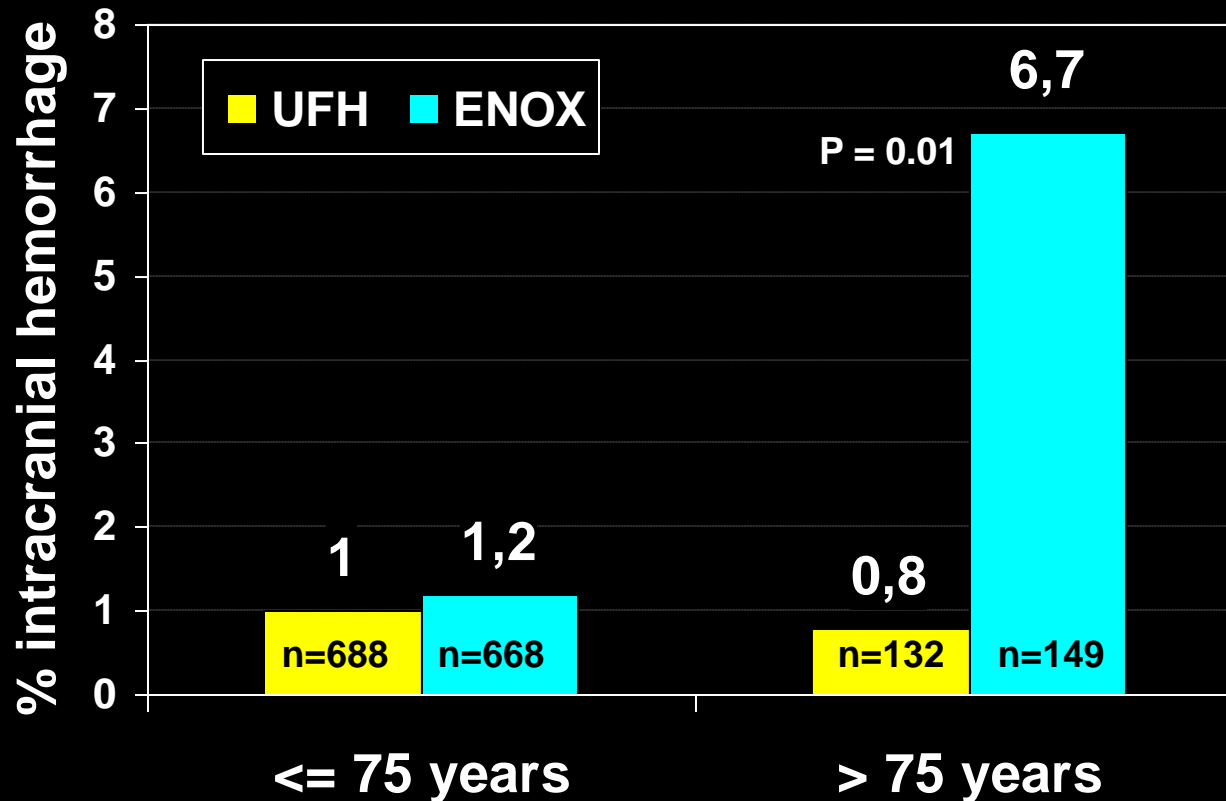
CV death, recurrent MI or stroke after PCI



FIBRINOLYSIS IN THE ELDERLY

Coadjuvant therapy: Enoxaparin vs UFH (ASSENT-3 Plus)

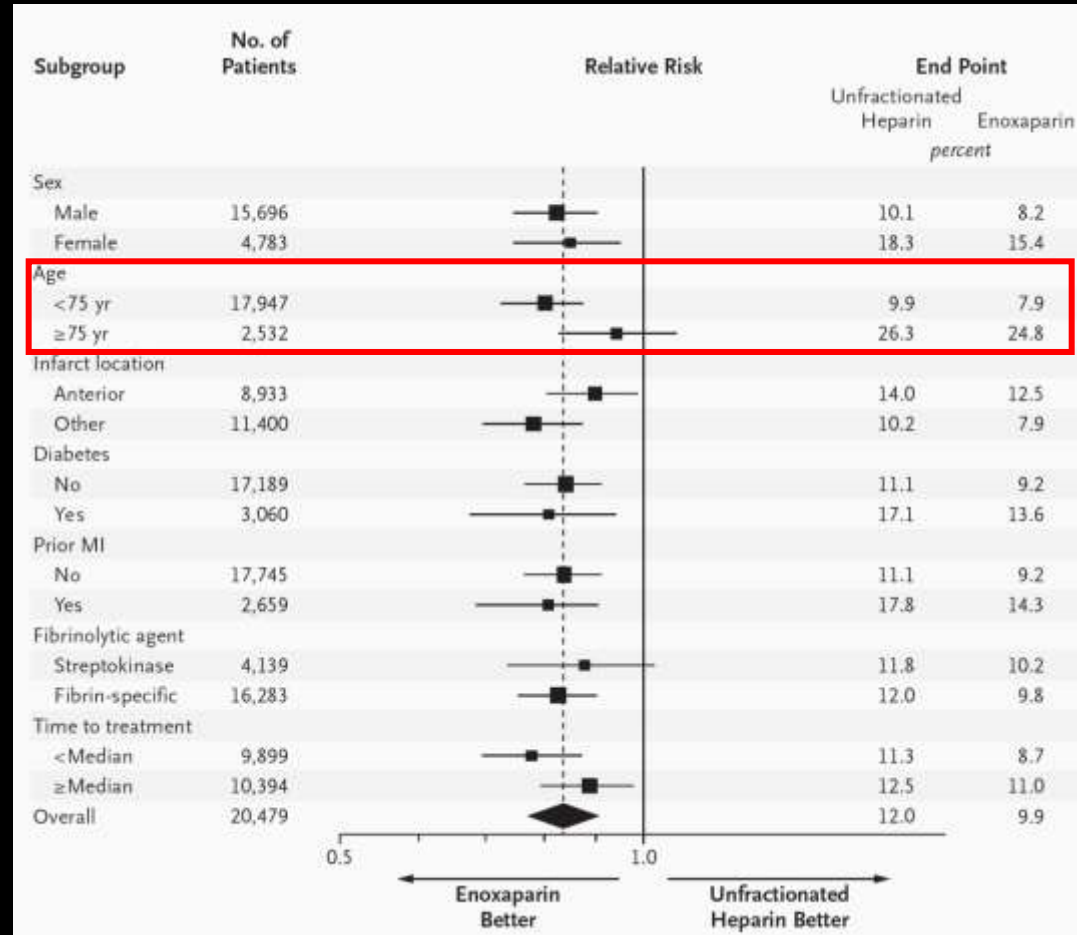
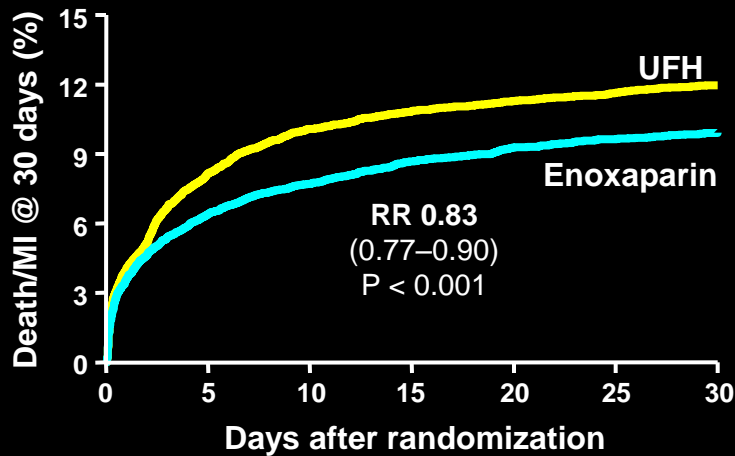
Enox: 30 mg iv + 1 mg/Kg/12 h



FIBRINOLYSIS IN THE ELDERLY

Coadjuvant therapy: Enoxaparin vs UFH (Extract-TIMI 25)

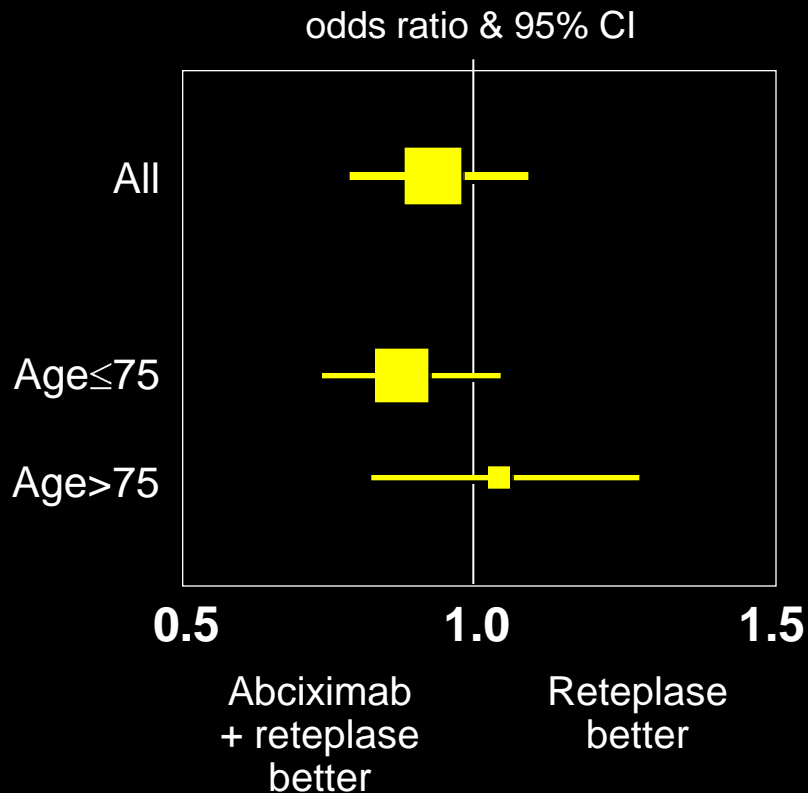
Enox (≥ 75 years): No bolus + 0.75 mg/Kg/12 h



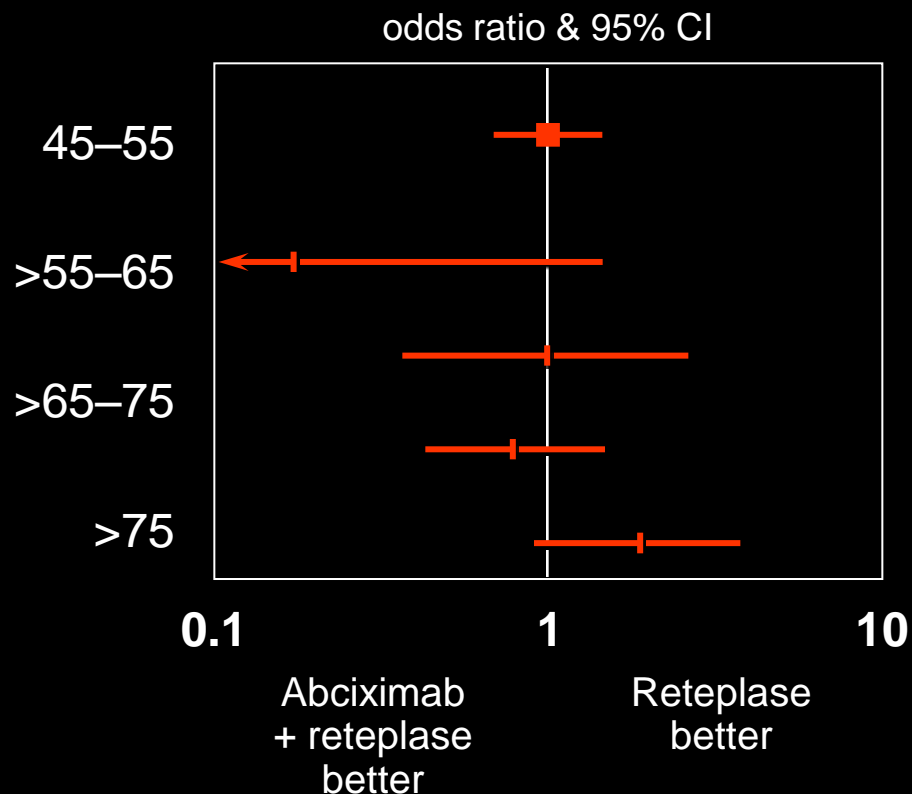
FIBRINOLYSIS IN THE ELDERLY

COMBINED THERAPY with Abciximab (GUSTO V – AMI)

Overall effect
(30-day mortality)

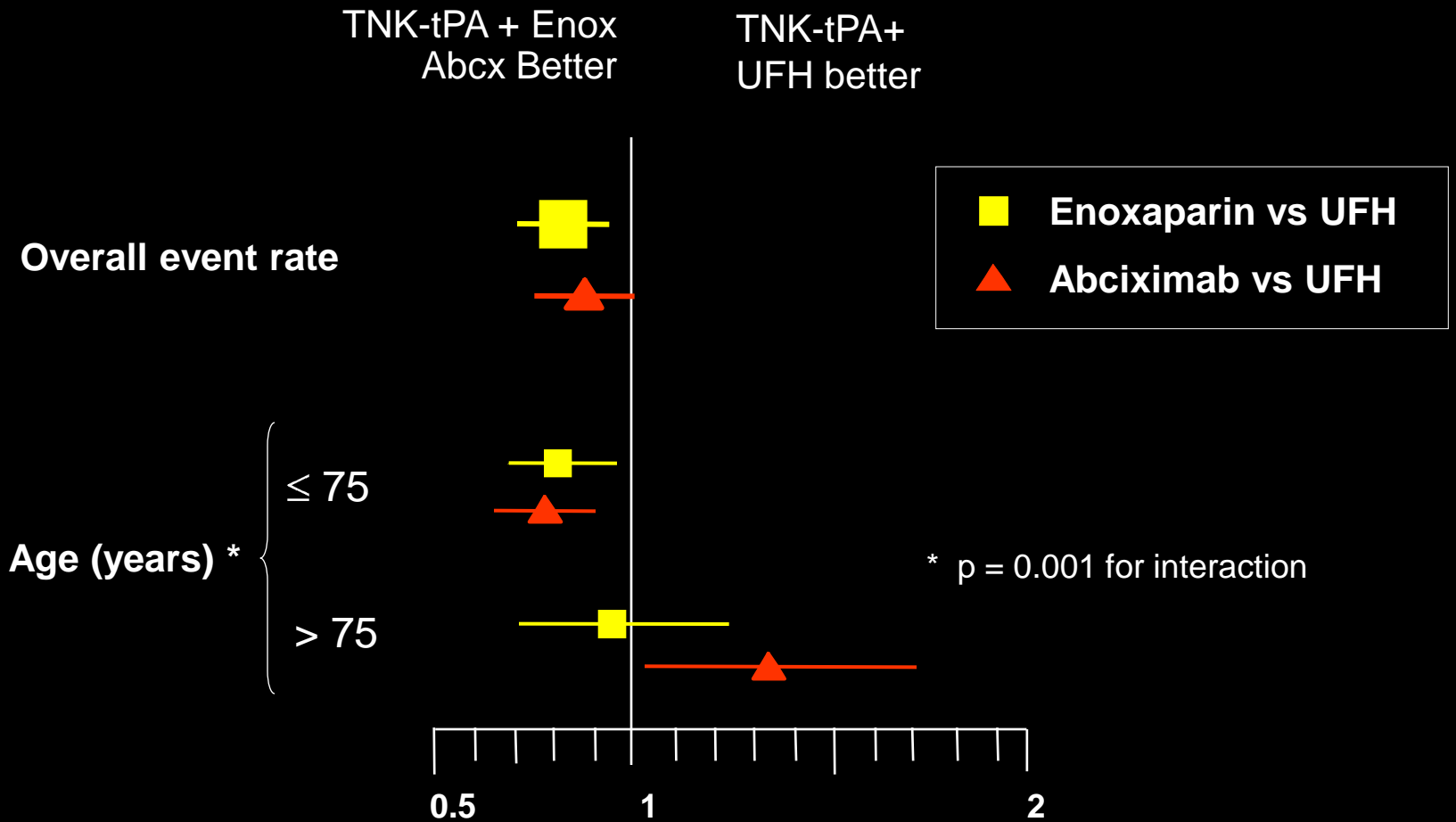


Intracranial hemorrhage rate



FIBRINOLYSIS IN THE ELDERLY

COMBINED THERAPY with Abciximab (ASSENT 4)



Primary efficacy and safety endpoint:
Death, recurrent MI, refractory ischaemia, ICH or other major bleeding

IAM con \uparrow ST

REPERFUSIÓN

Fibrinólisis

Angioplastia primaria

• Aspirina	300 / 100 mg		
• Clopidogrel	{	<75 años	Clopi 300 / 75 mg
			Enox 1mg/Kg/12h
• Enoxaparina	{	<75 años	Clopi 75 / 75 mg
			Enox 0,75 mg/Kg/12h

Angioplastia electiva

Angioplastia de rescate

**Si la opción fuera angioplastia primaria,
¿qué tratamiento antiagregante utilizarías?**

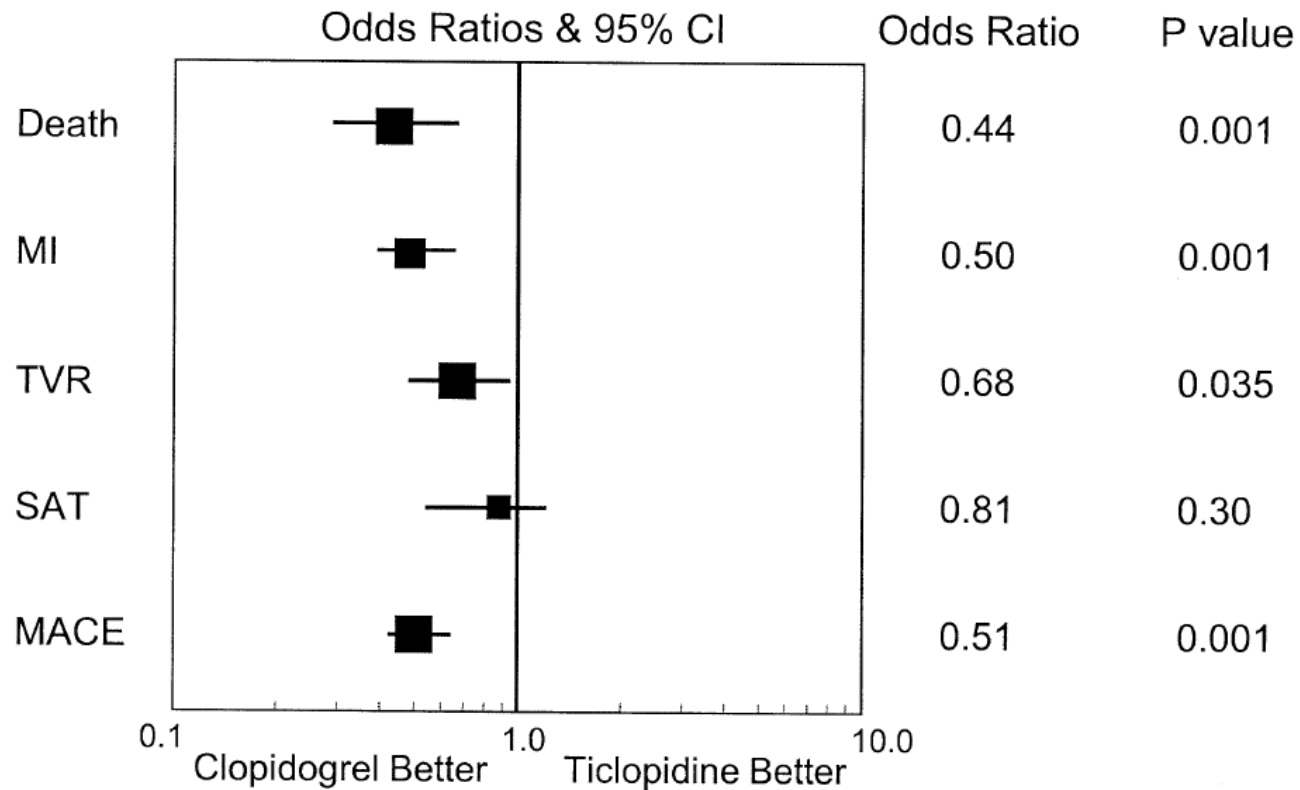
1. AAS 300 mg iv + Clopidogrel 600 mg p.o.
2. AAS 300 mg po + Clopidogrel 300 mg p.o. + Inh. GP IIb/IIIa
3. AAS 300 mg po + Prasugrel 60 mg
4. AAS 300 mg po + Ticagrelor 180 mg
5. Cualquiera de las anteriores sería válida

Table 12 Periprocedural antithrombotic medication in primary percutaneous coronary intervention

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-naïve patients, if no history of prior stroke/TIA, age <75 years.	I	B	109
• Ticagrelor:	I	B	110
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C	-
GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.	IIa	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
Options for GP IIb/IIIa inhibitors are (with LoE for each agent):			
• Abciximab		A	137
• Eptifibatid (with double bolus)		B	138, 139
• Tirofiban (with a high bolus dose)		B	140, 141
Anticoagulants			
An injectable anticoagulant must be used in primary PCI.	I	C	-
Bivalirudin (with use of GP IIb/IIIa blocker restricted to bailout) is recommended over unfractionated heparin and a GP IIb/IIIa blocker.	I	B	124
Enoxaparin (with or without routine GP IIb/IIIa blocker) may be preferred over unfractionated heparin.	IIb	B	122
Unfractionated heparin with or without routine GP IIb/IIIa blocker must be used in patients not receiving bivalirudin or enoxaparin.	I	C	I
Fondaparinux is not recommended for primary PCI.	III	B	118
The use of fibrinolysis before planned primary PCI is not recommended.	III	A	127, 143

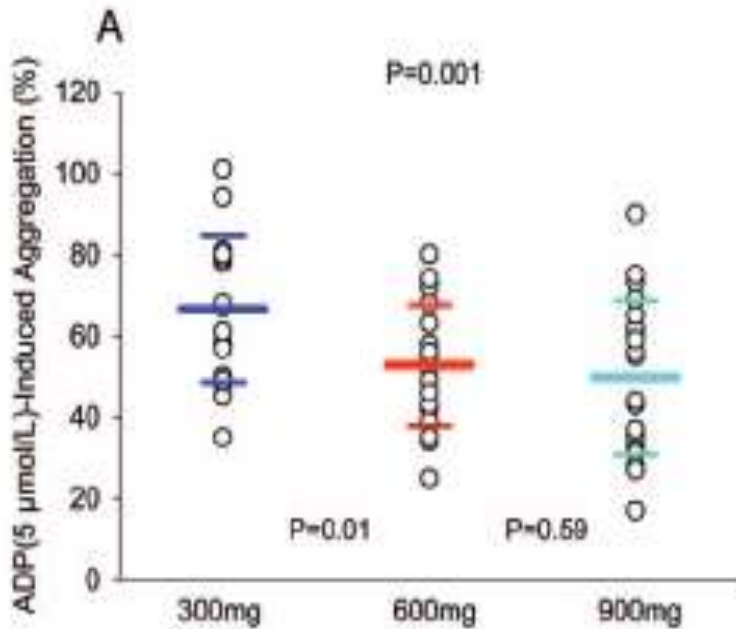
Efficacy of clopidogrel vs. ticlopidine in coronary stenting

Metanalysis

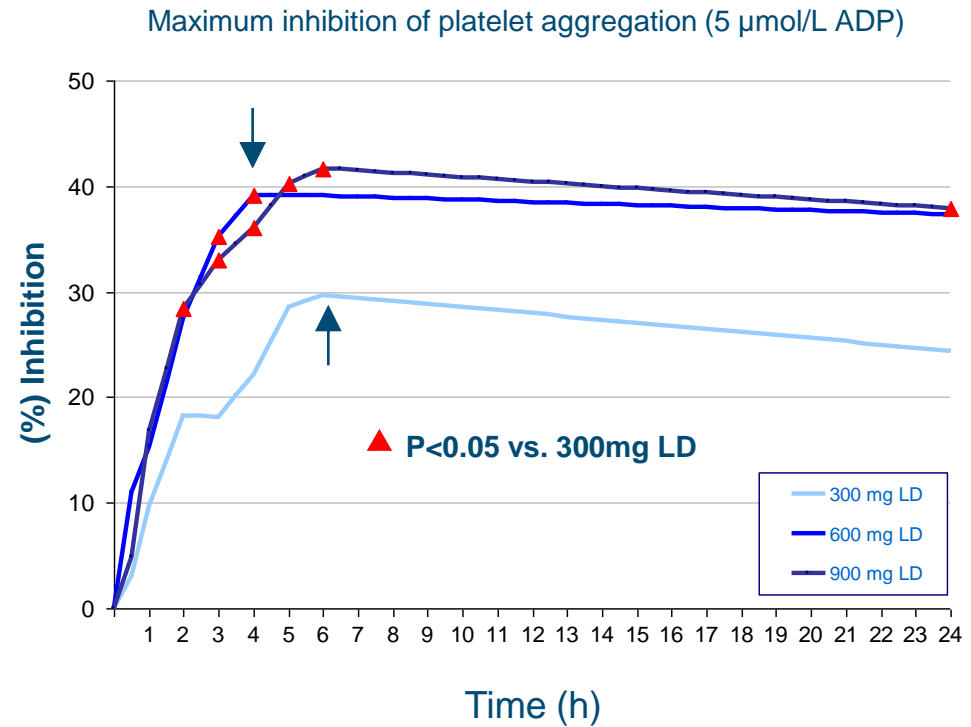


Effects of clopidogrel loading dose on platelet inhibition effect and timing

ISAR-CHOICE

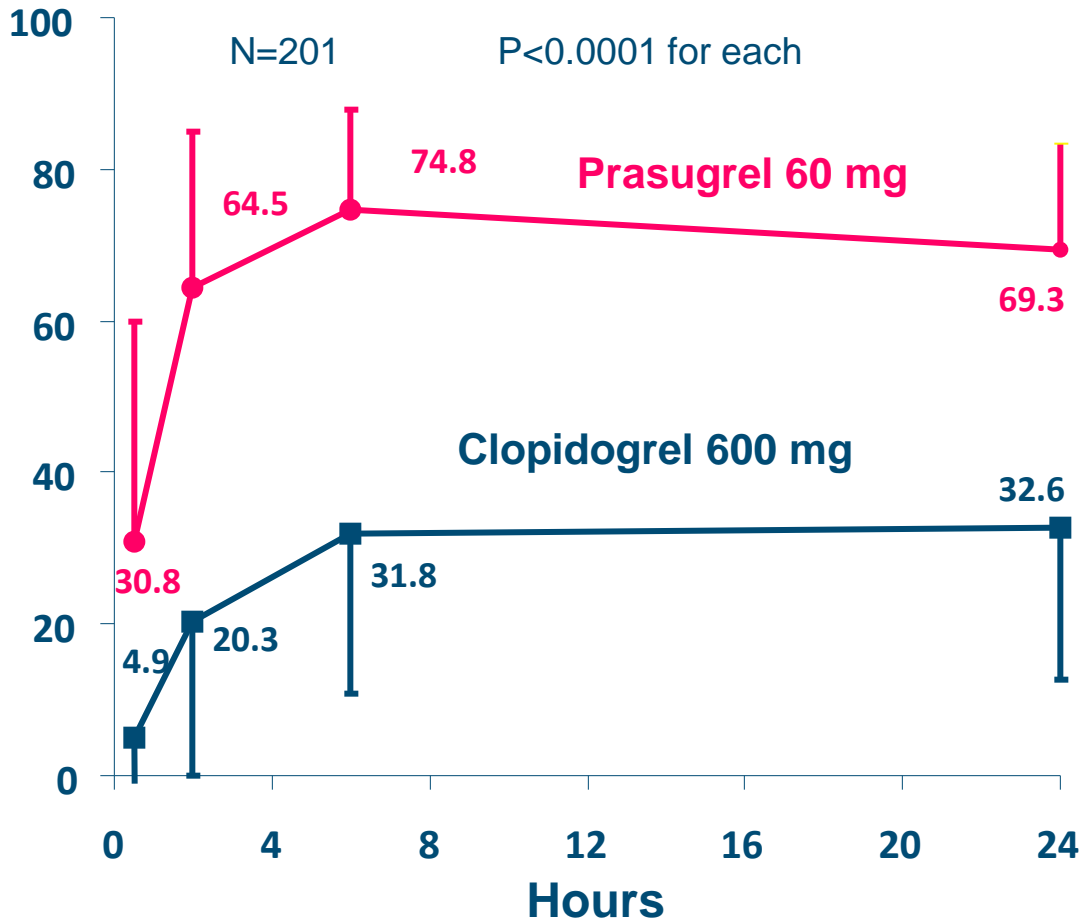


ALBION

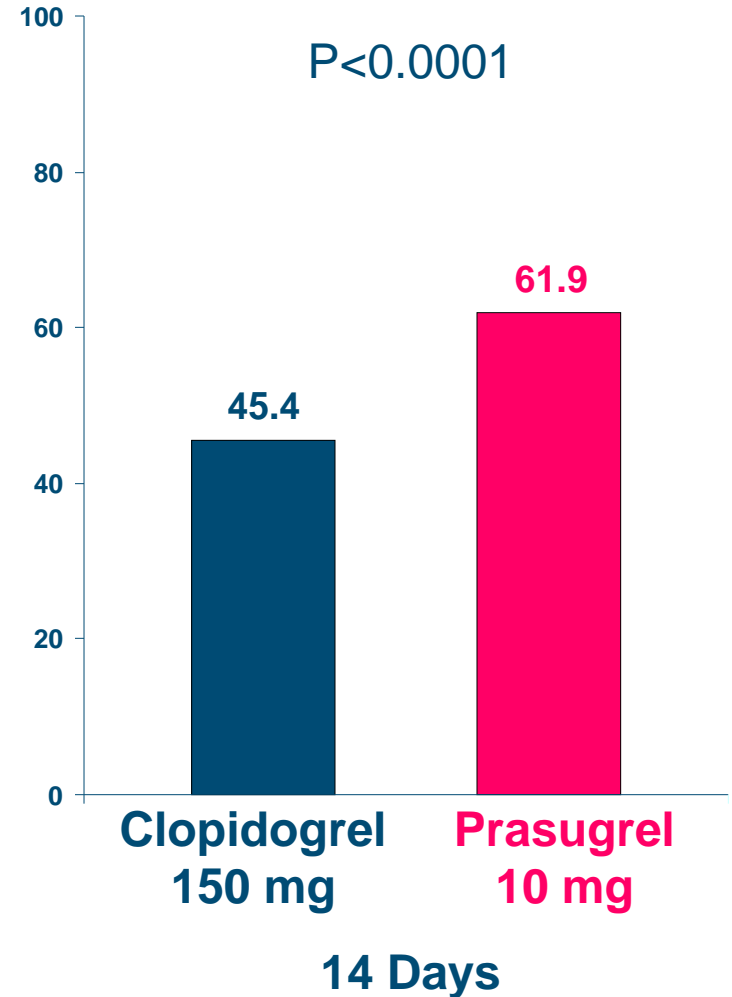


PRINCIPLE-TIMI 44: Effects of prasugrel and clopidogrel on IPA

IPA (%; 20 mM ADP)

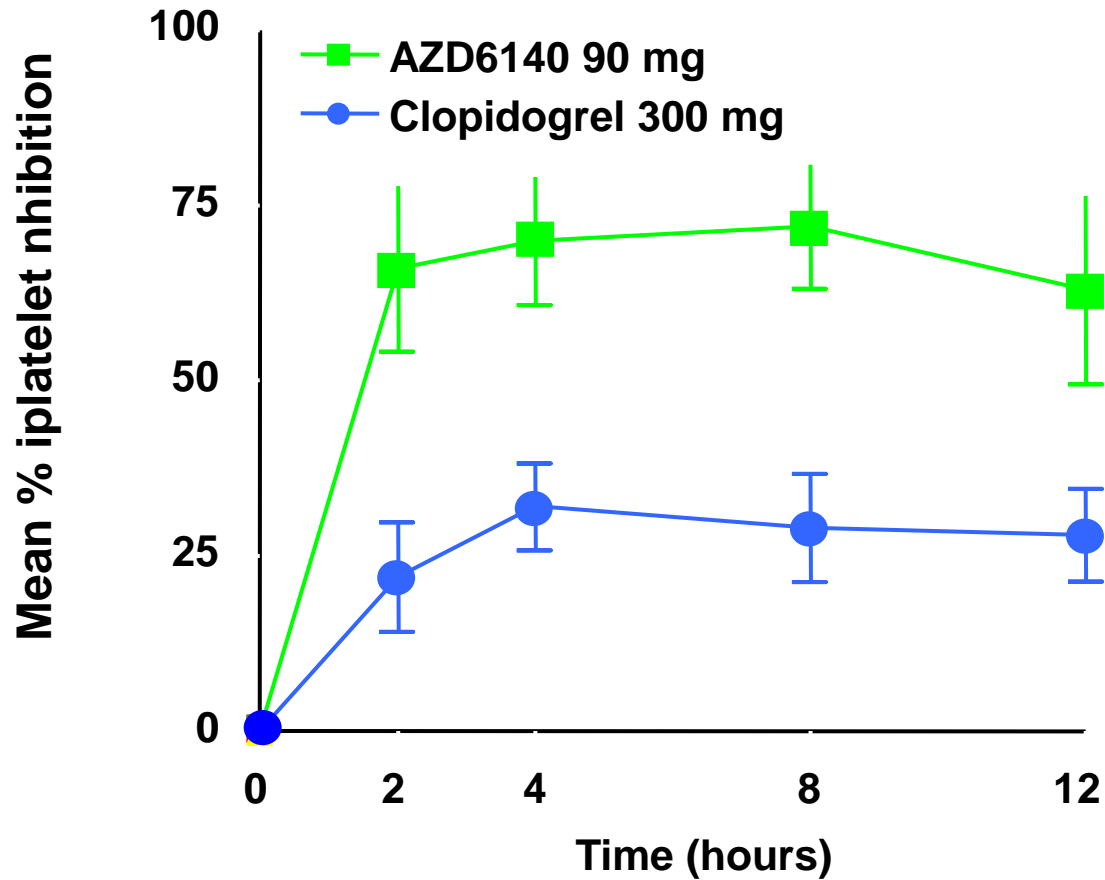


IPA (%; 20 mM ADP)

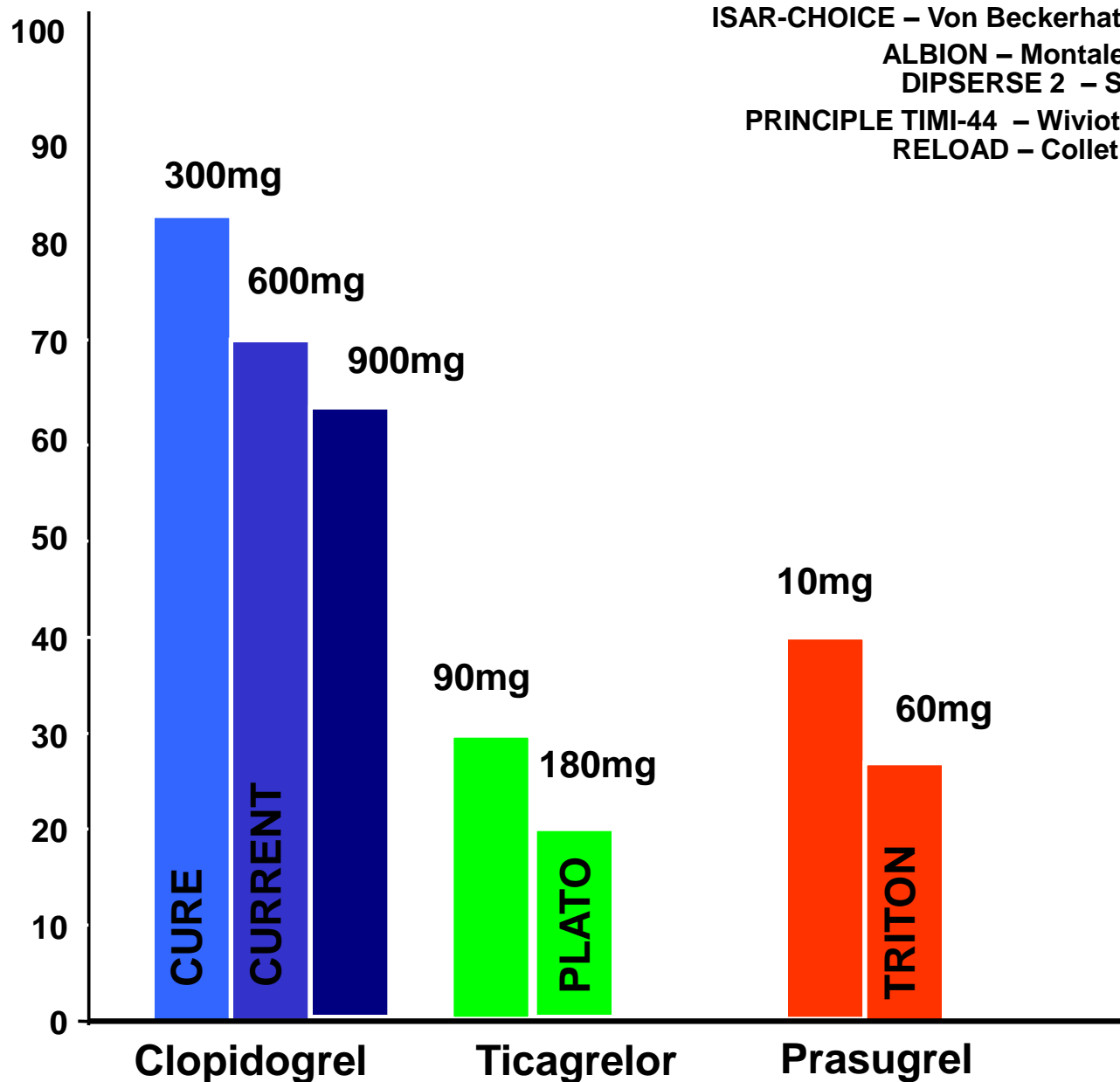


Ticagrelor 90mg vs Clopidogrel 300mg

(in NSTEMI-ACS Clopidogrel-Naïve Patients)



Platelet Aggregation at 4 hours



ISAR-CHOICE – Von Beckerhat et al .Circulation 2005

ALBION – Montalescot et al. JACC 2007

DIPSERSE 2 – Storey et al. JACC 2007

PRINCIPLE TIMI-44 – Wiviott et al. Circulation 2007

RELOAD – Collet et al. Circulation 2008

TRITON TIMI-38

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

26% STEMI

ASA

(75-162 mg/day)



Double-blind

n=13,500

CLOPIDOGREL

300 mg LD / 75 mg MD

PRASUGREL

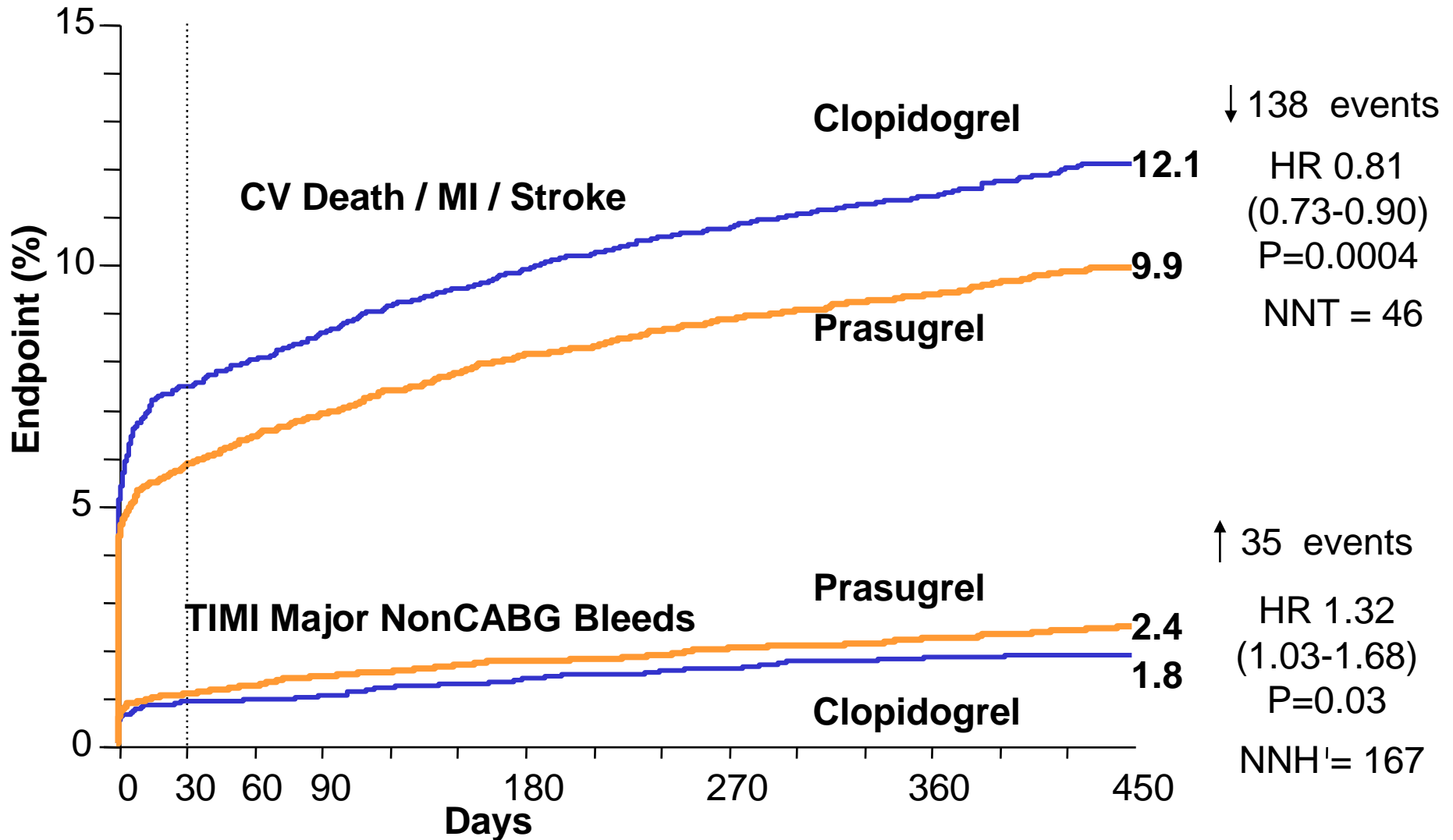
60 mg LD / 10 mg MD

Median duration of therapy: 12 months

1° endpoint:	Time to first: CV death, non-fatal MI, non-fatal stroke
2° endpoints:	CV death, MI, Stroke, Rehosp-Recurrent Ischemia CV death, MI, UTVR / Stent thrombosis
Safety endpoints:	Non-CABG related TIMI major bleeding / life-threatening bleeding / TIMI major+minor bleeding

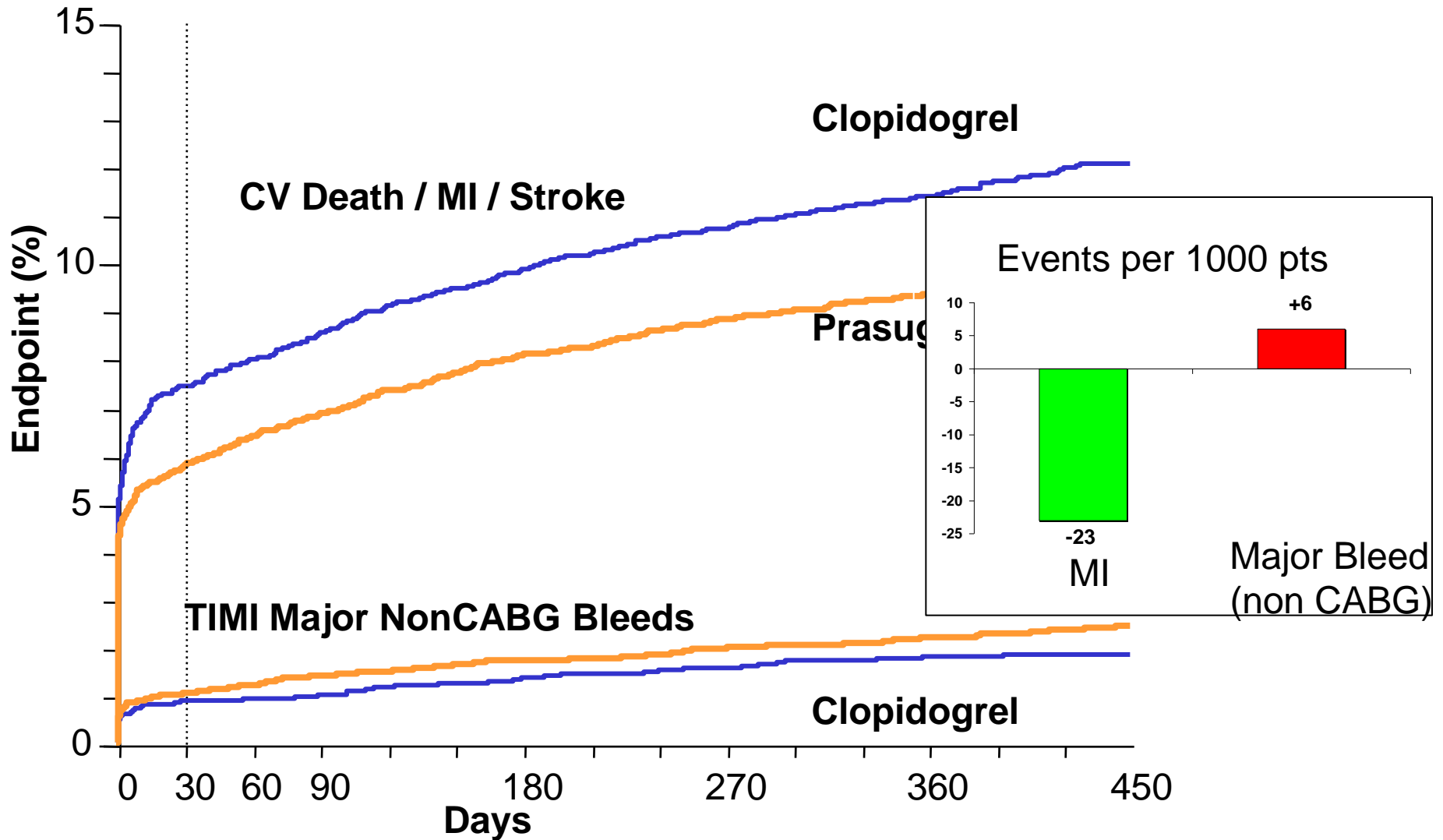
TRITON TIMI-38

Balance of Efficacy and Safety



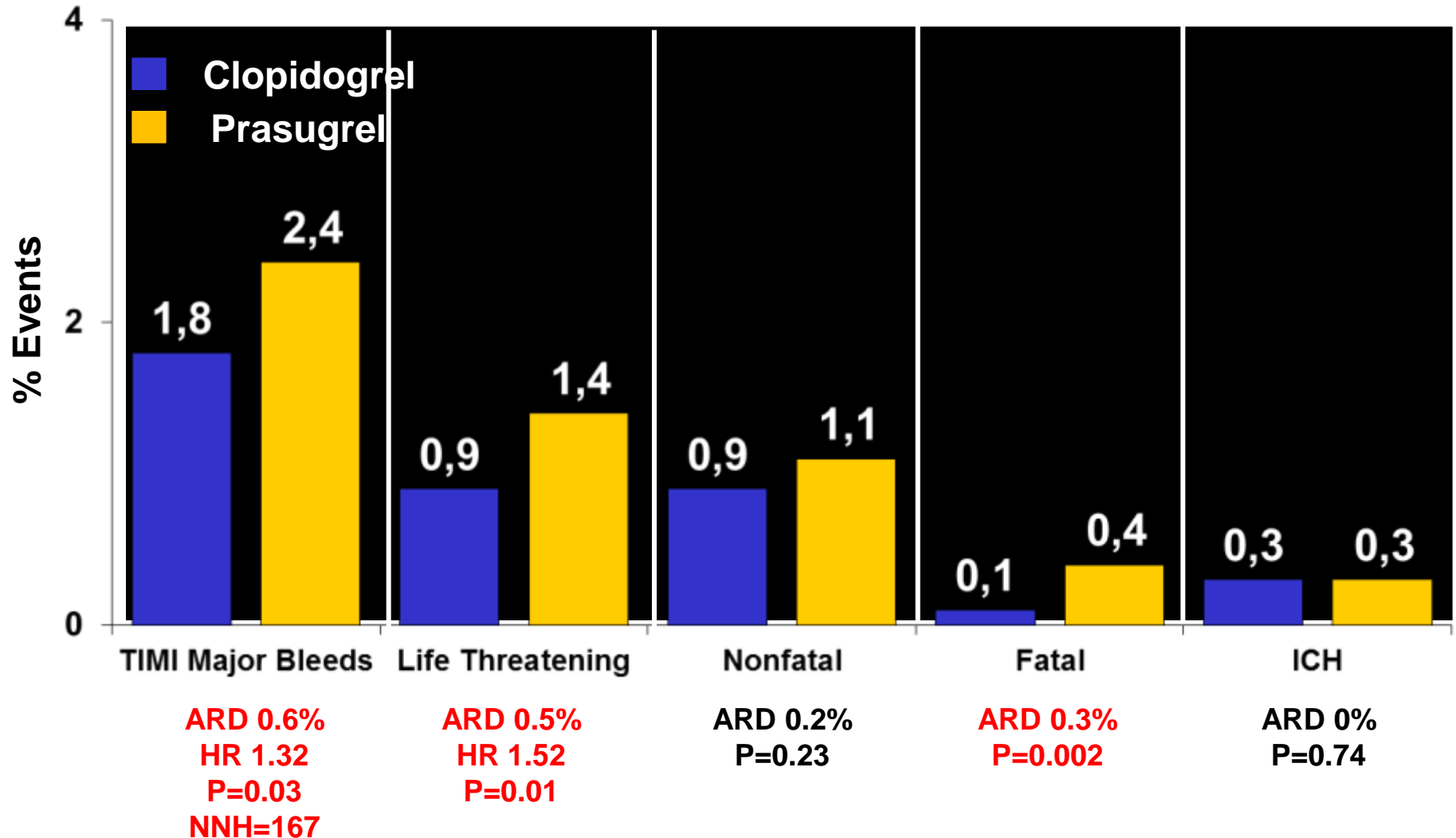
TRITON TIMI-38

Balance of Efficacy and Safety



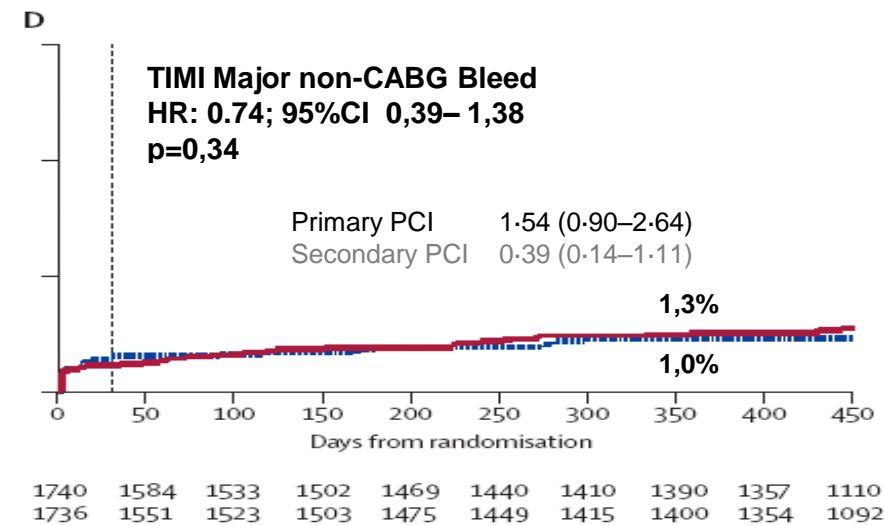
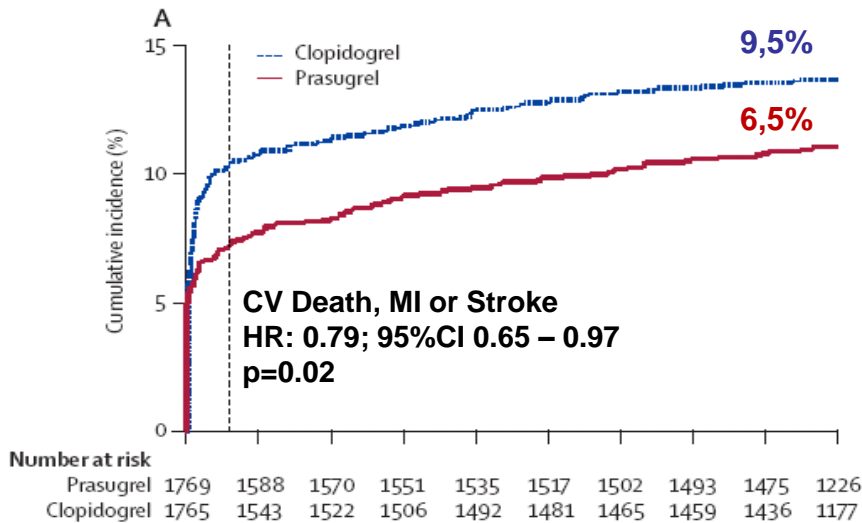
TRITON TIMI-38

Bleeding Events (Safety Cohort)



Población con STEMI

TRITON-TIMI 38 (Montalescot G. Lancet 209;373:723-731)

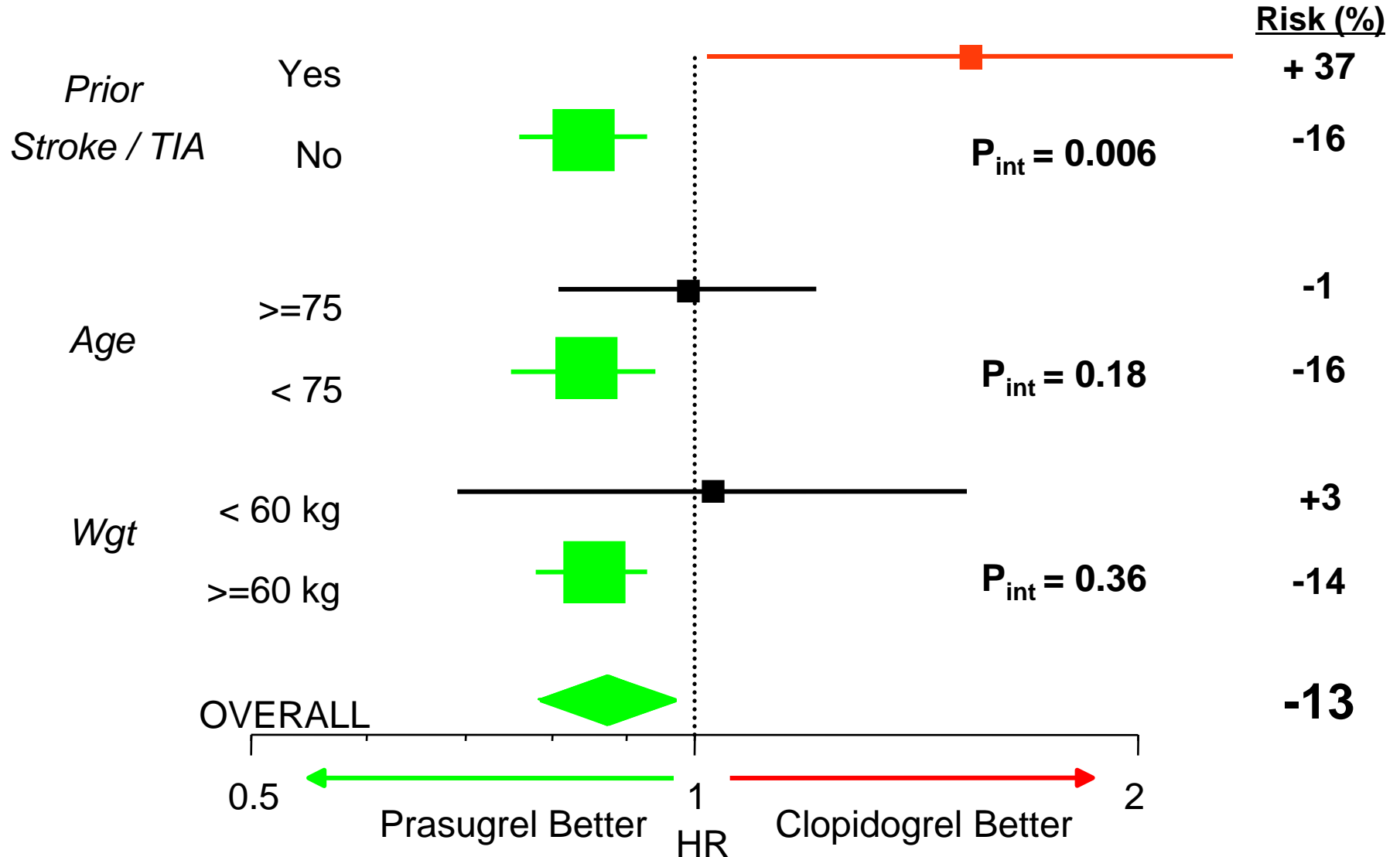


Primary PCI
0.87 (0.68–1.11)

Secondary PCI
0.65 (0.46–0.92)

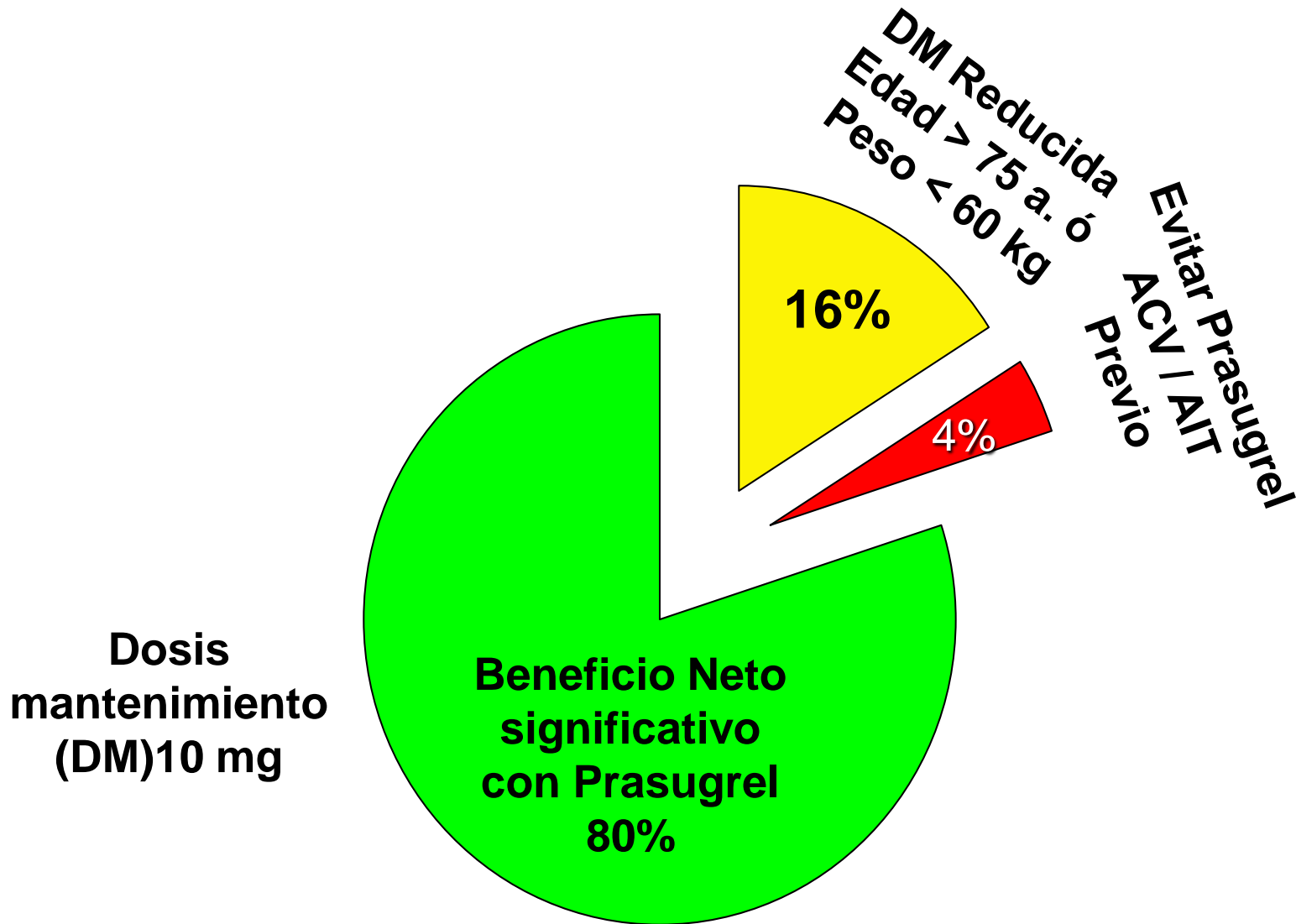
TRITON TIMI-38

Net Clinical Benefit Bleeding Risk Subgroups



TRITON TIMI-38: Subgrupos de Sangrado

Implicaciones terapéuticas



TRITON TIMI-38

Baseline Characteristics

	Clopidogrel (n=6795) %	Prasugrel (n=6813) %
UA/NSTEMI	74	74
STEMI	26	26
Age, median (IQR)	61 (53,69) y	61 (53, 70) y
≥75 y	13	13
Wgt, median (IQR)	83 kg (72, 92)	84 kg (73, 93)
< 60 kg	5.3	4.6
Female	27	25*
Diabetes	23	23
Prior MI	18	18
CrCl (ml/min) <60	12	11

PLATO: Diseño del Estudio

SCASEST (riesgo moderado/alto) y SCACEST (si PCI primaria)
aleatorizados en <24 horas desde evento índice
Todos recibiendo AAS - Tratados previamente con Clopidogrel o no;
(N=18,624)

38% STEMI

Clopidogrel

Pretratados: no carga adicional,
No pretratados: 300/600-mg dosis carga
+ 75-mg/24 h mantenimiento

Ticagrelor

180-mg dosis de carga
+ 90-mg/12 h mantenimiento
(90mg adicional si ICP>24 horas)

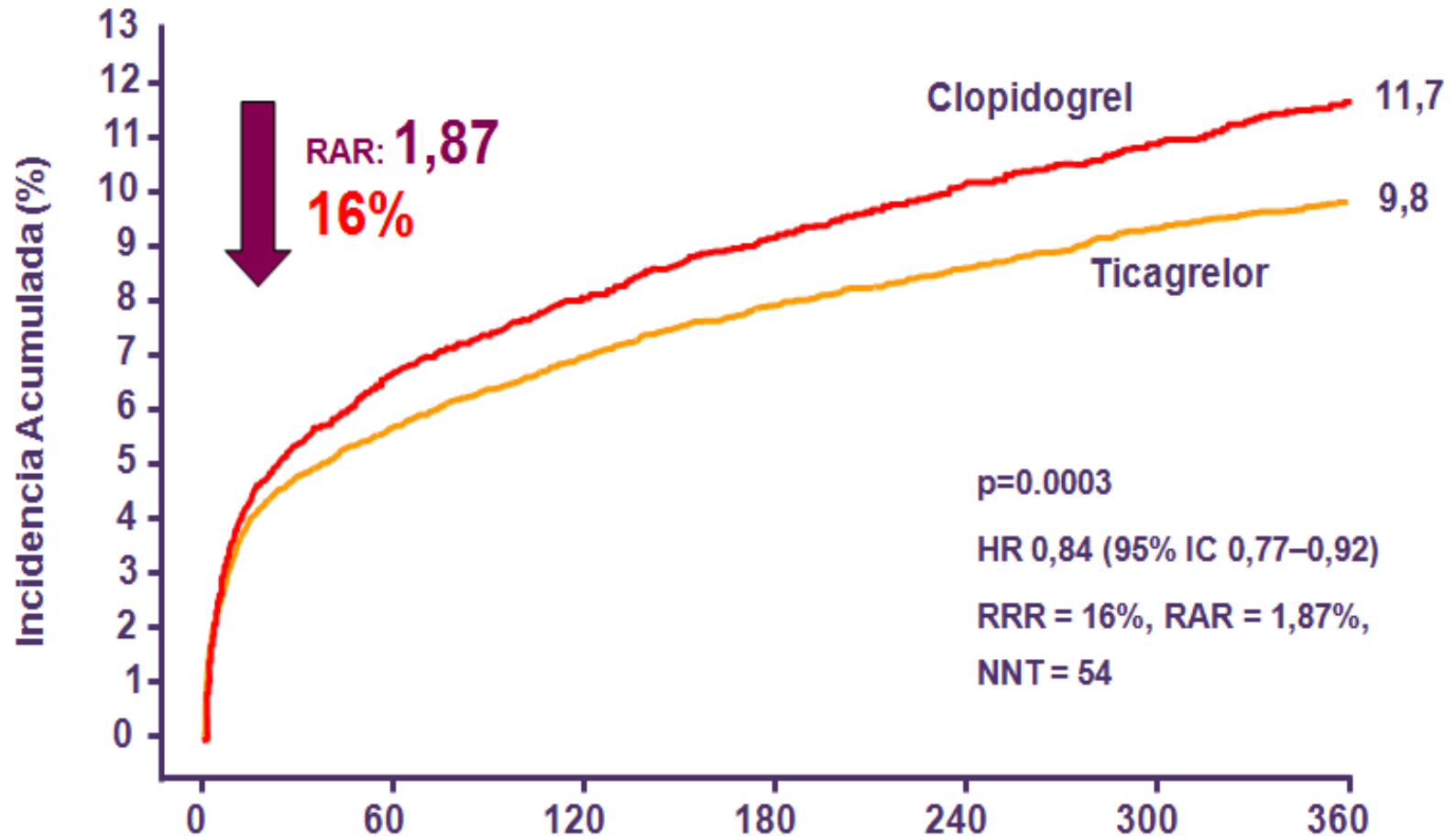
6-12 meses de tratamiento

Objetivo Primario de eficacia: Muerte CV + IAM + ACV

Objetivo Primario de Seguridad: Sangrado mayor total

PLATO: Objetivo Primario de Eficacia

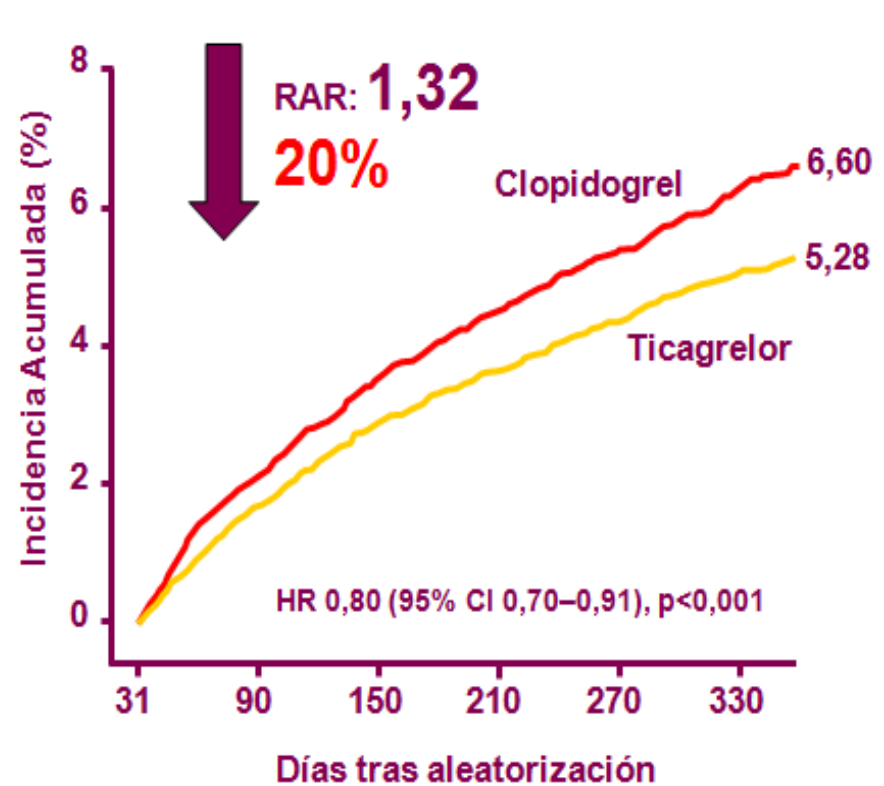
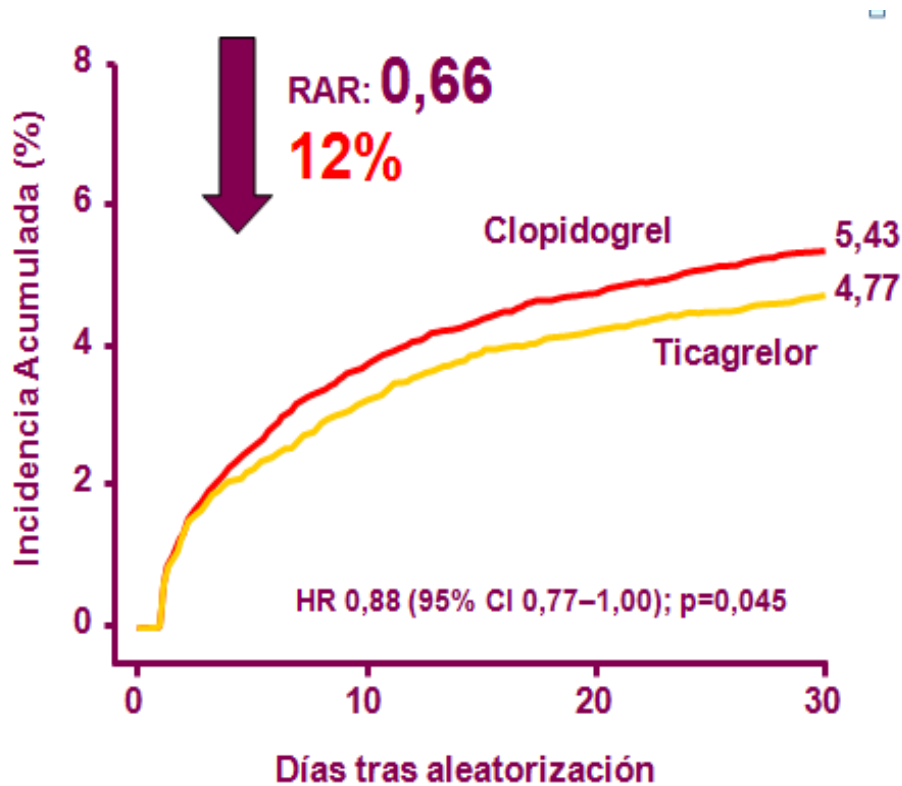
Tiempo hasta objetivo primario (Muerte CV, IAM ó ACV)



No. en riesgo

	0	60	120	180	240	300	360
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

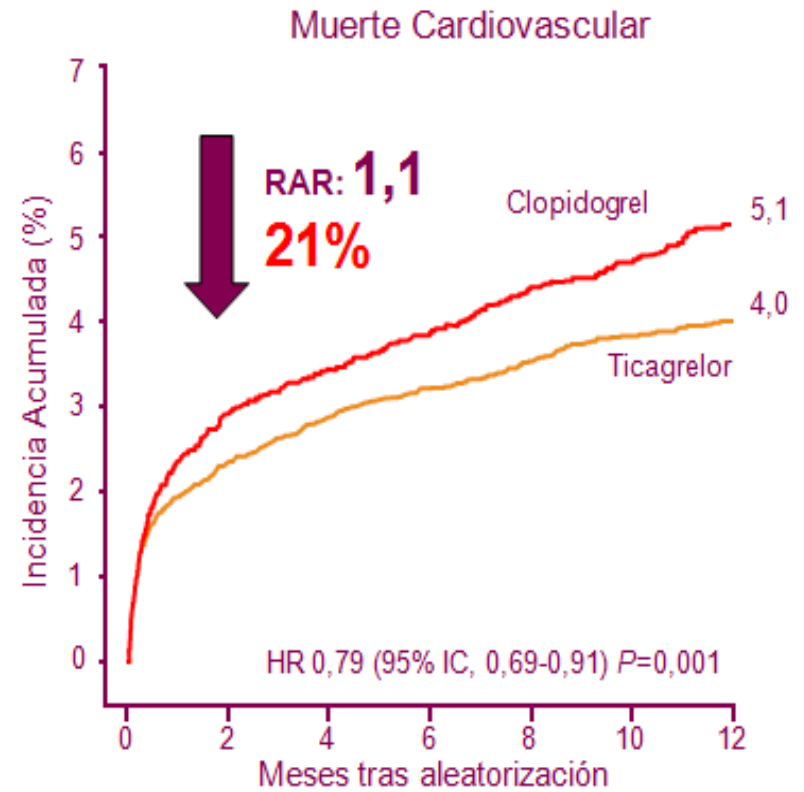
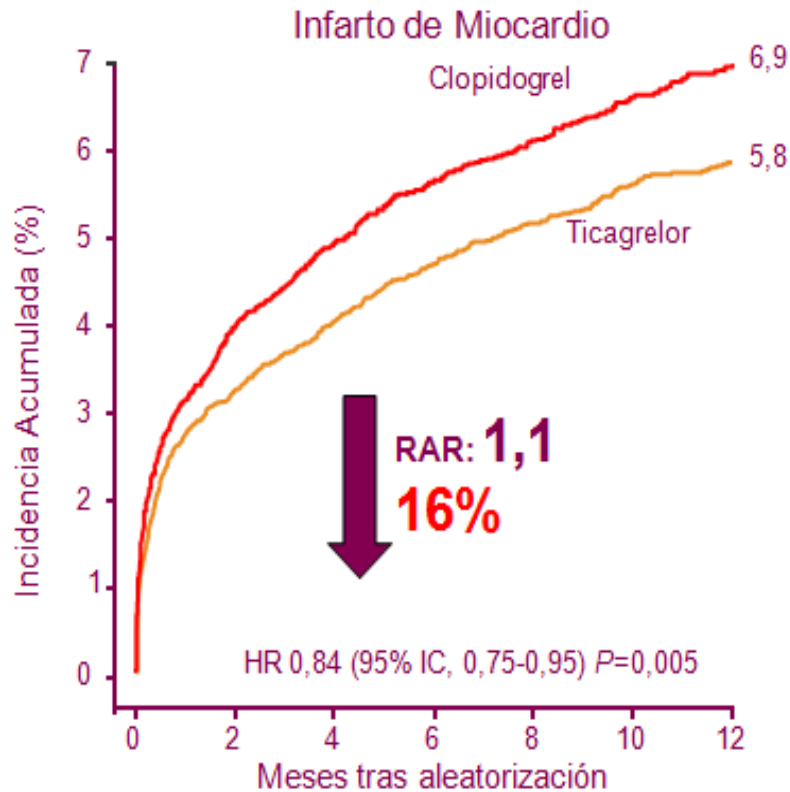
PLATO: Objetivo Primario de Eficacia en tiempo



No. en Riesgo

Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

PLATO: Objetivos Secundarios de Eficacia



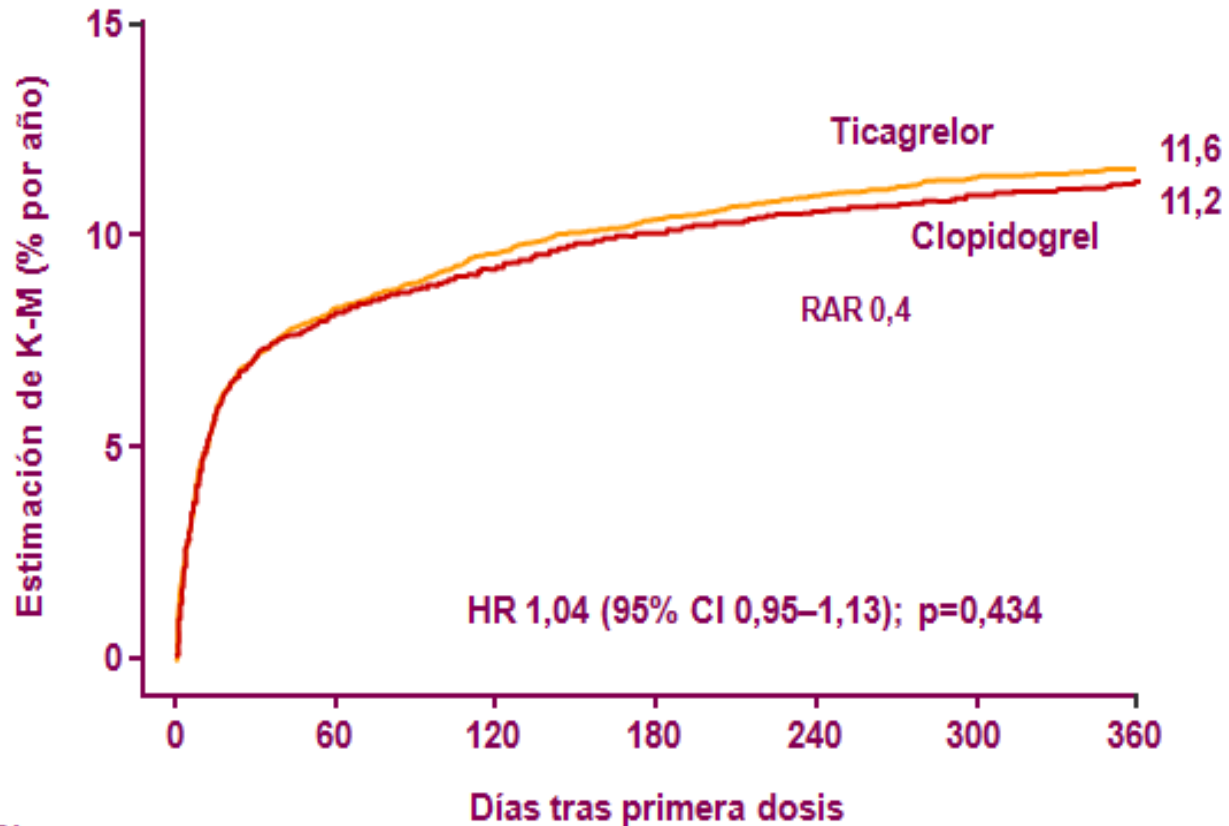
No. en riesgo

Ticagrelor	9333	8678	8520	8279	6796	5210	4191
Clopidogrel	9291	8560	8405	8177	6703	5136	4109

9333	8294	8822	8626	7119	5482	4419
9291	8865	8780	8589	7079	5441	4364

PLATO: Objetivo Primario de Seguridad

Sangrados Mayores Totales Criterio PLATO

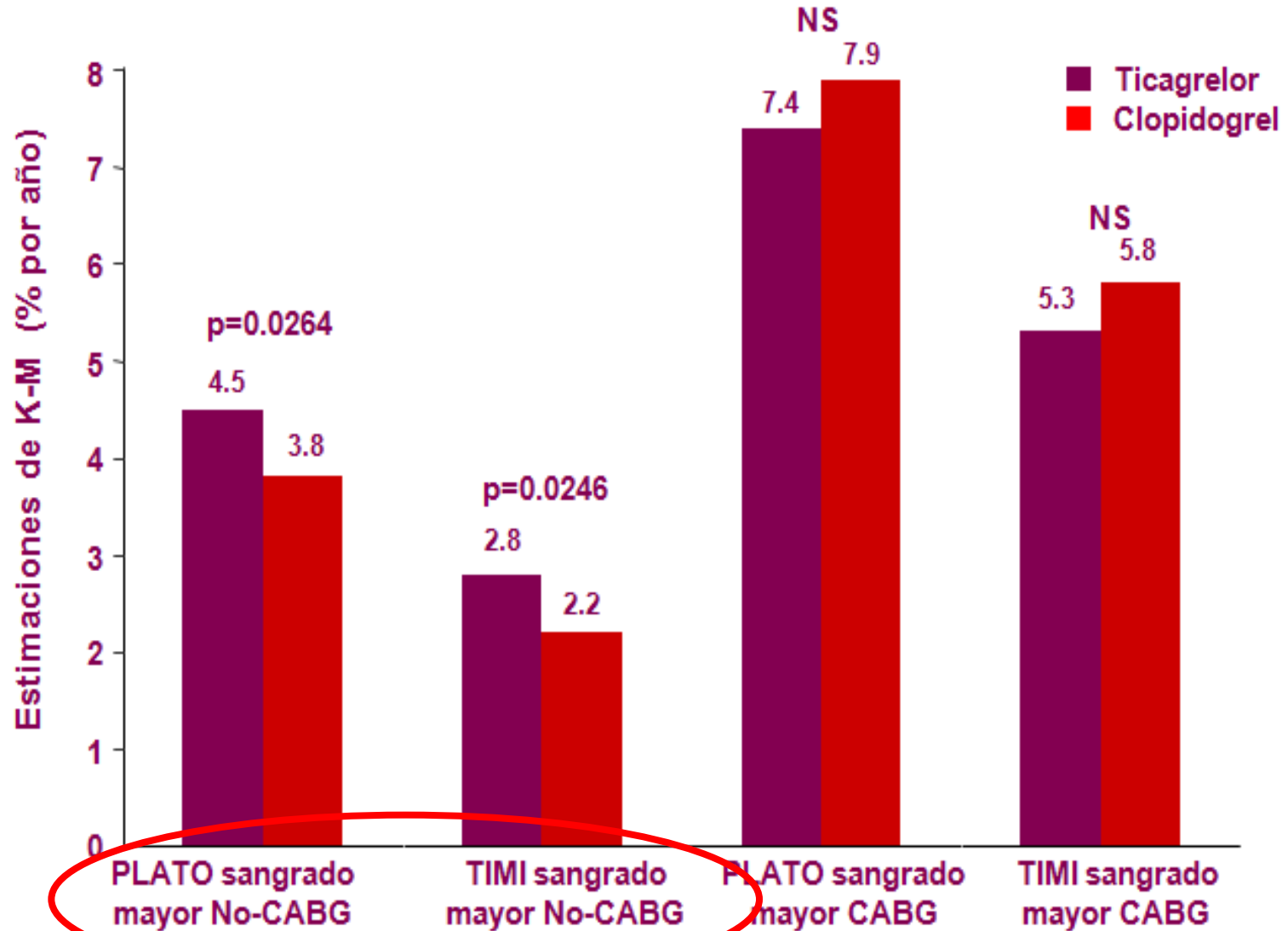


No. en Riesgo

Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

PLATO: Objetivos Secundarios de Seguridad

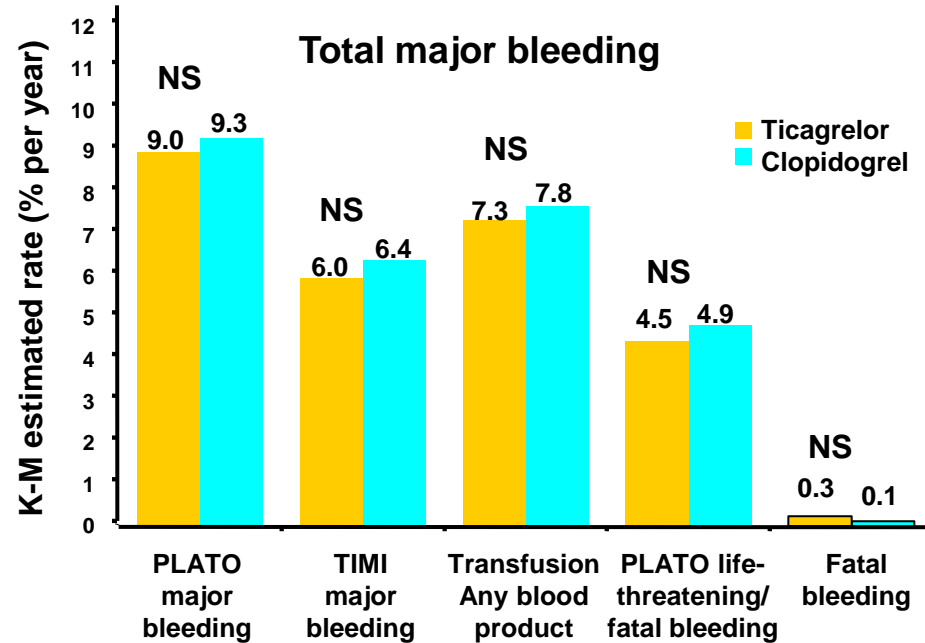
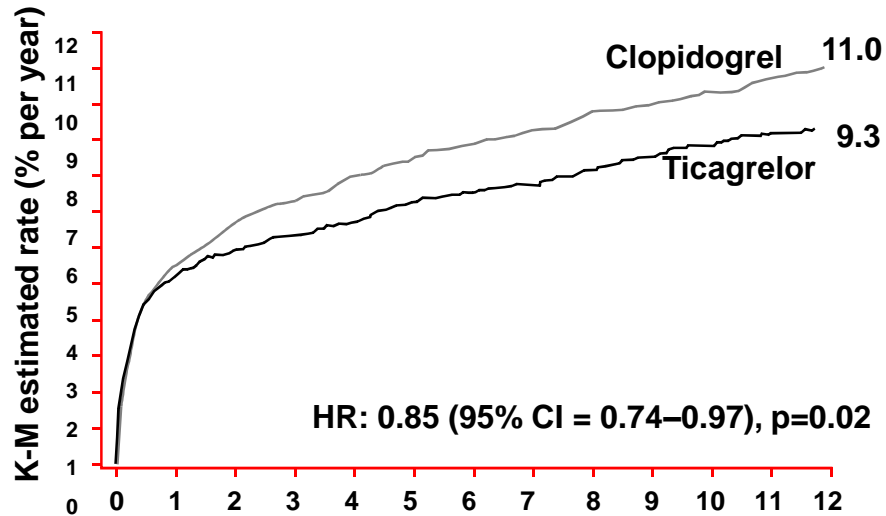
Sangrados Mayores No relacionados y relacionados con CABG



Población con STEMI

PLATO (Steg PG. Circulation 2010;122:2131-41)

Primary endpoint: CV death, MI or stroke



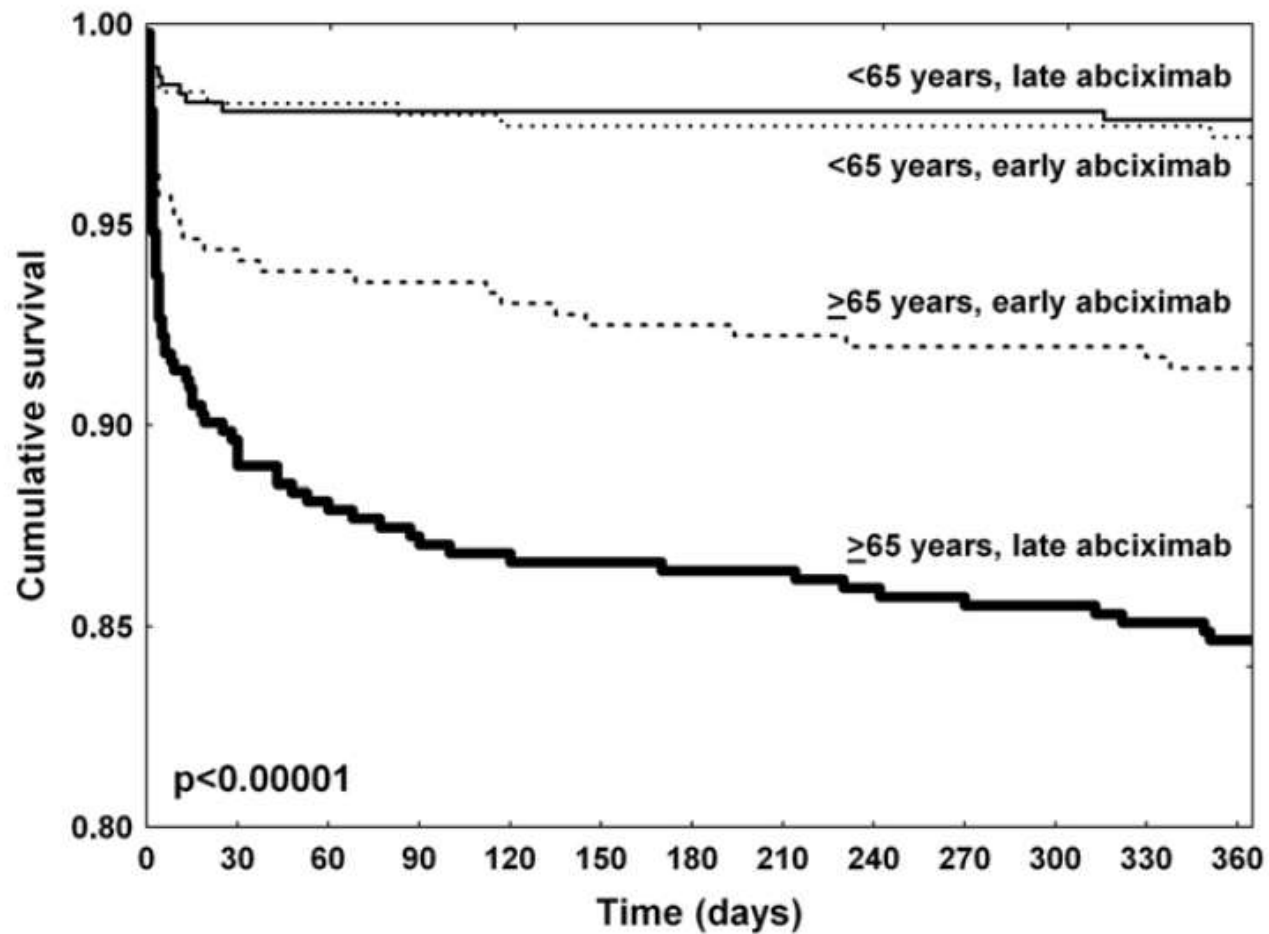
**Si la opción fuera angioplastia primaria,
¿como plantearía iniciar el antitrombótico?**

1. Iniciar tratamiento básico (AAS, NTG, morfina) y esperar al resultado de la coronariografía para completarlo
2. Iniciar tratamiento antiagregante y anticoagulante completo ya
3. Iniciar tratamiento básico y completarlo durante el traslado en la UVI móvil
4. Cualquiera es válido
5. No tengo ni idea

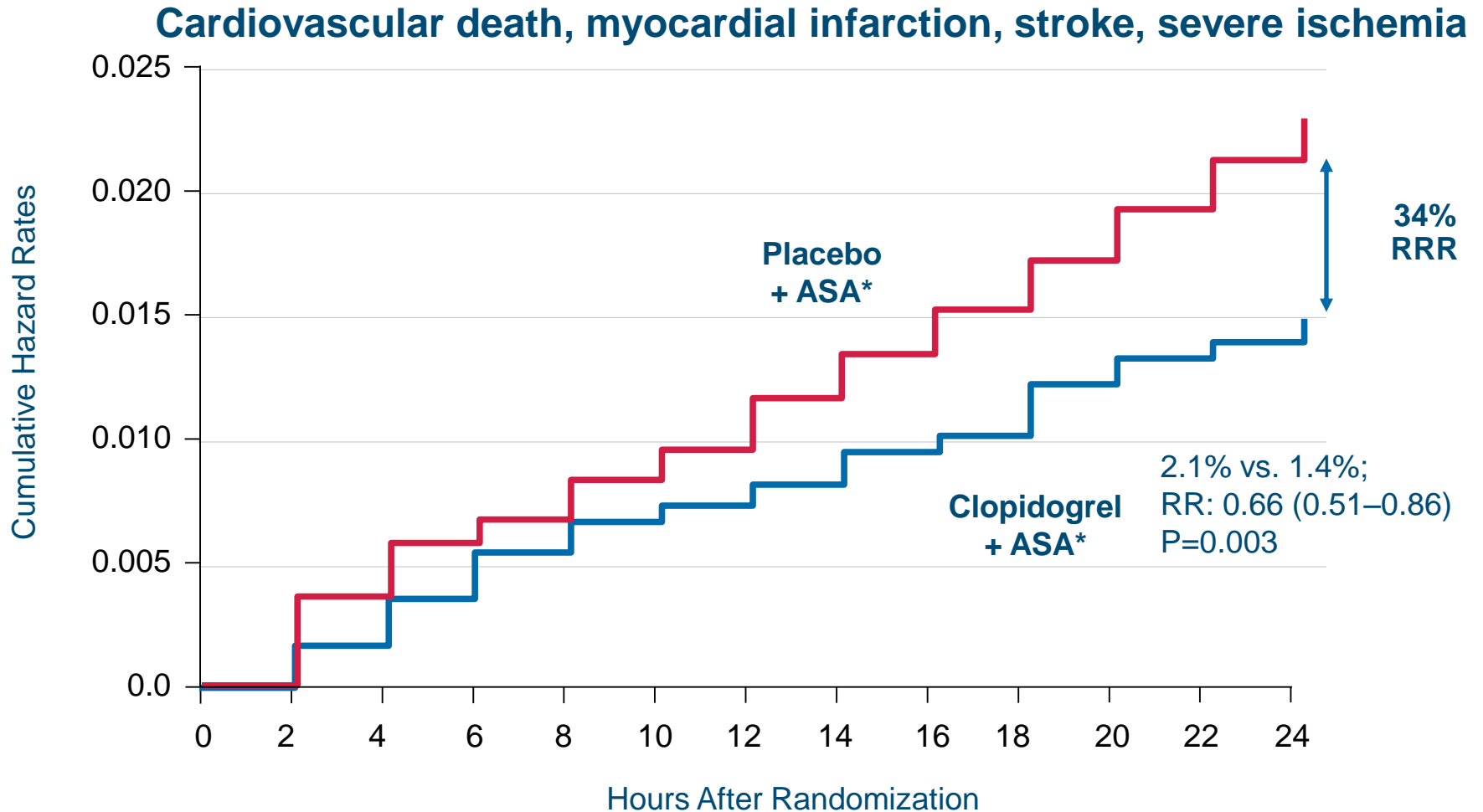
Table 12 Periprocedural antithrombotic medication in primary percutaneous coronary intervention

Recommendations	Class ^a	Level ^b	Ref ^c
Antiplatelet therapy			
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An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A	135, 136
• Prasugrel in clopidogrel-naïve patients, if no history of prior stroke/TIA, age <75 years.	I	B	109
• Ticagrelor.	I	B	110
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C	-
GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.	IIa	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
Options for GP IIb/IIIa inhibitors are (with LoE for each agent):			
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Anticoagulants			
An injectable anticoagulant must be used in primary PCI.	I	C	-
Bivalirudin (with use of GP IIb/IIIa blocker restricted to bailout) is recommended over unfractionated heparin and a GP IIb/IIIa blocker.	I	B	124
Enoxaparin (with or without routine GP IIb/IIIa blocker) may be preferred over unfractionated heparin.	IIb	B	122
Unfractionated heparin with or without routine GP IIb/IIIa blocker must be used in patients not receiving bivalirudin or enoxaparin.	I	C	I
Fondaparinux is not recommended for primary PCI.	III	B	118
The use of fibrinolysis before planned primary PCI is not recommended.	III	A	127, 143

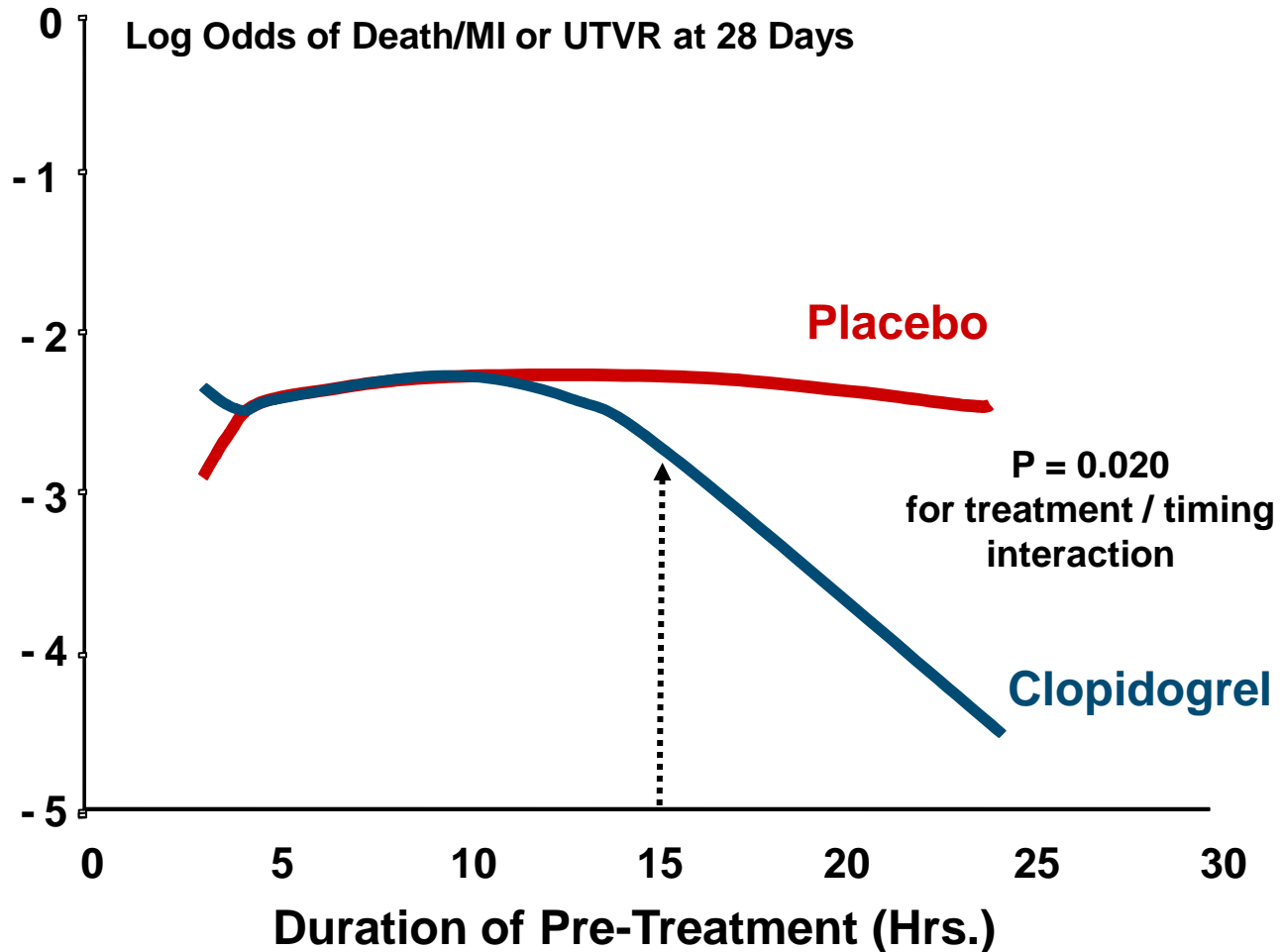
ABCIXIMAB BEFORE PCI (EUROTRANSFER)



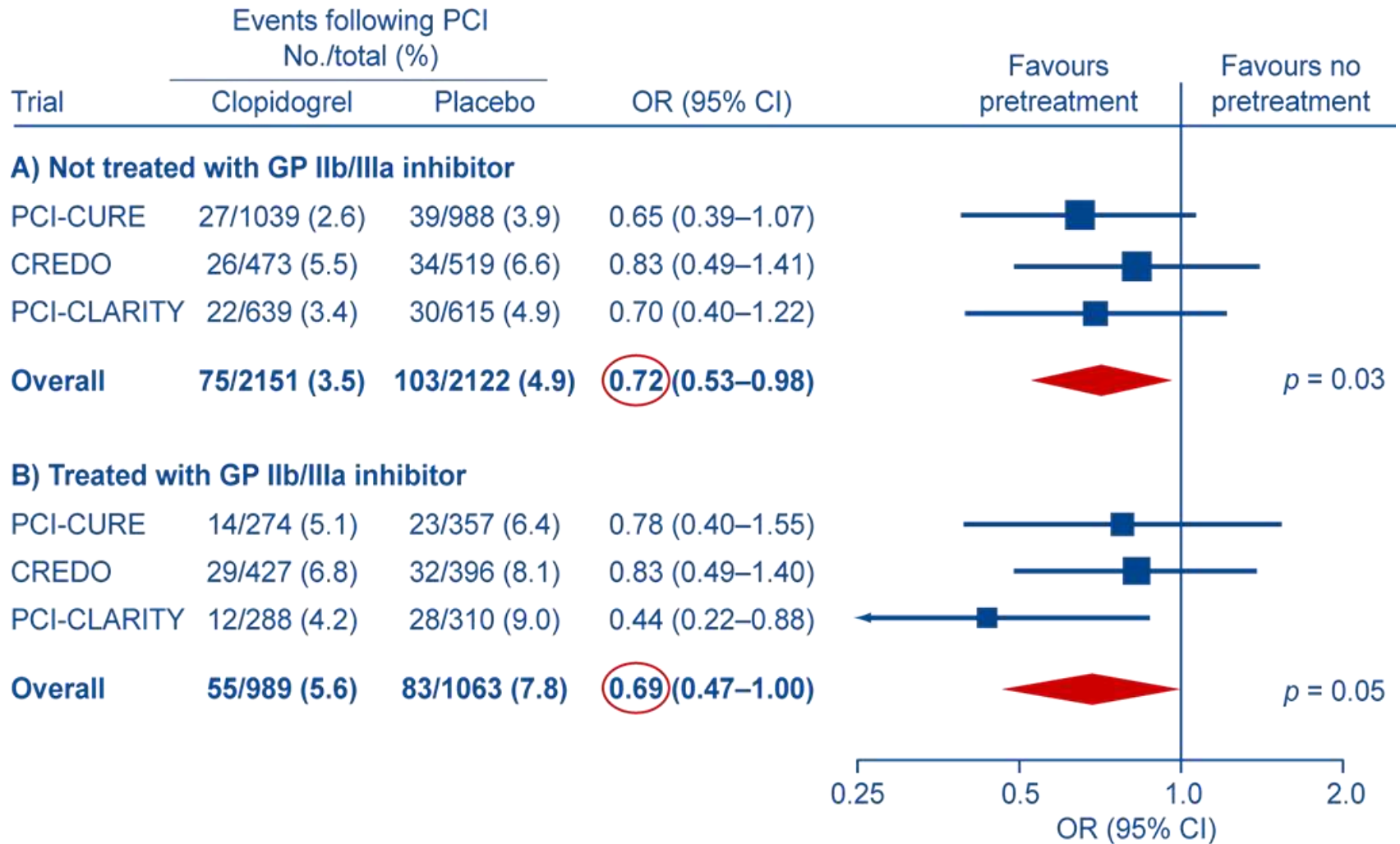
CURE: Early effects of clopidogrel on NSTEMI/ACS event reduction



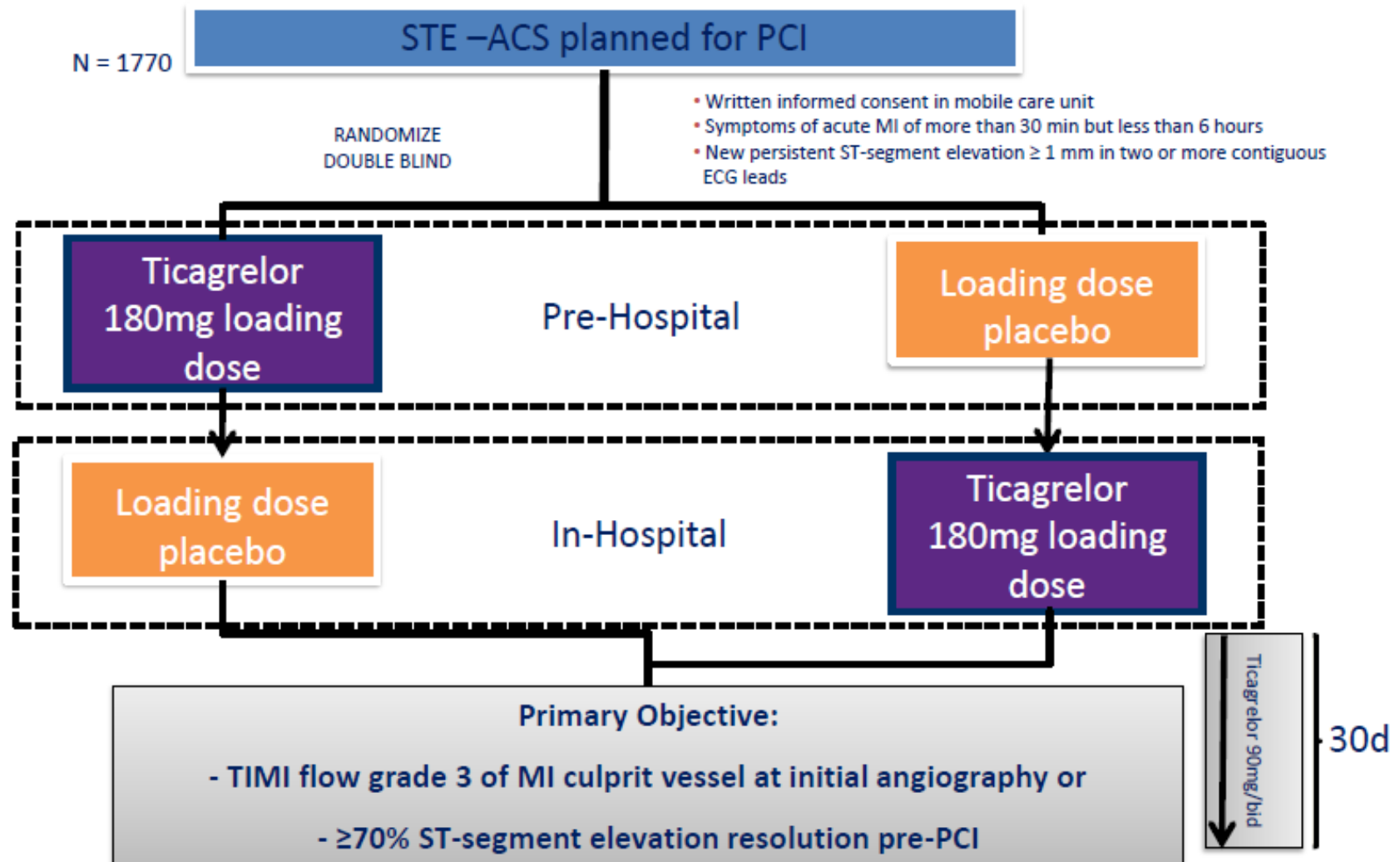
CREDO: Effects of loading dose timing of clopidogrel pretreatment on PCI outcomes



Meta-analysis of Clopidogrel Pretreatment in PCI: Effect on CV death, MI, or stroke after PCI



The ATLANTIC Trial- Principal Investigator G. Montalescot



IAM con \uparrow ST

REPERFUSIÓN

Fibrinólisis

**Angioplastia
primaria**

- Aspirina 300/100 mg
- +
 - Clopidogrel 600/75 mg
 - ó
 - Prasugrel 60/10 mg
 - ó
 - Ticagrelor 180/90 mg/12h

IAM con \uparrow ST

REPERFUSIÓN

Fibrinólisis

- | | | | |
|---------------|--------------|----------|---------------------|
| • Aspirina | 300 / 100 mg | | |
| • Clopidogrel | } | <75 años | Clopi 300 / 75 mg |
| | | | Enox 1mg/Kg/12h |
| • Enoxaparina | } | <75 años | Clopi 75 / 75 mg |
| | | | Enox 0,75 mg/Kg/12h |

Angioplastia
electiva

Angioplastia
de rescate

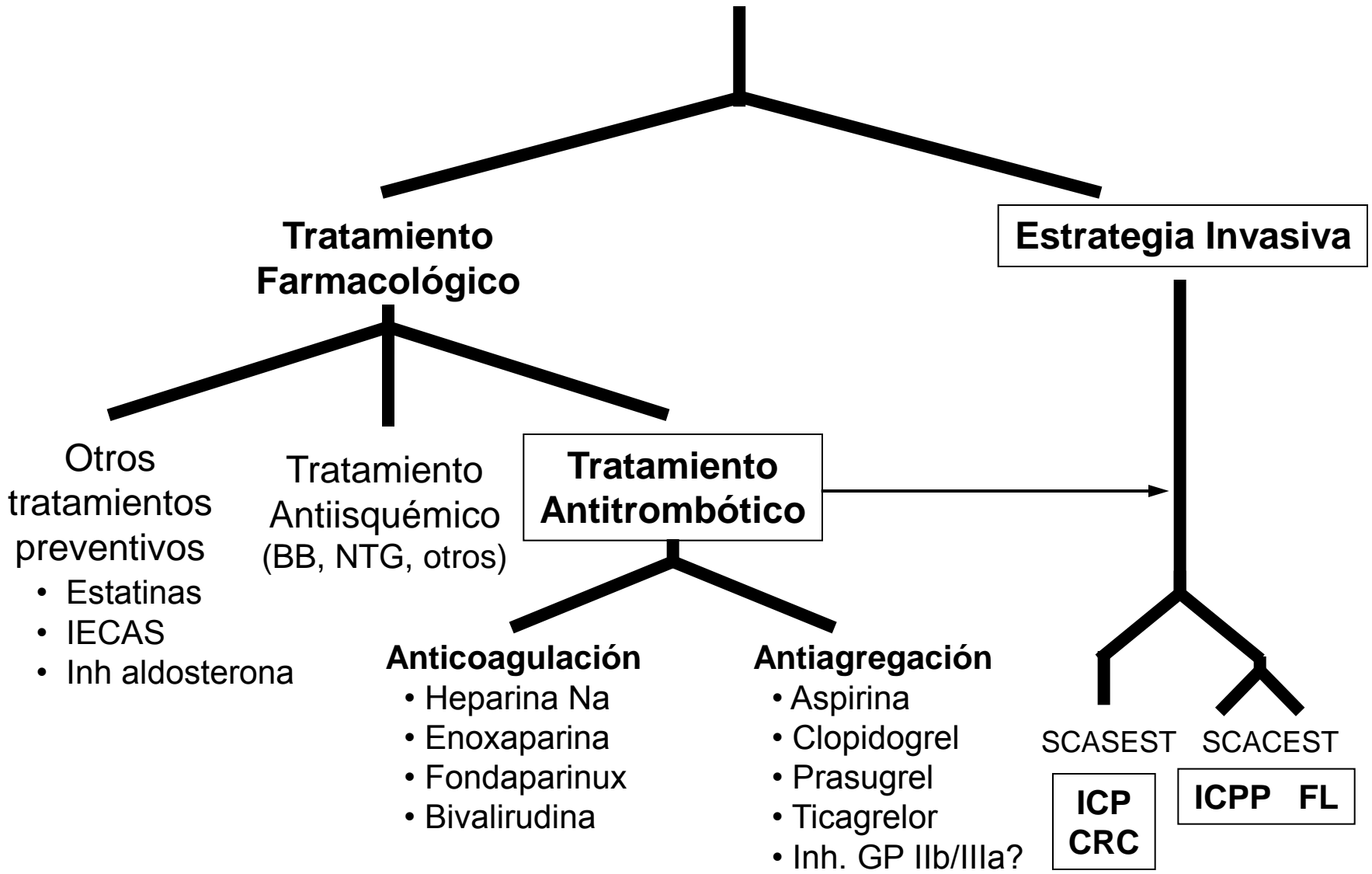
Angioplastia primaria

- | | |
|---------------|---------------|
| • Aspirina | 300/100 mg |
| | + |
| • Clopidogrel | 600/75 mg |
| | ó |
| • Prasugrel | 60/10 mg |
| | ó |
| • Ticagrelor | 180/90 mg/12h |

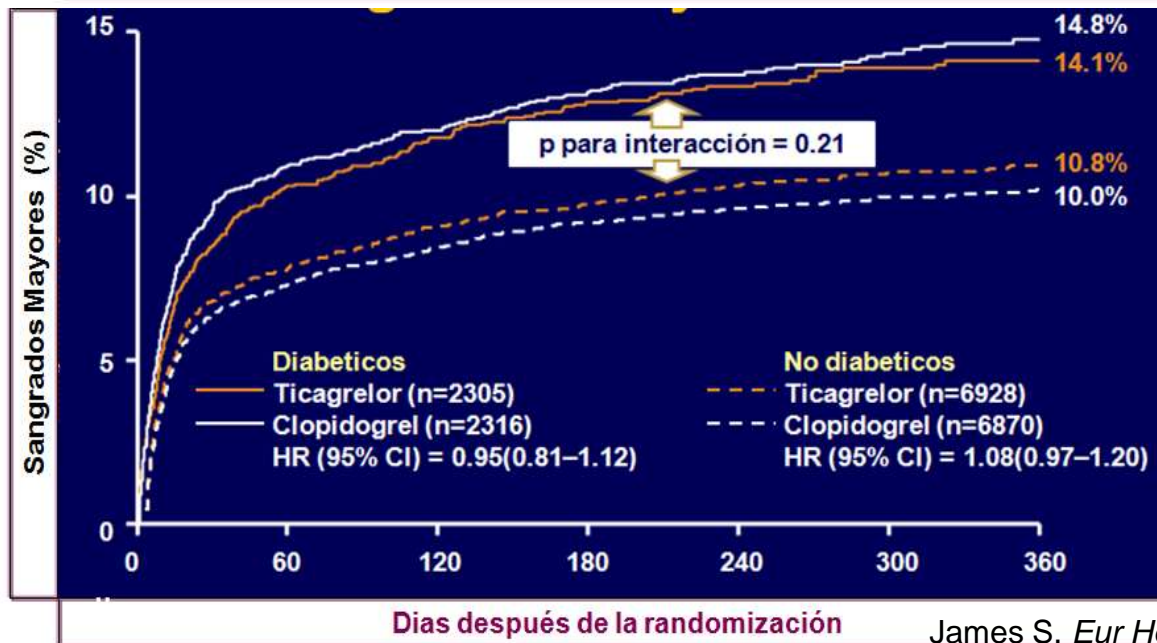
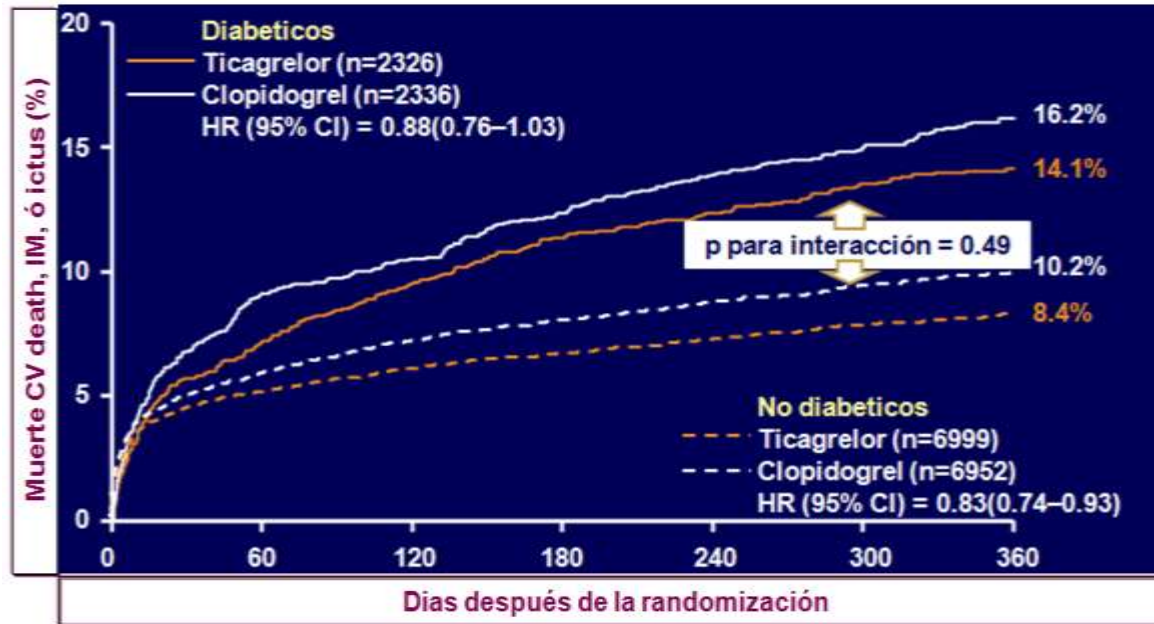
**Si la opción fuera angioplastia primaria,
¿qué tratamiento anticoagulante utilizarías ahora?**

1. Ninguno
2. Heparina Na 4000 UI iv.
3. Enoxaparina 30 mg iv.
4. Bivalirudina
5. Fondaparinux

Manejo de los SCA



PLATO: Subgrupo de diabéticos (n=4662)

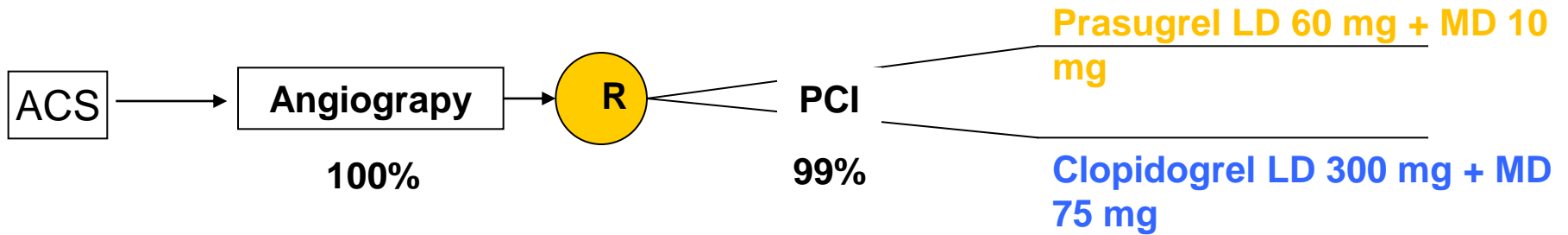


TRITON-TIMI-38 vs PLATO

Study Designs

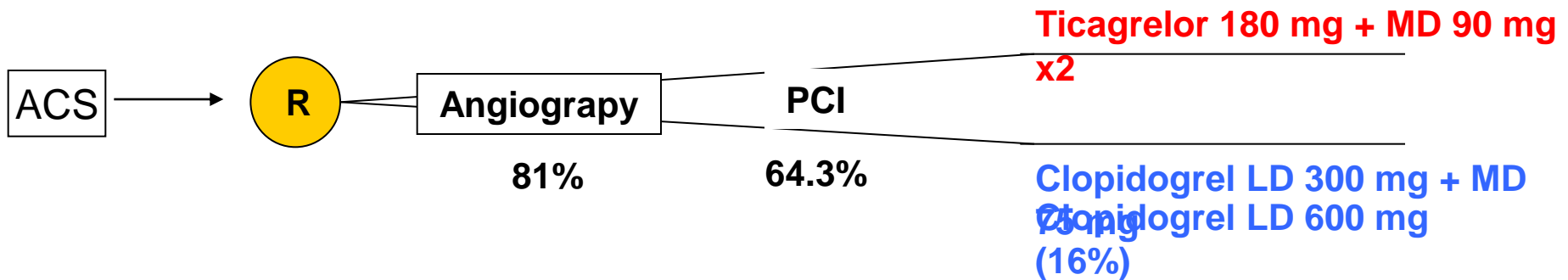
TRITON

n= 13,608



PLATO

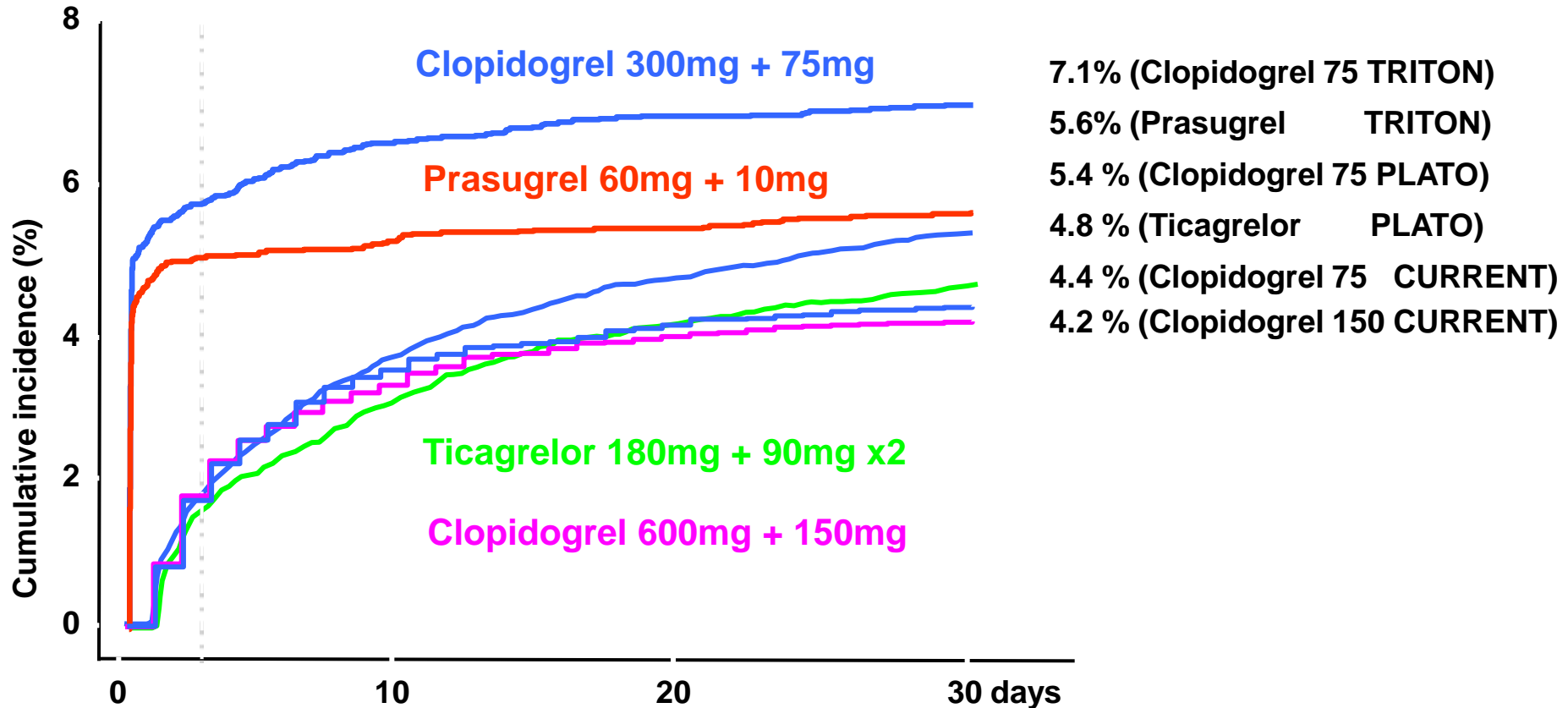
n= 18,624



	CURE	TRITON	PLATO
	12,562	13 608	18 624
Inclusion	NSTEACS	IR-HR (TIMI>3) ACS with cath → PCI	IR-HR ACS
Timing	NSTEACS < 24 h	NSTEACS <72 h with cath → PCI STEMI <12 h → PPCI STEMI 12h - 14 days → PCI	NSTEACS < 24 h STEMI <24 h → PPCI
Contraindic	Thienop	Thienop < 5 days FL < 24-48 h	FL < 24 h
Pretreatment	Clopi naïve 100%	Clopi naïve 100%	Clopi naïve (54%) / Clopi pretreated (46%)
% Tn +	-	75%	86%
% STEMI	0	26%	37.6%
Diabetes	22.4%	23%	25%
% USA	¿	32%	8.7%
% Angio		100%	69%
% PCI	21%	99%	55%
% CABG		1%	4.2%
Max FU	12 mo	15 mo (464 days)	12 mo
% EndPoint	9.3% - 11,4%	9.9% -12.1%	9% - 10.7%
% Mortality	5,8% - 6,2%	3.0% - 3.2%	3.9% - 5.0%
% CVDeath	5,1% - 5,4%	2.1% - 2.4%	3.4% – 4.3%
% MI	5,6% - 6,7%	7.3% - 9.5%	5.3% - 6.6%
Discontinuati on	46.2%		

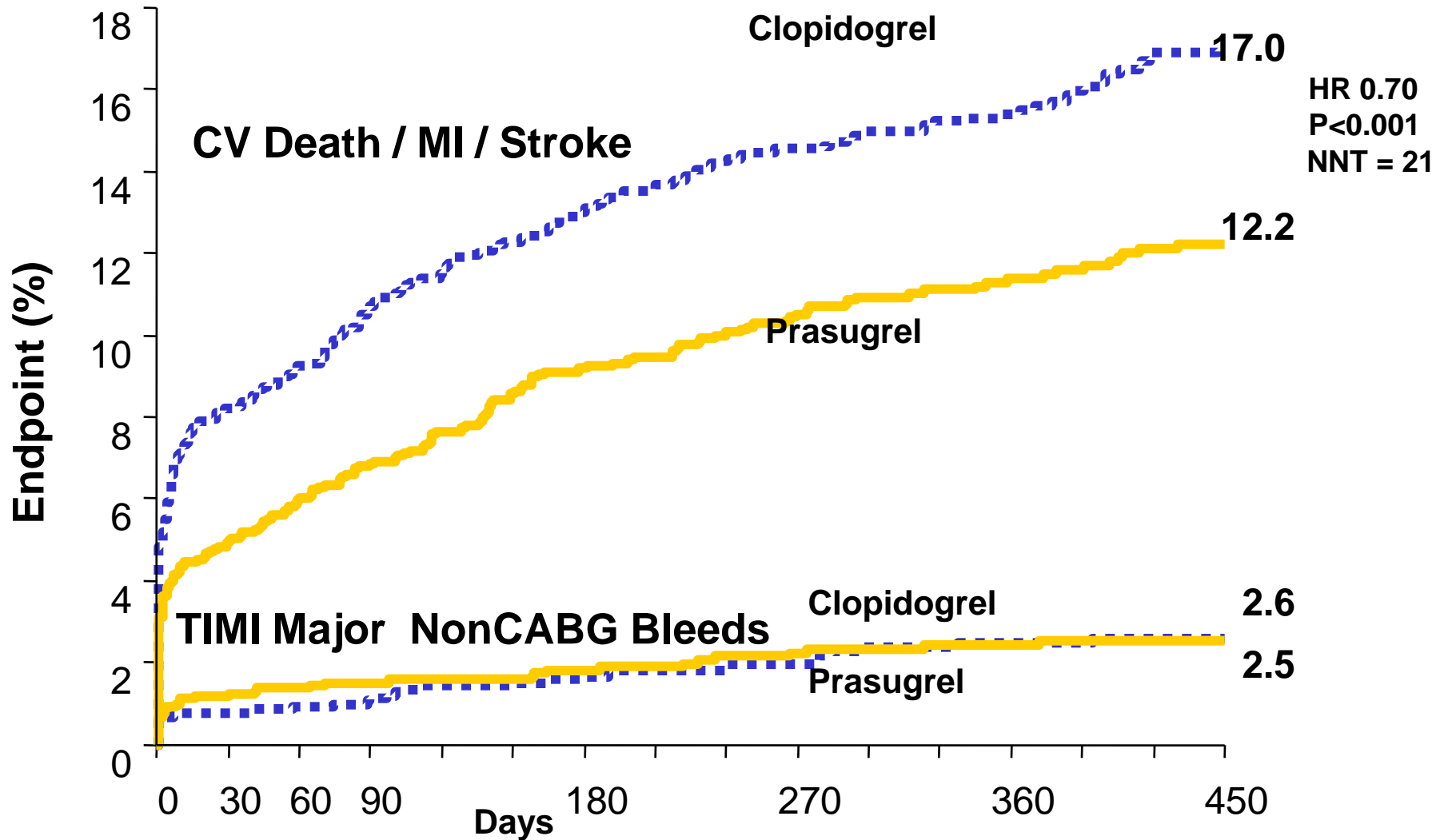
TRITON and PLATO and CURRENT

EARLY CV Death / MI / Stroke (30days)

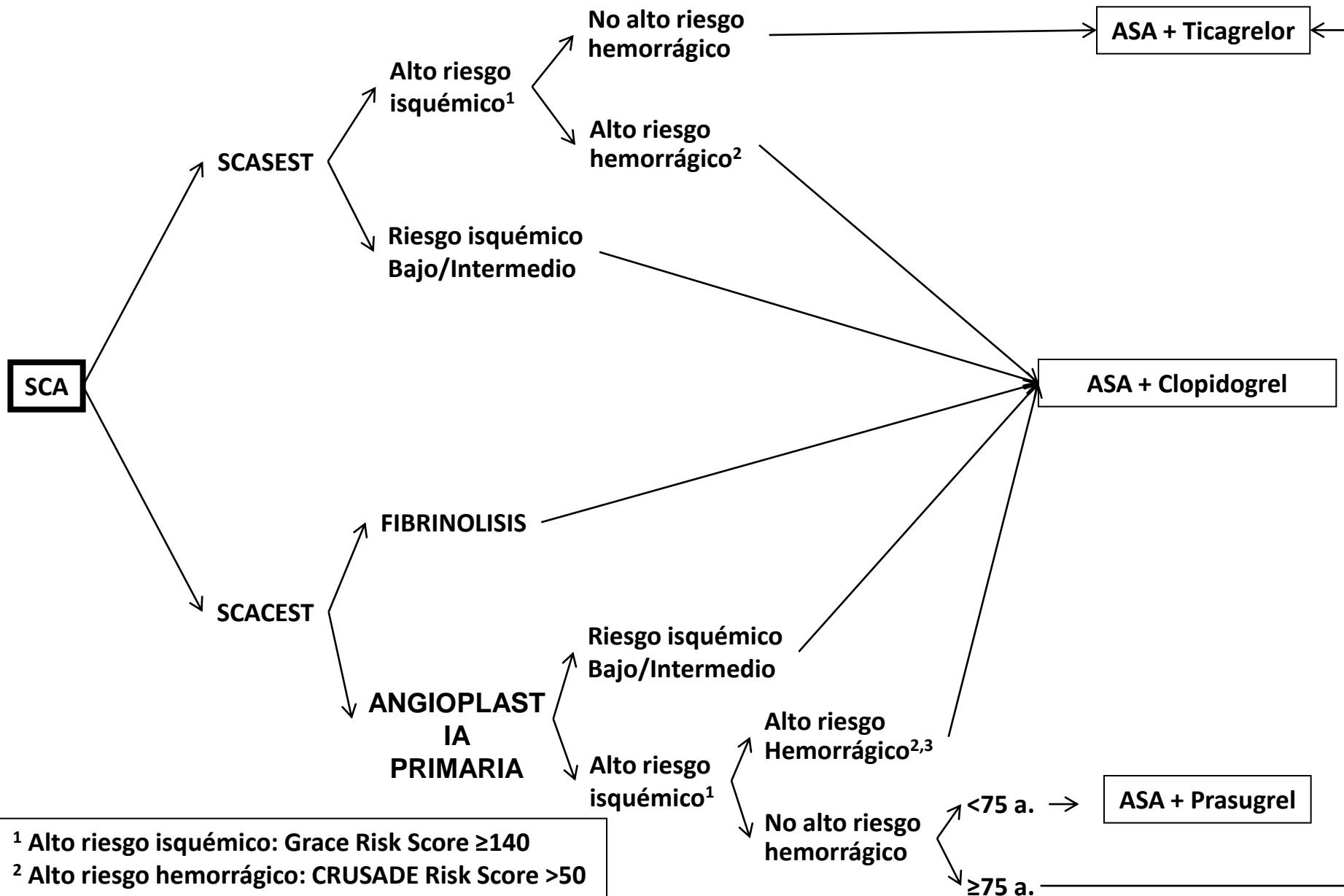


Clopidogrel 75mg vs Prasugrel 10mg	HR 0.77 (95% CI 0.67–0.88), <u>p<0.001*</u>	- 23%
Clopidogrel 75mg vs Ticagrelor 90mg x2	HR 0.88 (95% CI 0.77–0.95), <u>p=0.045*</u>	- 12%
Clopidogrel 75mg vs Clopidogrel 150mg	HR 0.96 (95% CI 0.85-1.08), p=0.47	- 4%

TRITON TIMI-38: Subgrupo de diabéticos (n=3146)



Protocolo tratamiento antiagregante en SCA HGUGM



¹ Alto riesgo isquémico: Grace Risk Score ≥ 140

² Alto riesgo hemorrágico: CRUSADE Risk Score > 50

³ ACV ó AIT previos, Peso < 60 Kg