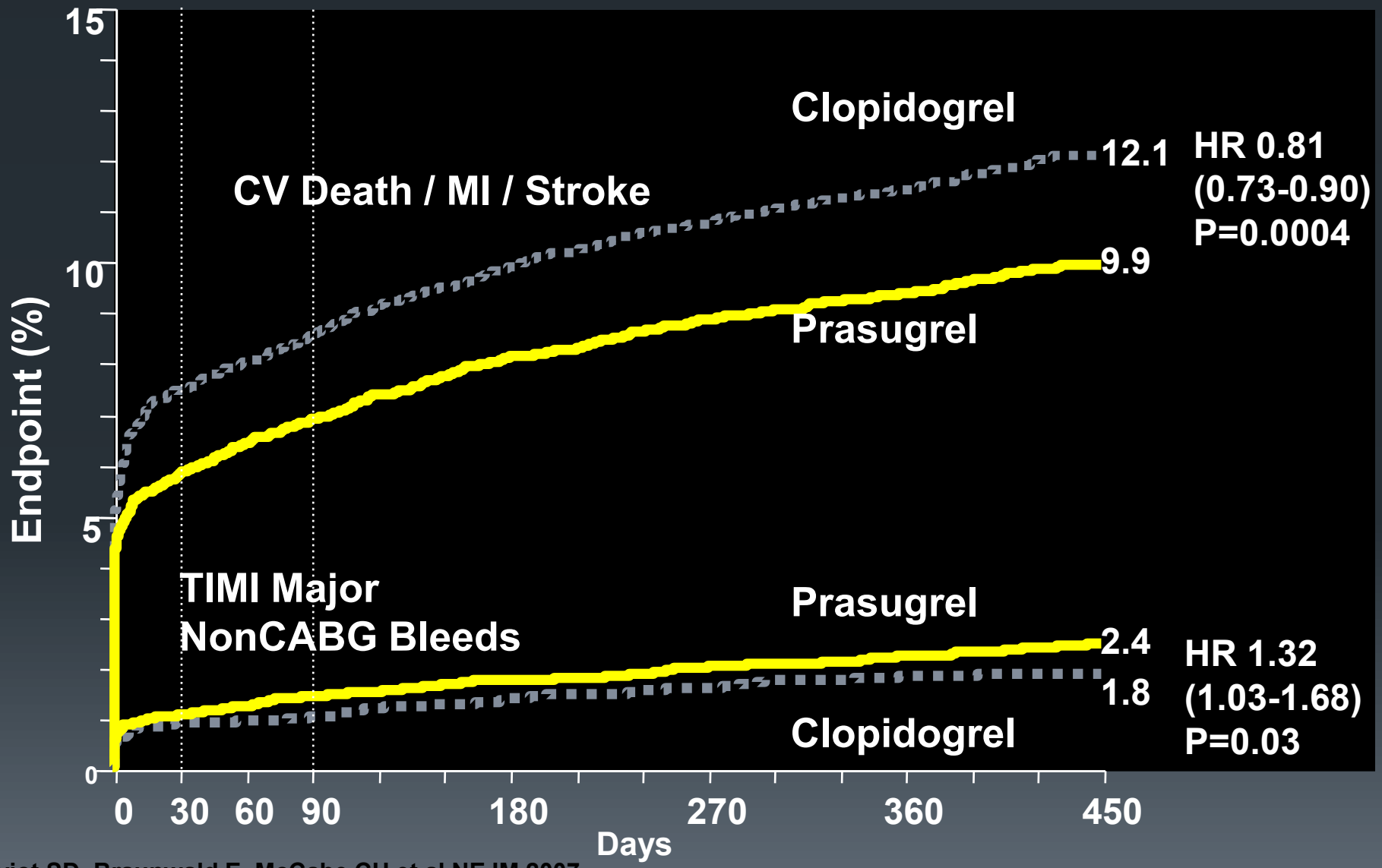
Tratamiento prolongado antiagregante en subgrupos de pacientes

José F. Díaz, MD, FESC
Complejo Hospitalario de Huelva

TRITON TIMI-38

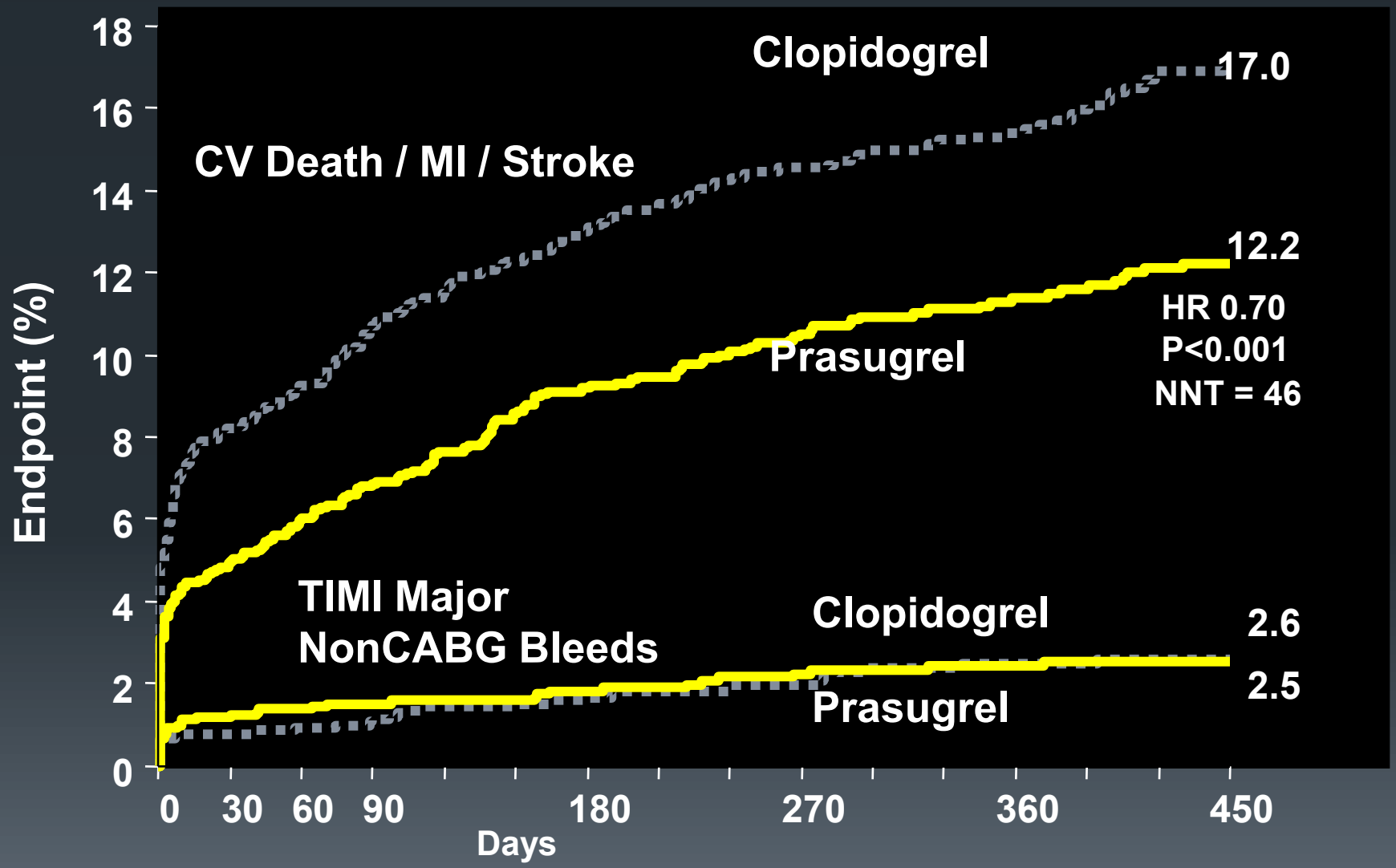
Primary Endpoint CV Death,MI,Stroke



Wiviot SD, Braunwald E, McCabe CH et al NEJM 2007

TRÎTON TIMI-38

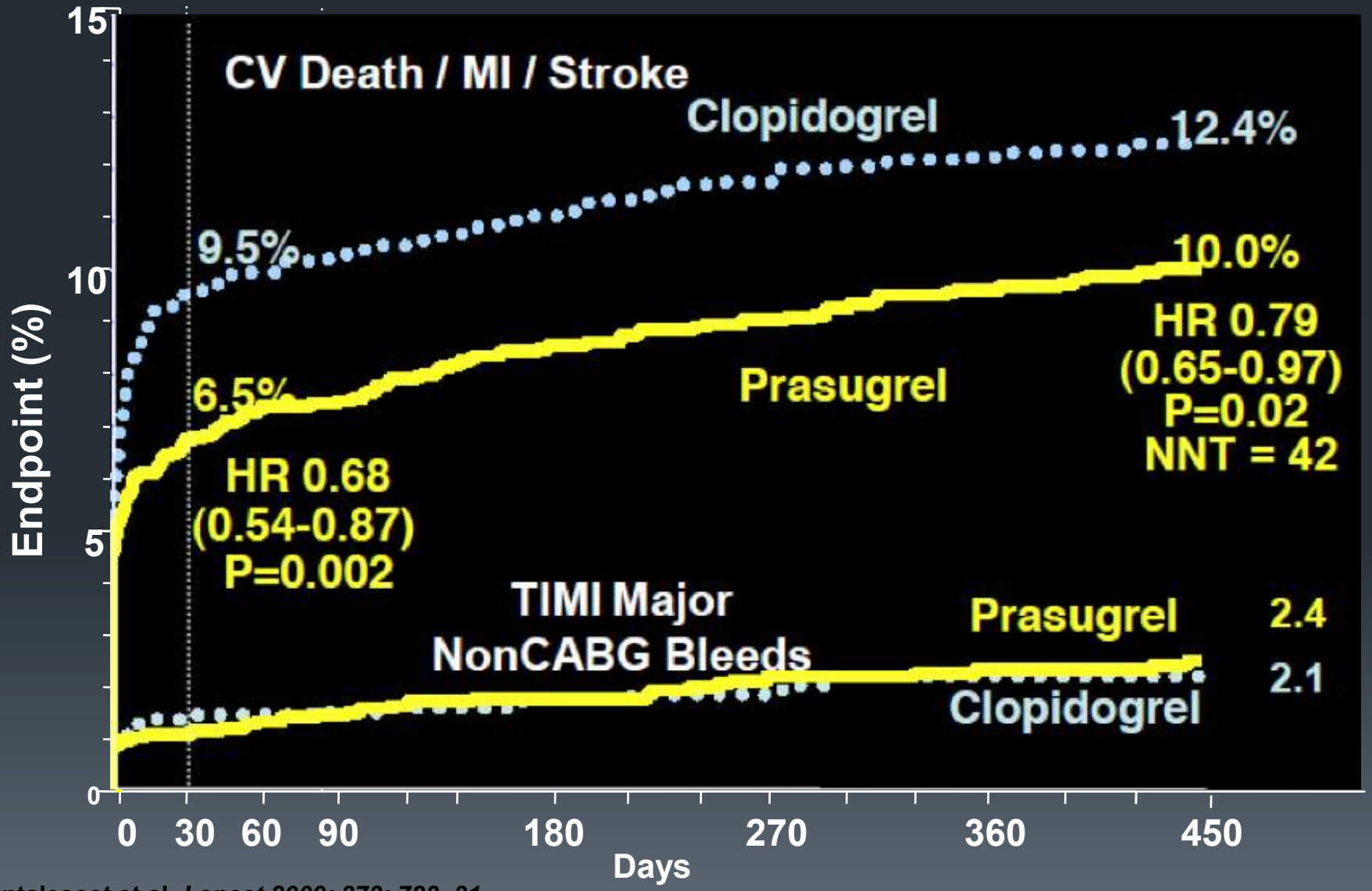
Diabetic Subgroup N=3146



Wiviot SD, Circulation 2008

TRÎTON TIMI-38

STEMI Cohort
N: 3534

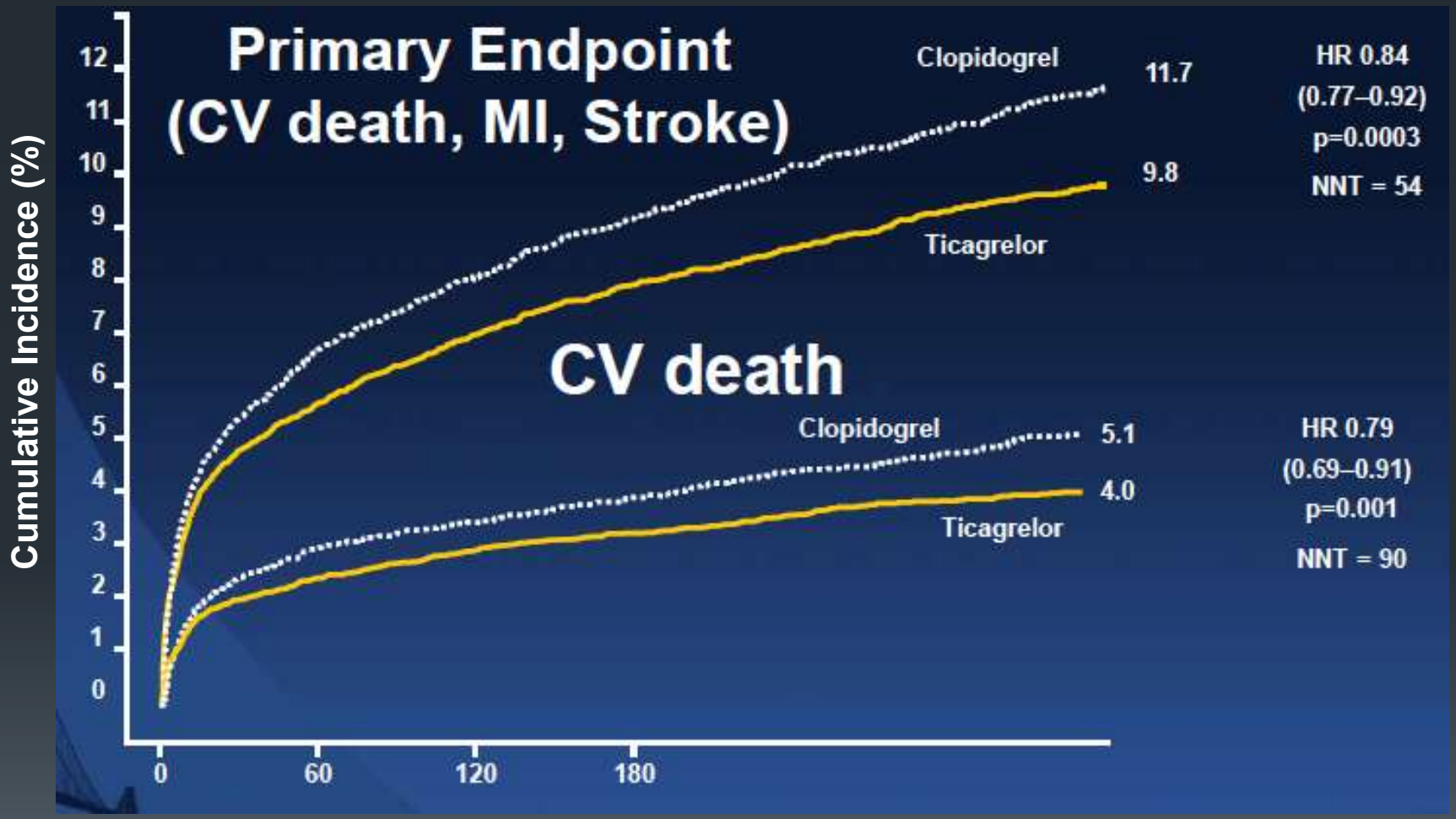


Montalescot et al. *Lancet 2009; 373: 723–31*

TRITON TIMI 38 Net clinical benefit: Bleeding risk subgroups

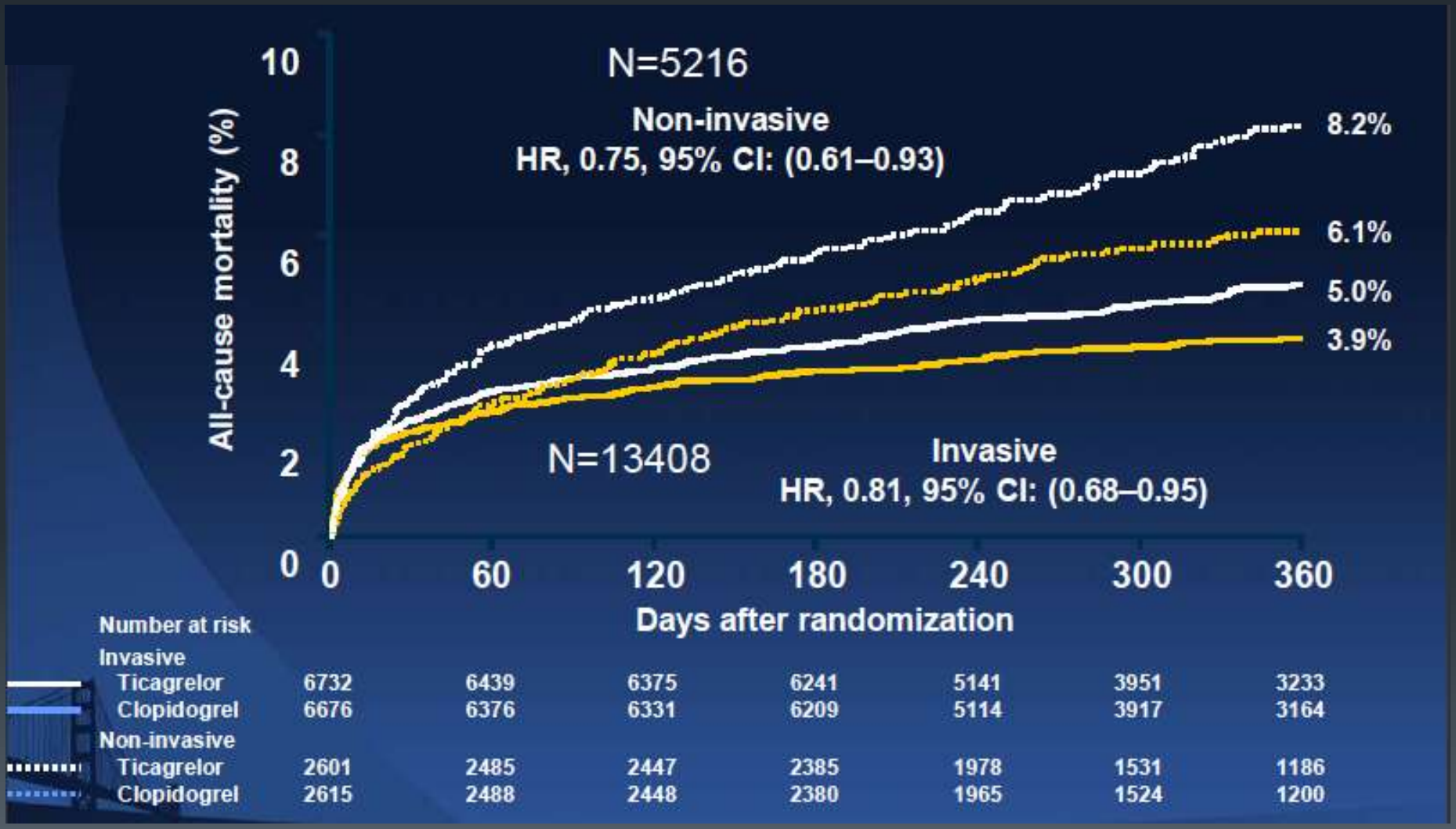
Wiviot SD, Braunwald E, McCabe CH et al NEJM 2007

PLATO Study
N: 18.624



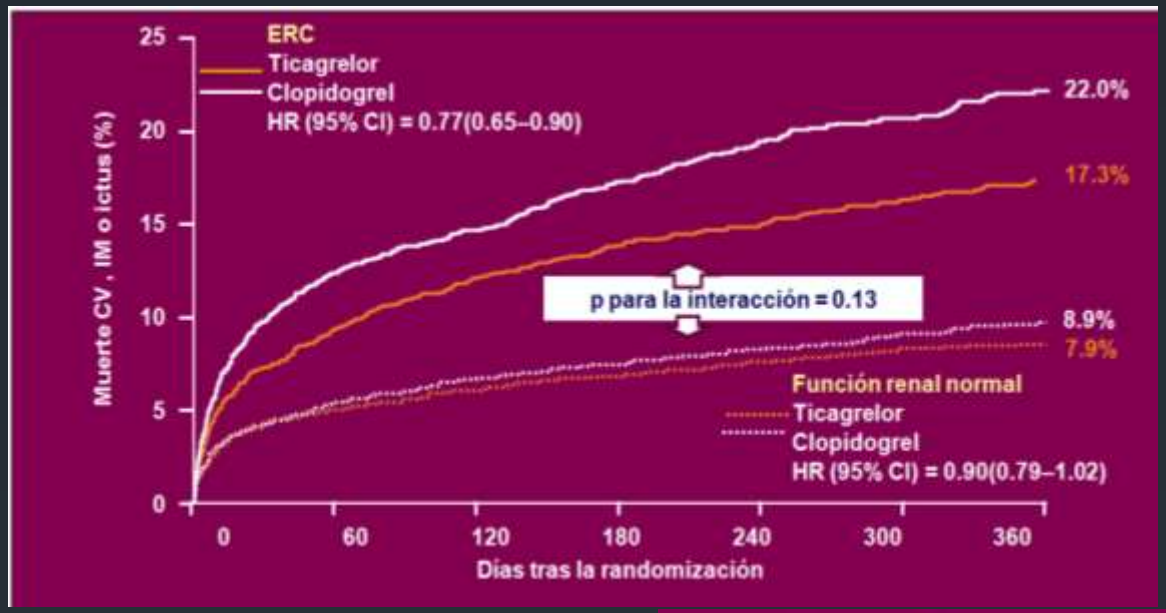
Wallentin L et al. N Engl J Med 2009;361:1045-57.

Mortality reduction in Invasive and non-invasive treatment strategies



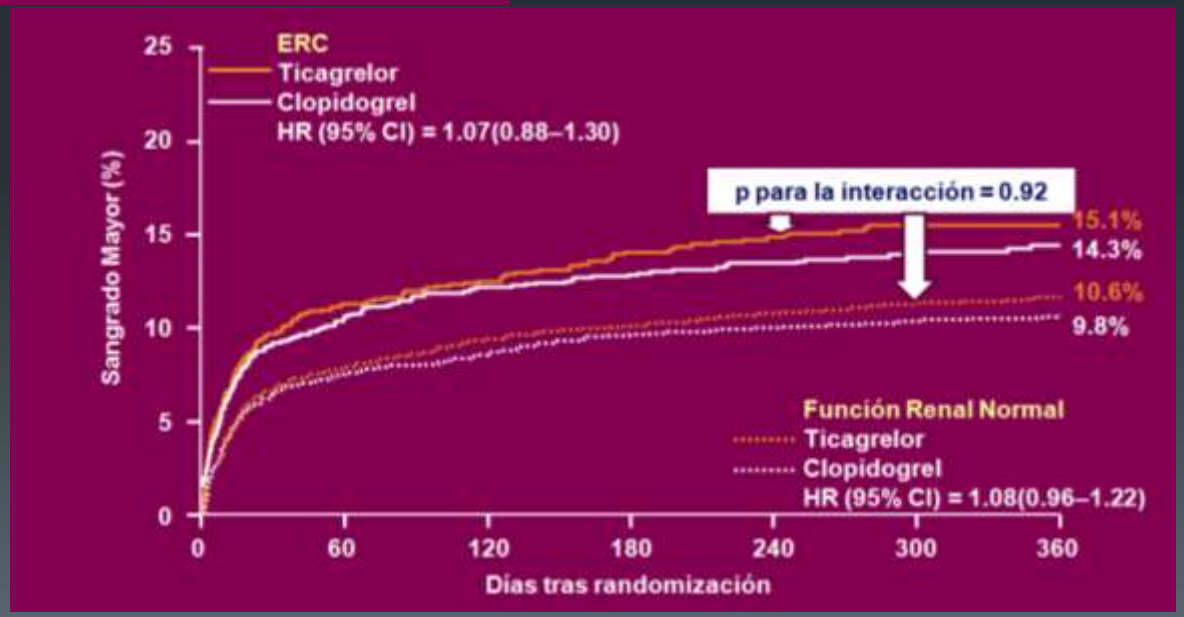
James SK et al. BMJ 2011; 342:d3527

Ticagrelor y función renal



Variable primaria compuesta MuerteCV, IM, Ictus

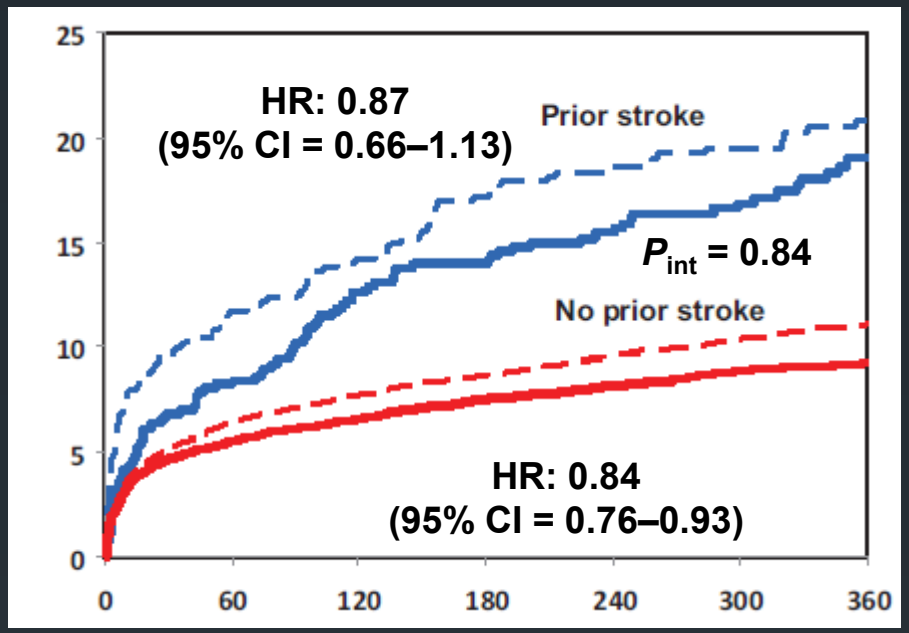
Variable de Seguridad



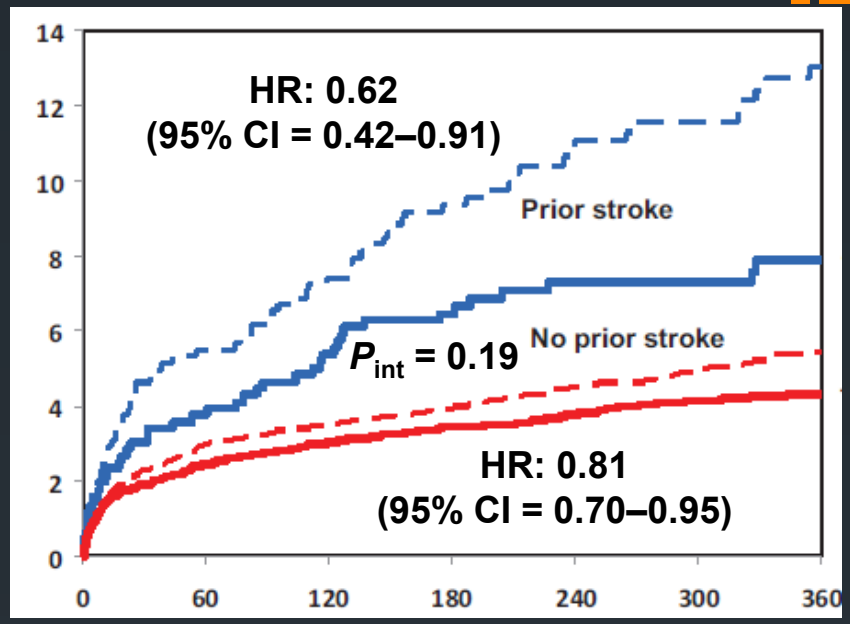
James S. *Circulation* 2010;122:1056–1067.

Población con Ictus/TIA previo

Variable primaria compuesta MuerteCV, IM, Ictus

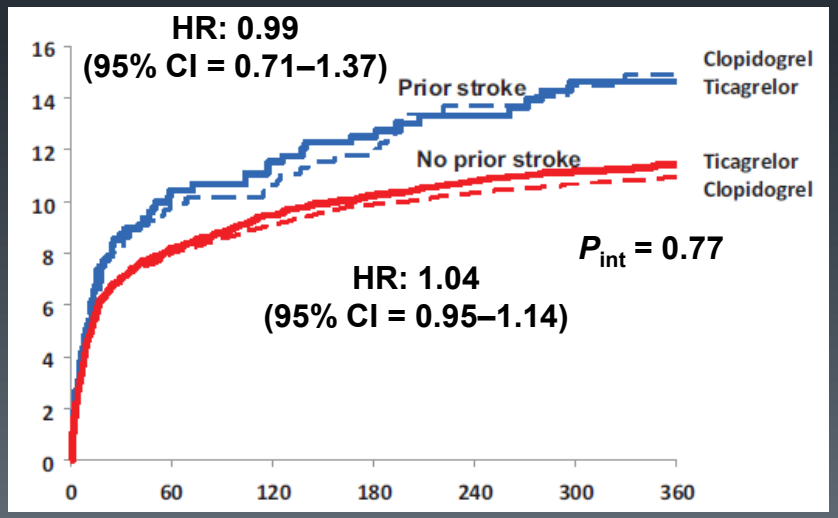


Mortalidad Total



Clopidogrel

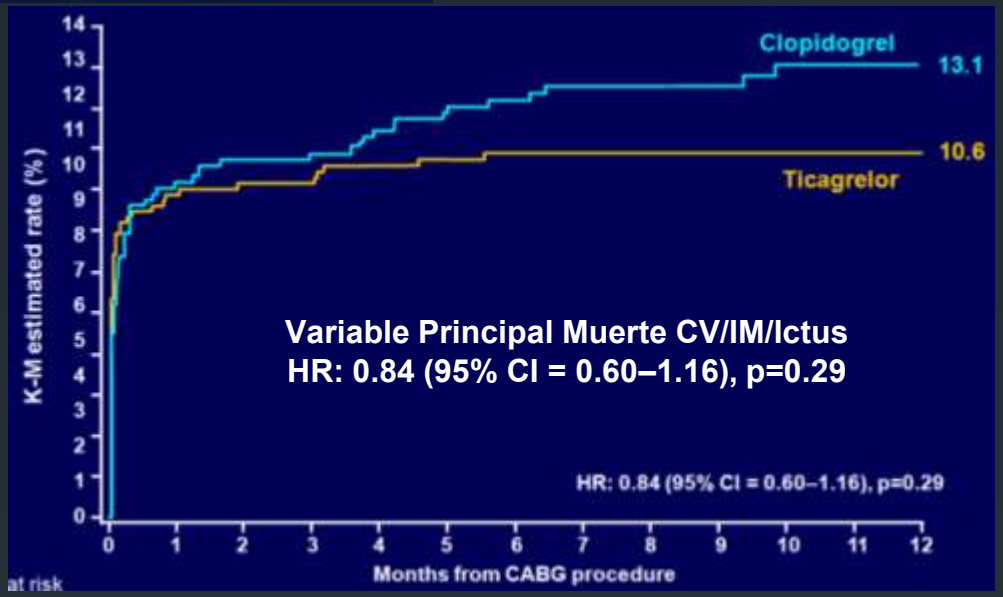
Ticagrelor

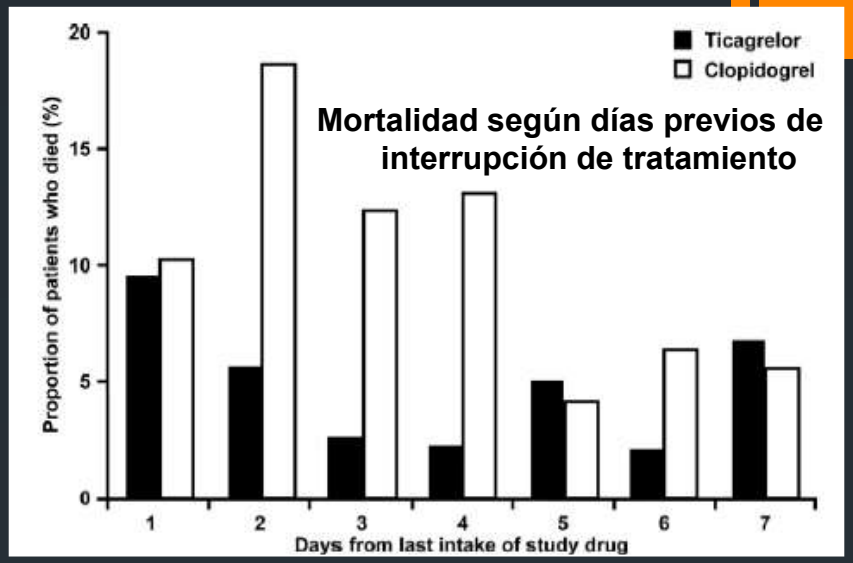


Sangrados Mayores

James SK, et al. *Circulation.* 2012;125:2914-2921

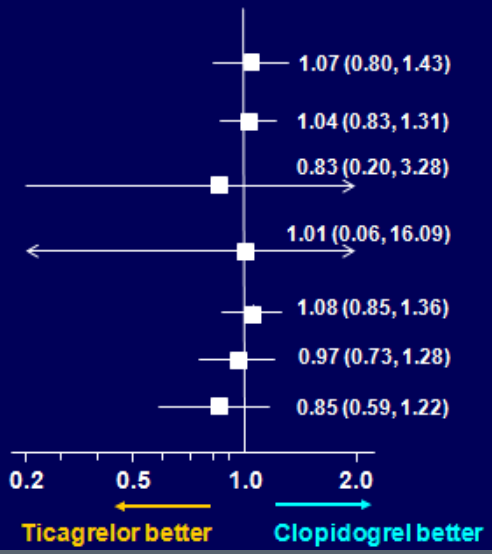
PLATO CABG





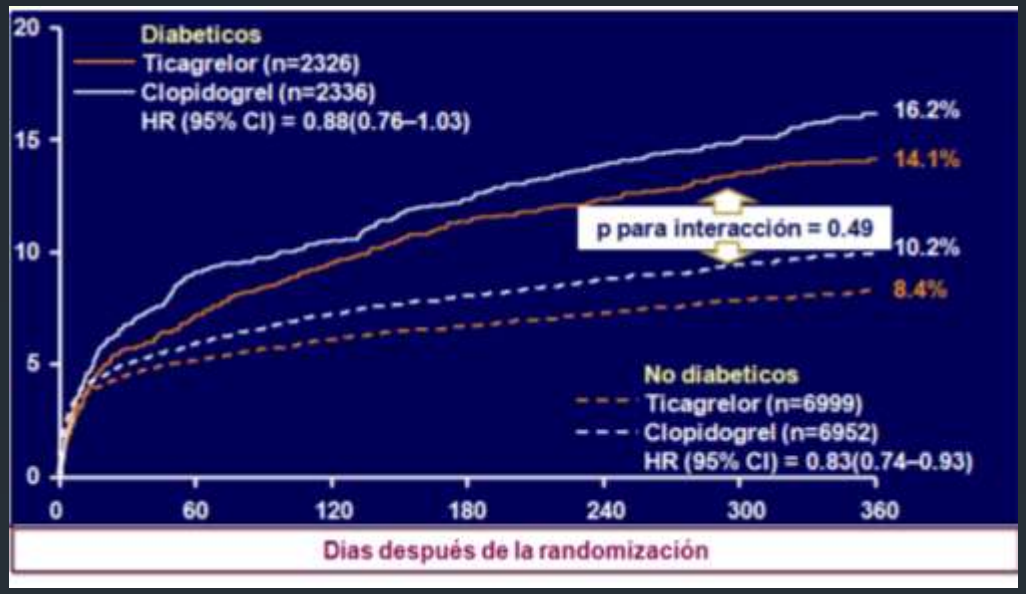
Sangrados

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)	Odds Ratio (95% CI)	p-value
CABG-related bleeding				
Major bleeding	81.2	80.1	1.07 (0.80, 1.43)	0.67
Life-threatening/ fatal bleeding	43.7	42.6	1.04 (0.83, 1.31)	0.73
Fatal bleeding	0.8	1.0	0.83 (0.20, 3.28)	0.77
All intracranial bleeding post-CABG*	0.2	0.2	1.01 (0.06, 16.09)	1.00
TIMI major bleeding	59.3	57.6	1.08 (0.85, 1.36)	0.53
TIMI minor bleeding	21.0	21.6	0.97 (0.73, 1.28)	0.84
GUSTO severe bleeding	10.6	12.2	0.85 (0.59, 1.22)	0.38



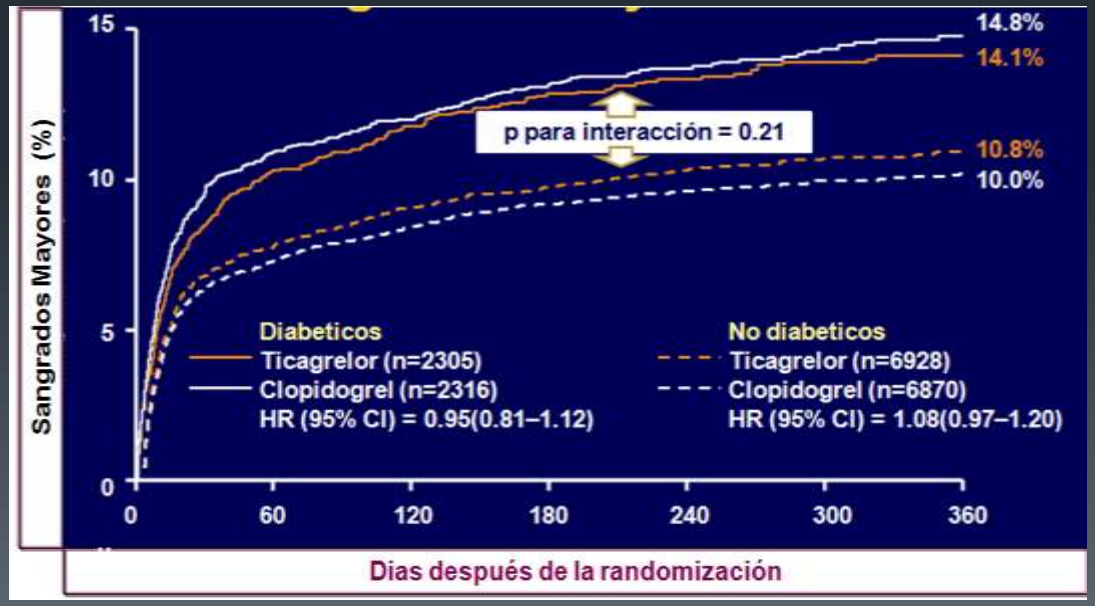
Held C, et al. J Am Coll Cardiol 2011;57:672–684.

Subgrupo de Diabéticos (n=4662)



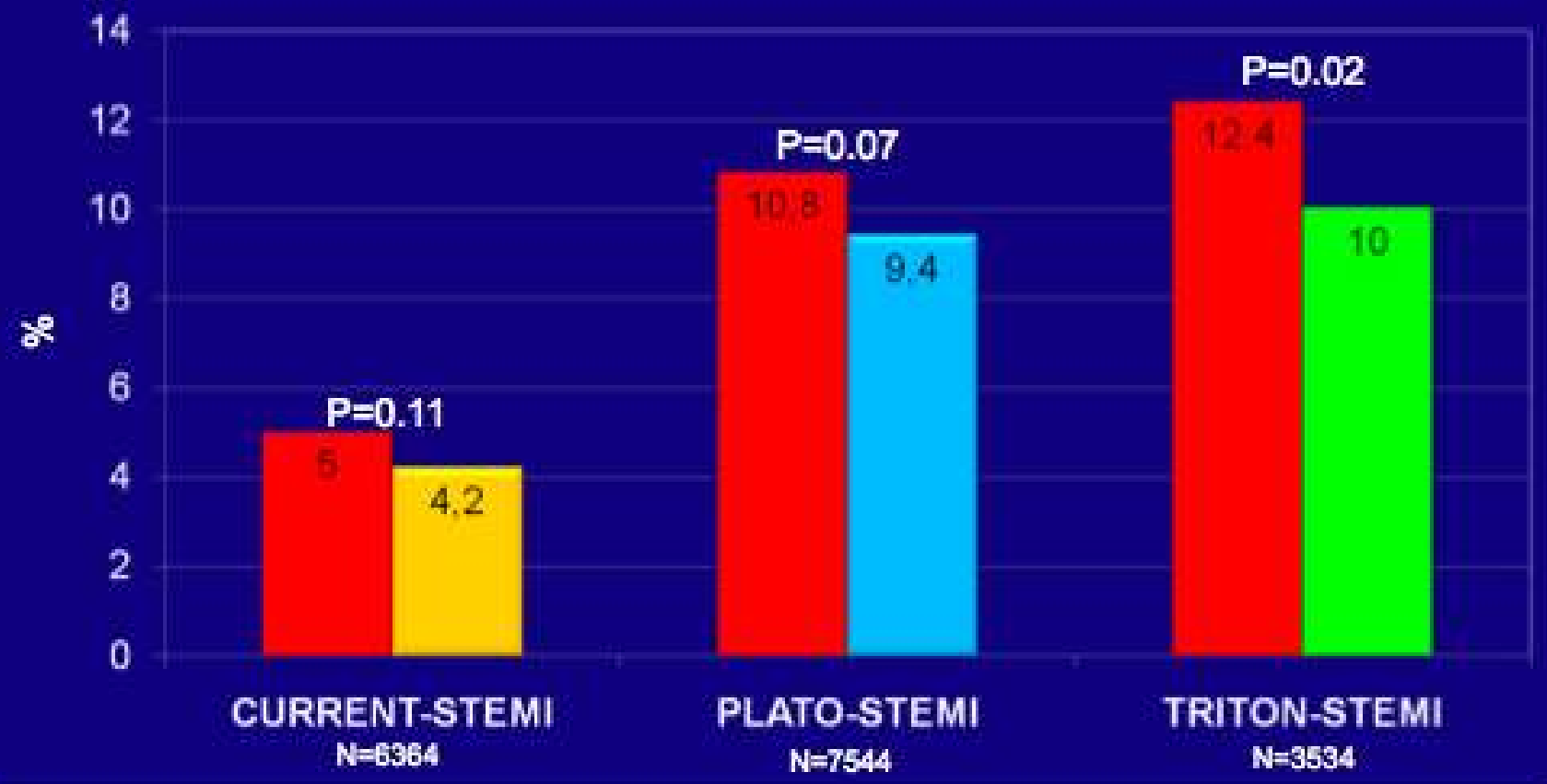
Variable primaria según presencia de DM

Sangrado según presencia de DM



James S. *Eur Heart J* 2010;31:3006–3016.

STEMI-PCI



Drug	Double dose clopidogrel	Ticagrelor	Prasugrel
Follow-up	1 month	6-12 months	15 months

TRITON STEMI-PCI

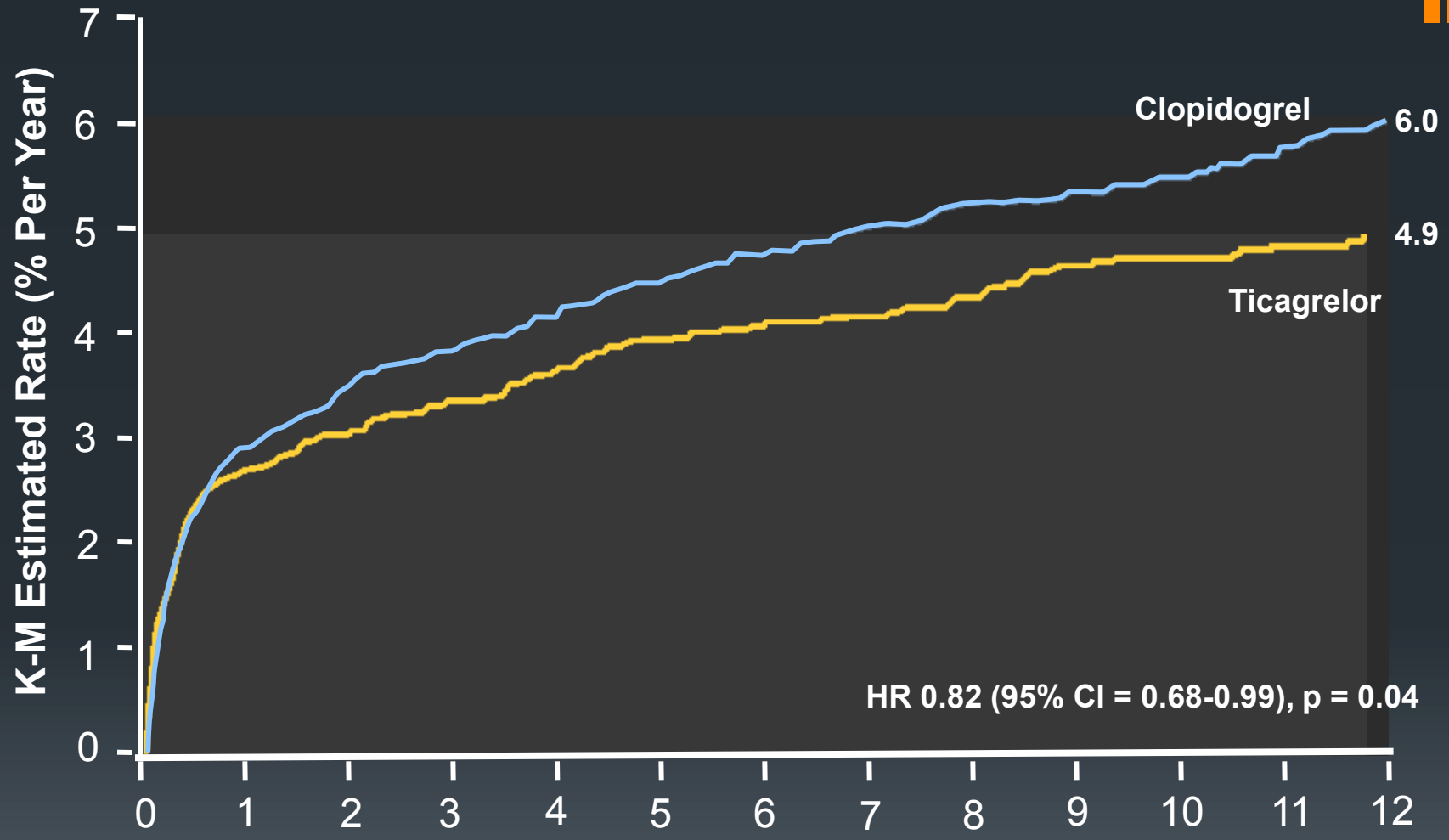
Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial

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

	Clopidogrel	Prasugrel	Hazard ratio (95% CI)	p
Efficacy endpoints				
Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)				
All STEMI cohort	166 (9·5%)	115 (6·5%)	0·68 (0·54–0·87)	0·0017
Primary PCI	101 (8·2%)	79 (6·6%)	0·80 (0·60–1·08)	0·1440
Secondary PCI	65 (12·3%)	36 (6·4%)	0·50 (0·34–0·76)	0·0008

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

PLATO STEMI: All Cause Mortality

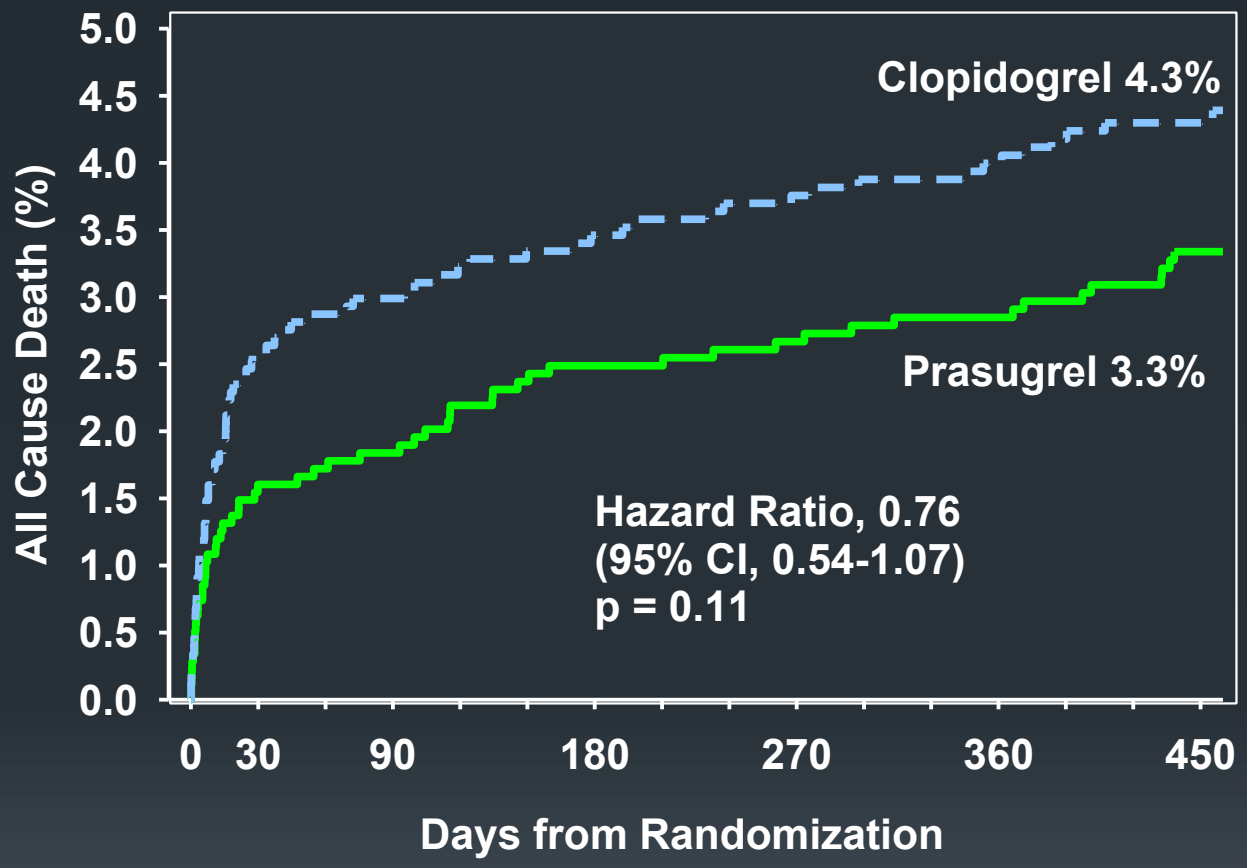


No. at risk							
Ticagrelor	4,201	4,005	3,962	3,876	3,150	2,413	1,993
Clopidogrel	4,229	4,029	3,989	3,912	3,195	2,471	1,980

CI=Confidence Interval; HR=Hazard Ratio; K-M=Kaplan-Meier; PLATO=**PLAT**elet Inhibitiion and Patient **O**utcomes; STEMI=ST-Elevation Myocardial Infarction

Steg PG, et al. *Circulation* 2010;122:2131-2141

TRITON-TIMI 38: Mortality in STEMI



Number at Risk:

Prasugrel -	1769	1694	1666	1644	1619	1605	1324
Clopidogrel -	1765	1683	1653	1636	1615	1598	1299

Data on File, Daiichi Sankyo, Inc. and Eli Lilly and Company

CI=Confidence Interval; STEMI=ST-Elevation Myocardial Infarction; TRITON-TIMI=TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thromobolysis In Myocardial Infarction

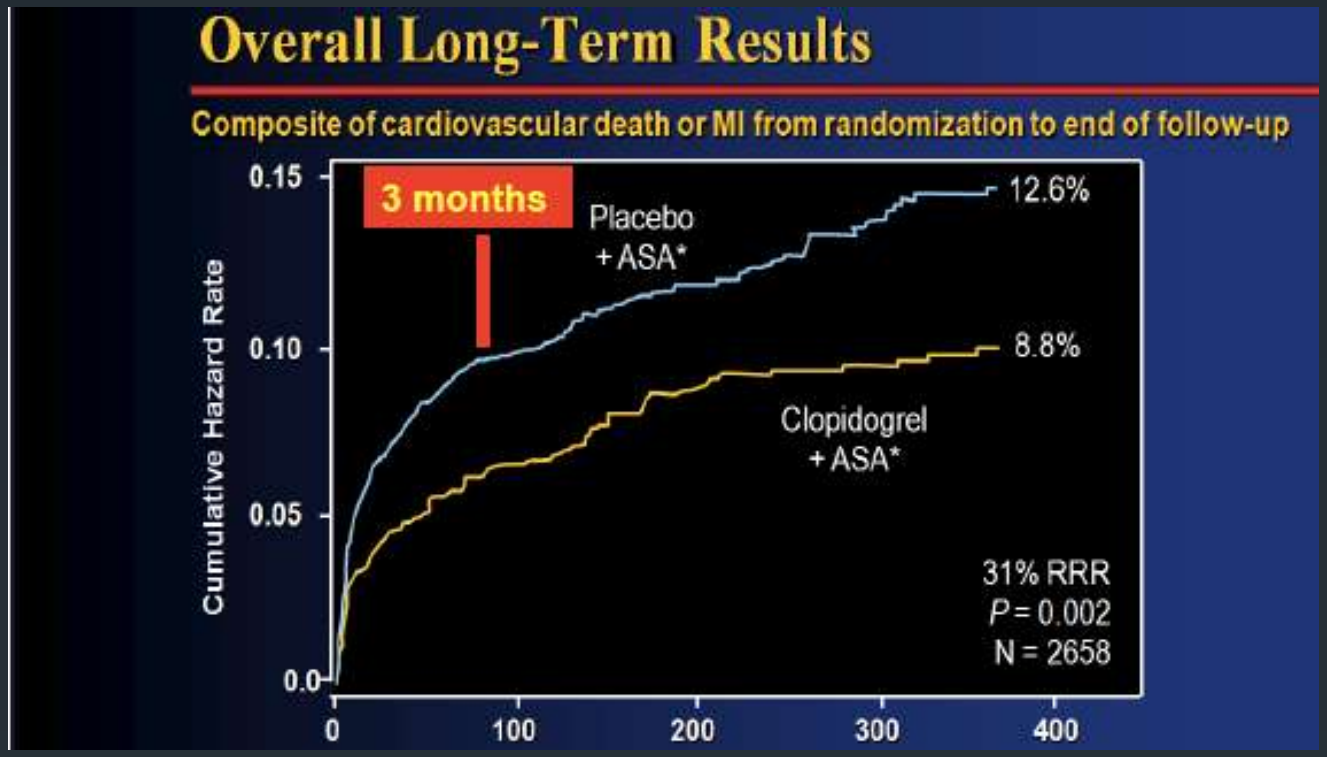
Tratamiento en subgrupos

	Clopidogrel	Prasugrel	Ticagrelor
Riesgo bajo	+++	—	—
Riesgo moderado-alto	+	+++	+++
Estrategia invasiva	++	+++	+++
Estrategia no invasiva	+	—	+++
SCACEST	+	+++	++
SCASEST	+	++	+++
Trombosis de *stent*	+	+++	++
Diabetes mellitus	+	+++	++
Insuficiencia renal	++	+	+++
Ictus	++	—	+
Riesgo hemorrágico elevado	+	—	+
Uso de anticoagulación oral	+	—	—
Edad > 75 años	+++	+	+++
Peso < 60 kg	++	+	+++
CRC	+	—	+++

*D. Vivas et al / Rev Esp Cardiol Supl. 2013;**13(B)**:29-34*

	TRITON	PLATO
N	13,608	18,624
Study population	Early invasively managed ACS scheduled for PCI (including STEMI and STEMI patients undergoing same admission PCI) Symptom onset within past 72 hours	Broad ACS population (including STEMI) Symptom onset within past 24 hours
Prior clopidogrel	Excluded	Allowed (including in-hospital Rx prior to randomization)
% STEMI	26% (18% undergoing primary PCI)	40.5% (all intended for primary PCI)
Timing of randomization	Later After angiography After decision to perform PCI	Early Before angiography (if done)
Randomization	Prasugrel 60 mg load; 10 mg qd or Clopidogrel 300 mg load; 75 mg qd	Ticagrelor 180 mg load; 90 mg bid or Clopidogrel 300–600 mg load; 75 mg qd
Administration of study drug	Started in the time interval from randomization up to 1 hour after PCI	Started immediately after randomization
Primary efficacy endpoint	CV death/MI/stroke	CV death/MI/stroke
Primary safety endpoint	Non-CABG TIMI major bleeding	PLATO major bleeding
PCI	99% (all at randomization)	61% (49% within 24 hrs of randomization)
CABG	3.2% (0.35 % on primary admission)	10.2% (4.5 % on primary admission)
Medical management (no revasc)	1.1%	34%
IIb/IIIa use	54%	27%
Follow-up	Up to 15 months	Up to 12 months

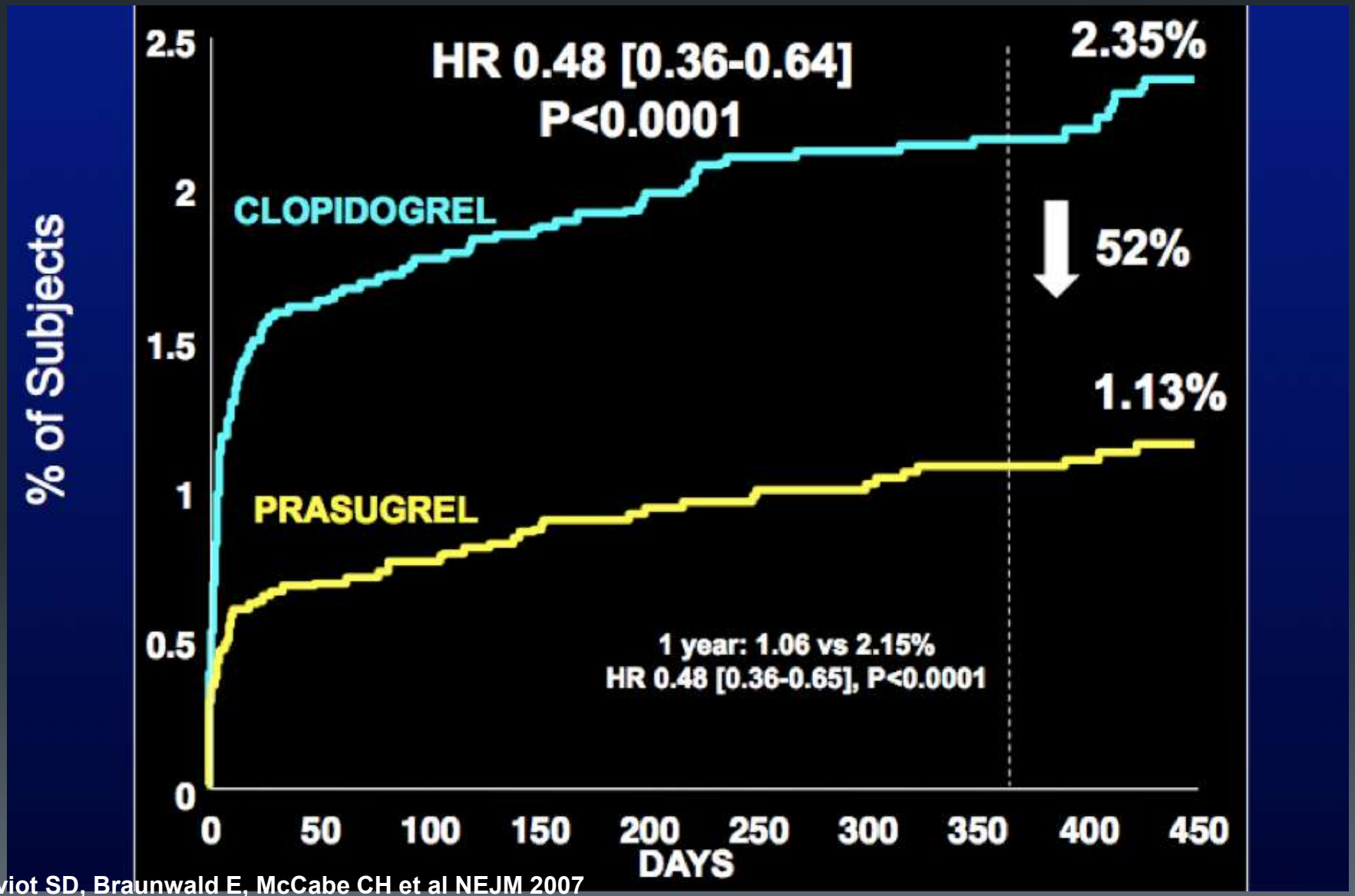
PCI CURE



- *DAPT prevented 22CV events/1000 Pts during the 12 months*
- 50% (11CV events/1000) in the first 30 days
- *50% of the benefit ocurred from 1 month to 12 months*
- 9 of the 11 prevented CV events ocurred between 1 & 3 months
- *Only 2 CV events/1000 pts were prevented between 3 & 12 months*
- That works out to a NNT of 500 for the time period 3-12 months

TRÎTON TIMI-38

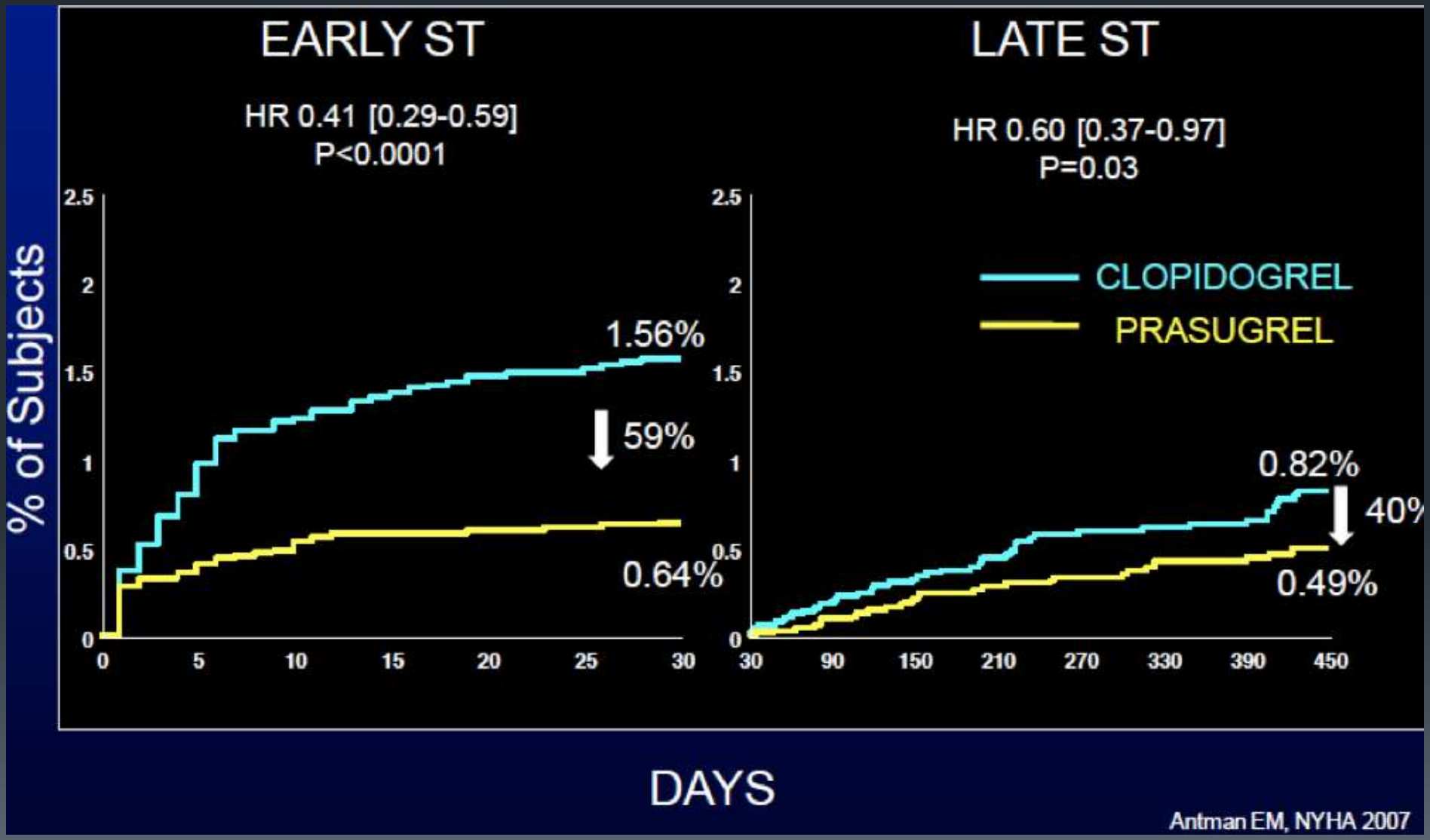
Definite/Probable ST Any Stent (N=12.844)



Wiviot SD, Braunwald E, McCabe CH et al NEJM 2007

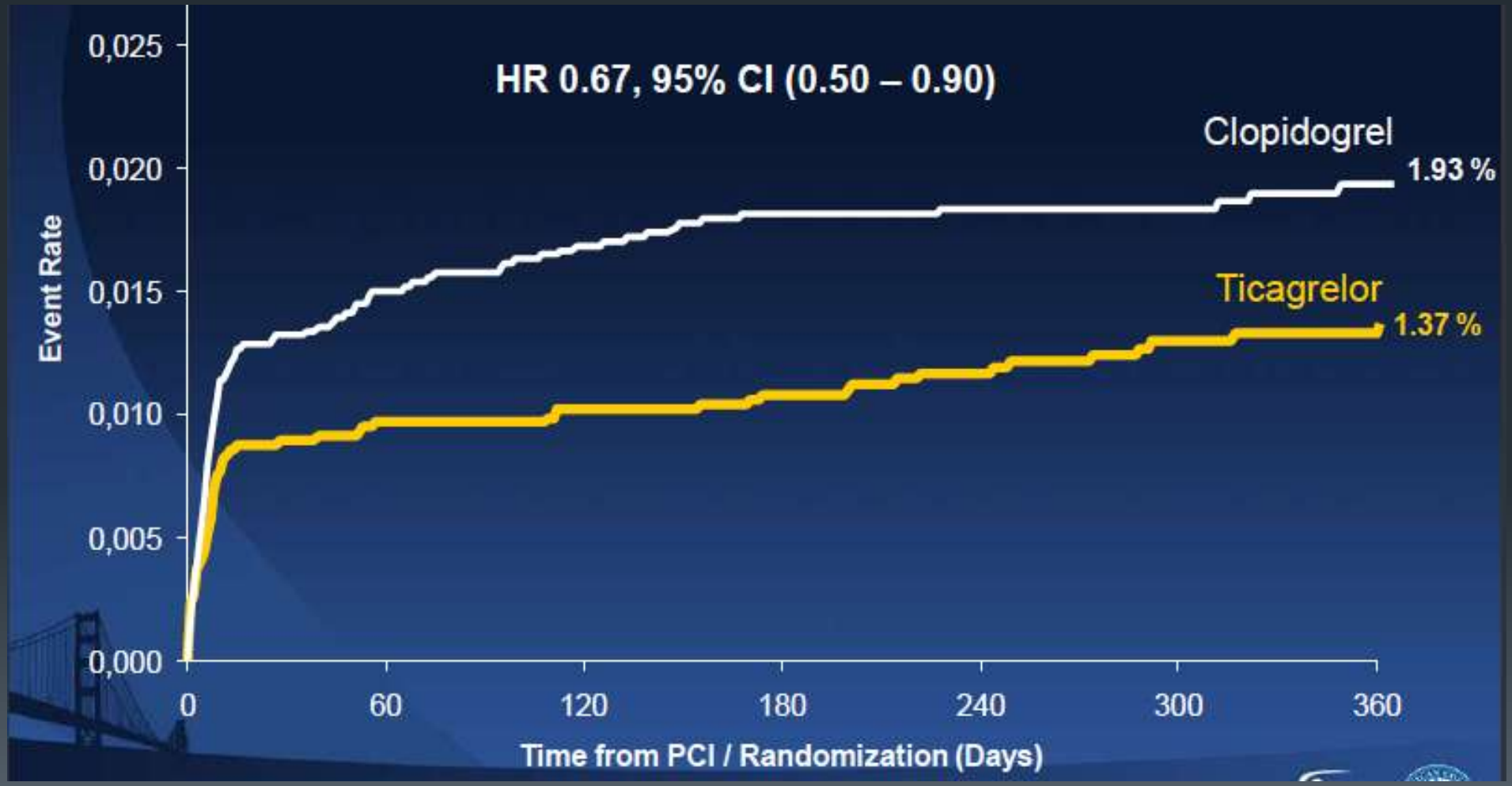
TRITON TIMI-38

Definite/Probable ST Any Stent (N=12.844)

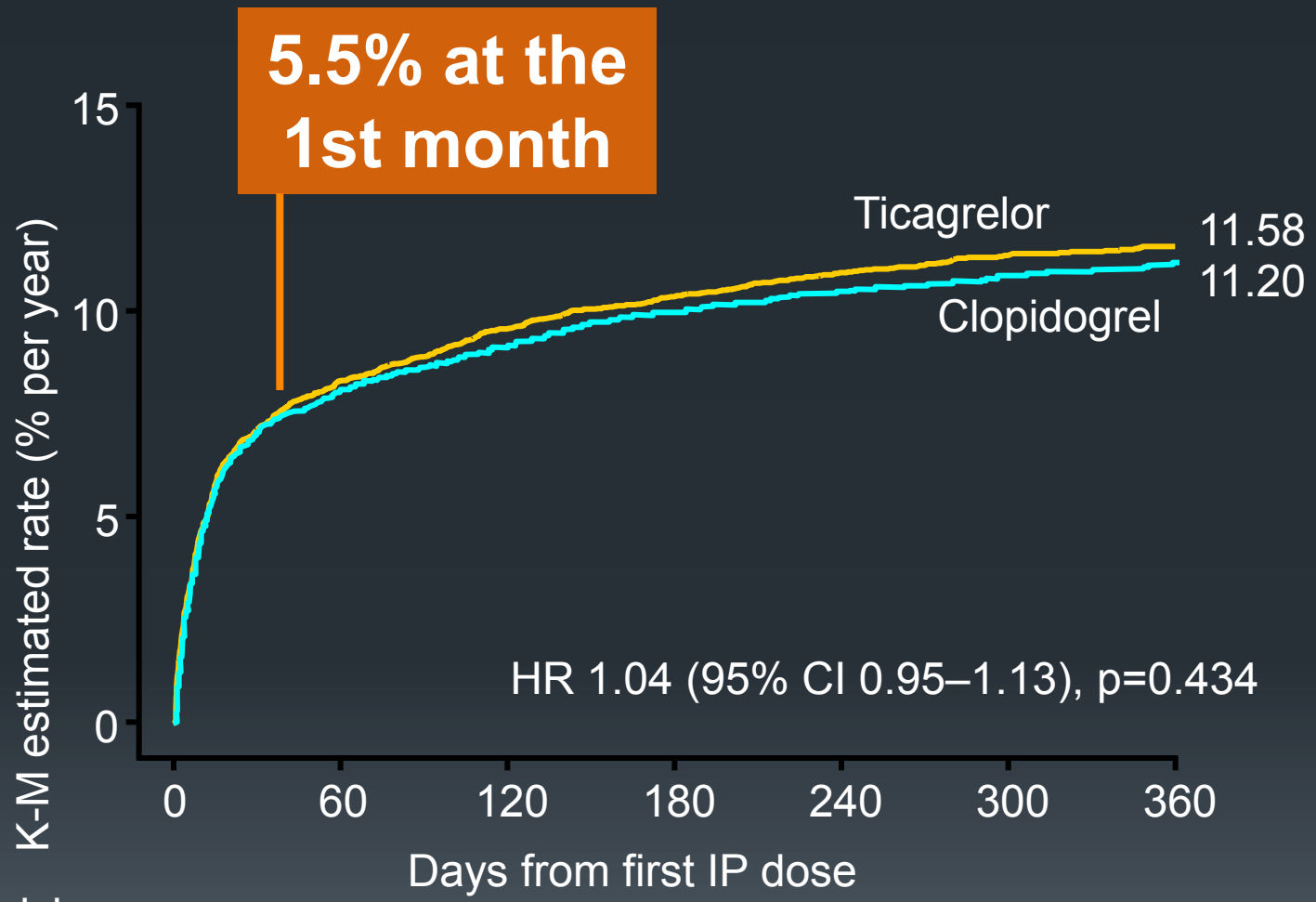


Antman EM. NYHA 2007

Definite Stent Thrombosis



Safety of Long Term DAPT



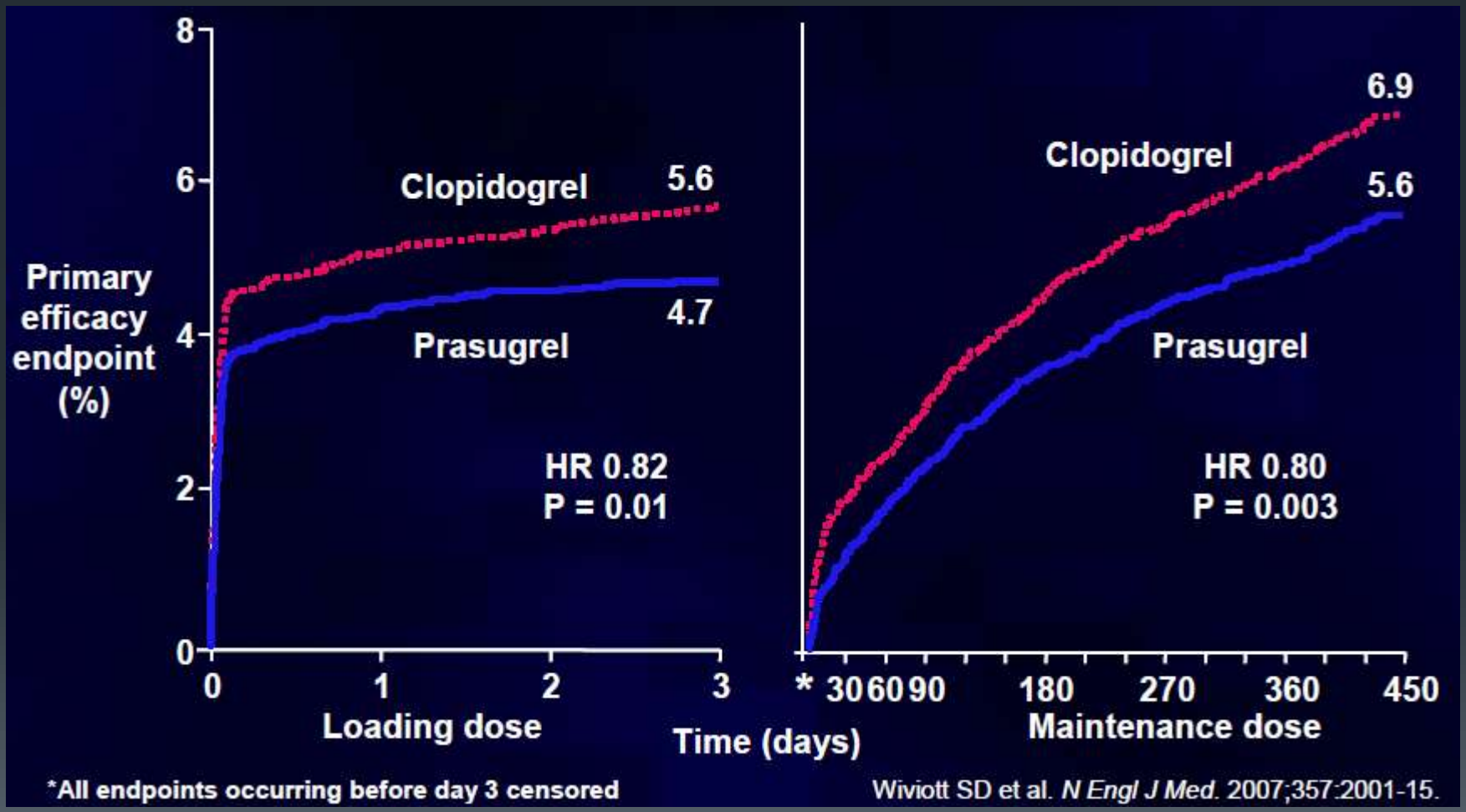
No. at risk

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

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

TRITON TIMI-38

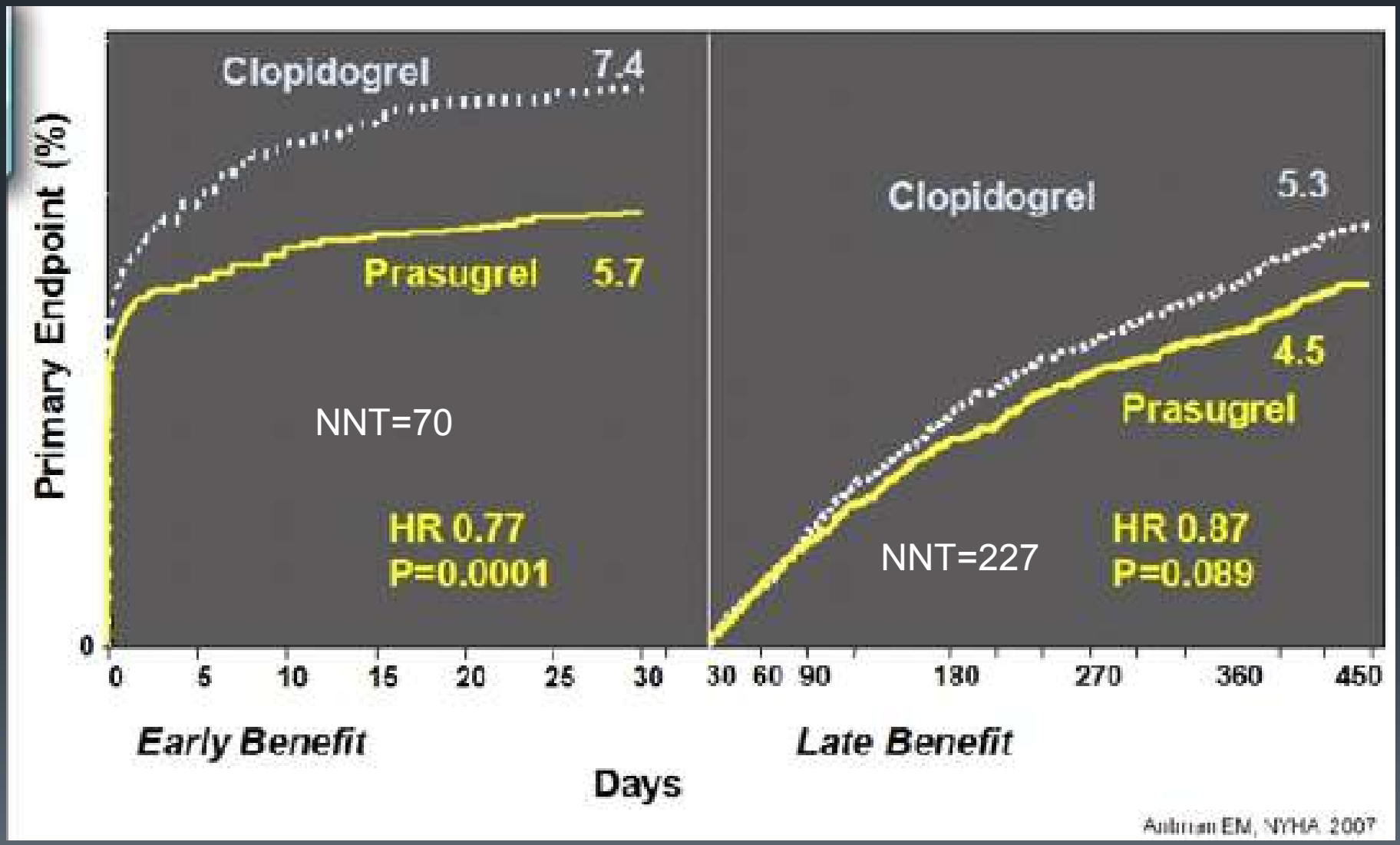
Timing of Benefit
Landmark Analysis



Wiviot SD, Braunwald E, McCabe CH et al NEJM 2007

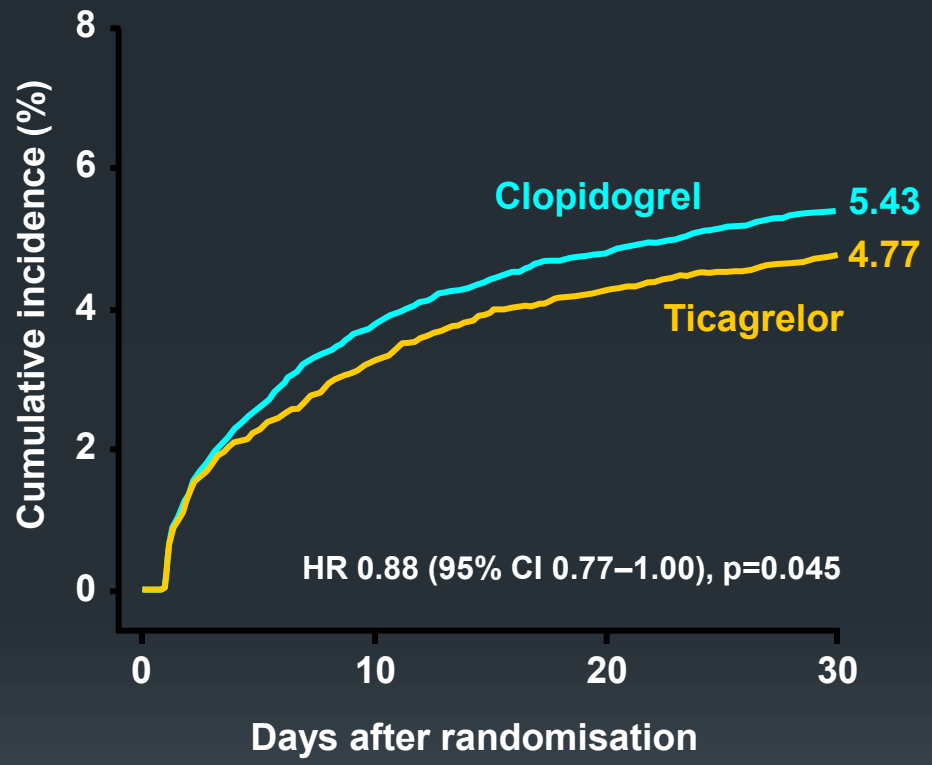
TRITON TIMI-38

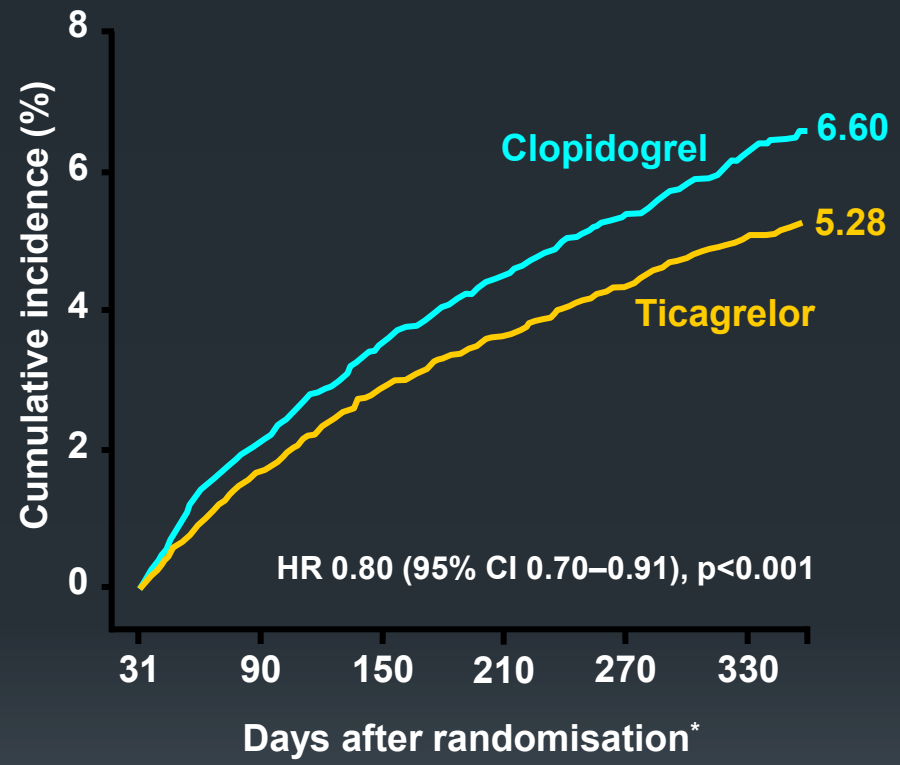
Timing of Benefit
(Landmark Analysis – 30 days)



Antman EM. NYHA 2007; http://circ.ahajournals.org/cgi/content/meeting_abstract/118/18_MeetingAbstracts/S_818-c

Primary efficacy endpoint over time (composite of CV death, MI or stroke)





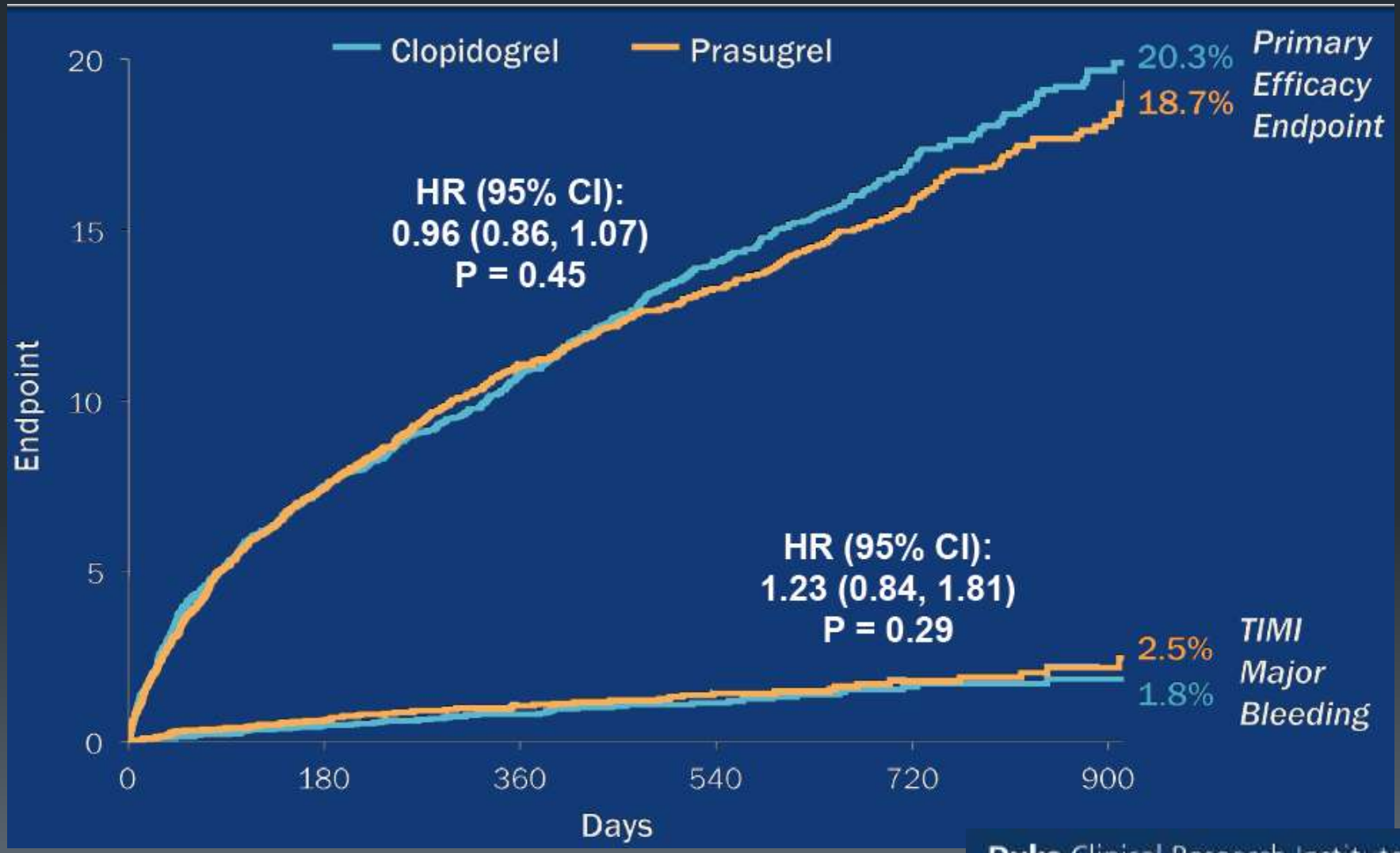
No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

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

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

TRILOGY ACS

Primary efficacy endpoint and TIMI Major Bleeding Through 30 months (Overall Population)



Duke Clinical Research Institute

GLOBAL LEADERS

The purpose of Global LEADERS is to compare:

Standard 12 months of DAPT following PCI

(and subsequent maintenance [12 month] antiplatelet therapy with ASA)

with

A new regimen involving 30 days of DAPT with ASA + ticagrelor

(and subsequent maintenance [23 month] therapy with ticagrelor)

In an <u>all-comers</u> population undergoing PCI with unrestricted biolimus eluting stent (BES) use

GLOBAL LEADERS

All-Comers PCI Population
ACS and Elective/Stable patients
(n=16,000)

Biolimus-eluting stent (BES)
BioMatrix Flex ™

1:1 Randomization, Open-Label Design

ASA Ticagrelor

Study Treatment Strategy

1-month
ASA + Ticagrelor

23-months
monotherapy Ticagrelor

Reference Treatment Strategy

12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + Clopidogrel)

12-months
monotherapy ASA

ASA Ticagrelor Clopidogrel

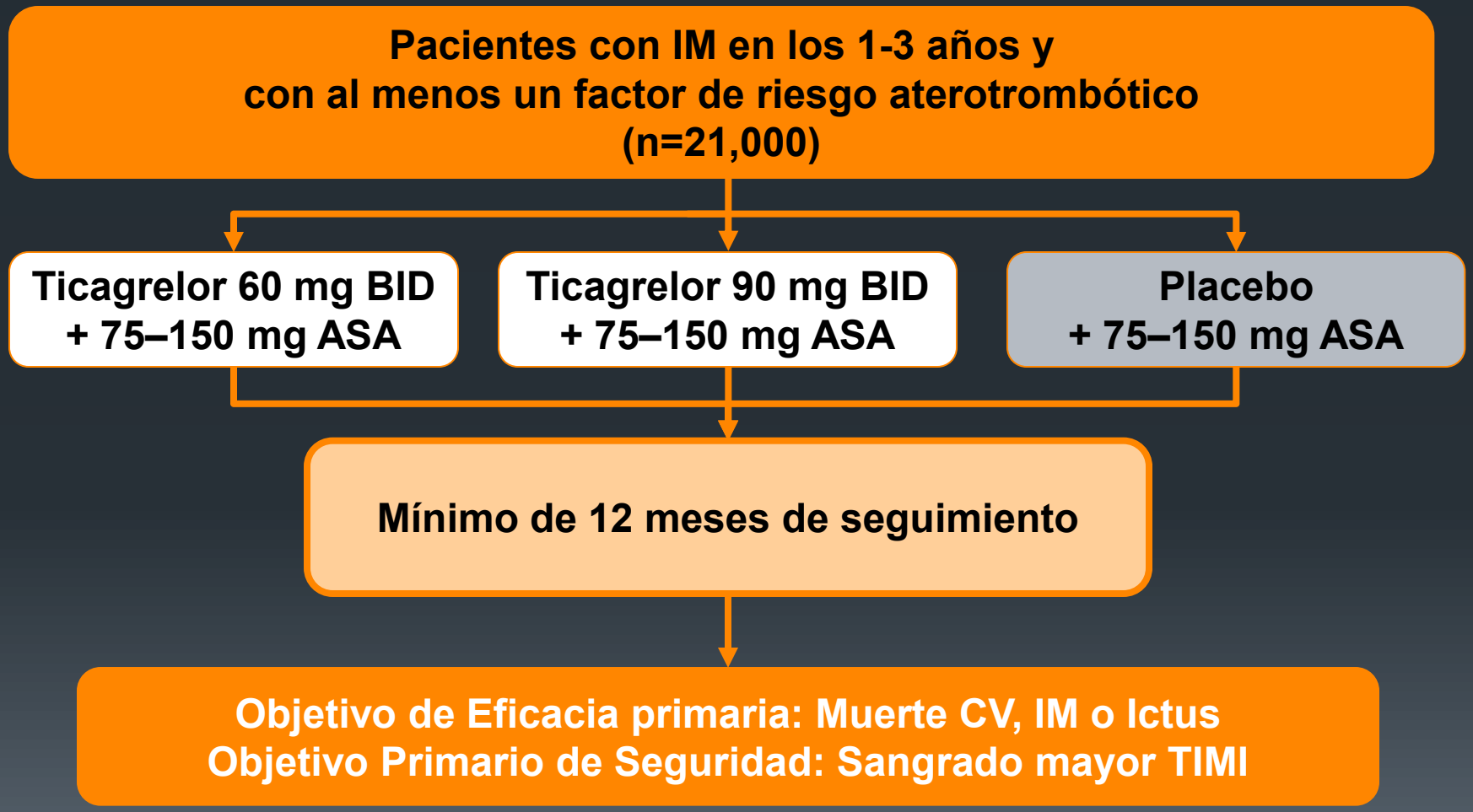
[Not allowed in elective pts]

[Only in elective pts]

Primary Endpoint

Study treatment strategy superior to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI

PEGASUS TIMI 54



CONCLUSIONES

- **Los nuevos antiagregantes nos dan la opción de adaptar el tipo de tratamiento al tipo de paciente**
- **A diferencia de clopidogrel, ambos, aunque sobre todo ticagrelor, mantienen e incluso incrementan la eficacia en el seguimiento.**
- **La seguridad no parece verse comprometida**

La importancia del tratamiento “a medida”

HUELVA