Antiagregacion plaquetaria y stents coronarios.

Que no sabemos aun?

Dr. Pedro Hidalgo Useche

Cardiólogo Intervencionista

Maracaibo-Venezuela

Un sismo de 5,5° Richter se sintió ayer viernes

Presidente de Perú: "Los muertos posiblemente llegan a 500"

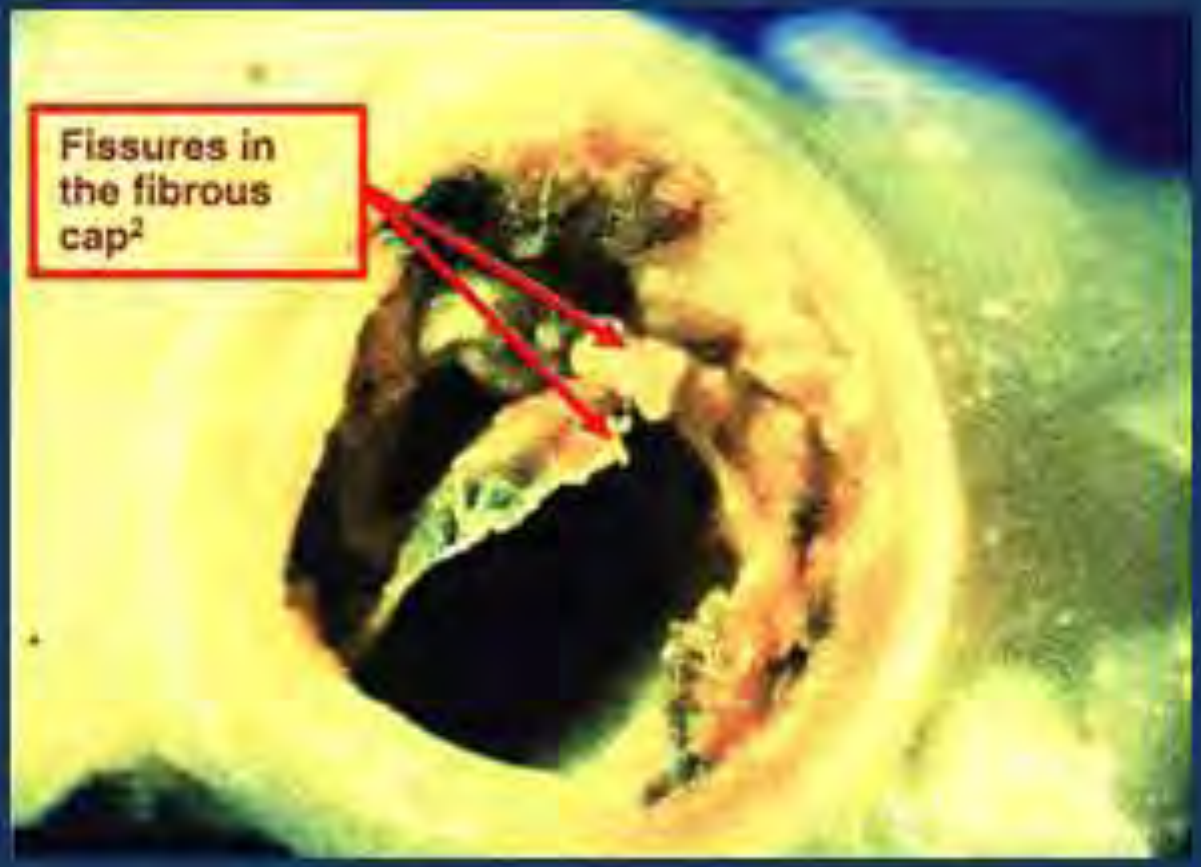
EFE. AFP. Lima. El número de muertos por el terremoto que se produjo el miércoles en Perú es actualmente de 497 y "posiblemente puedan pasar de 500", dijo el viernes el presidente peruano, Alan García, desde Pisco, una de las ciudades más afectadas, precisando que se trata de un reporte parcial, señaló AFP.

"Hasta la madrugada, sin precisión exacta ni de nombres, el balance es de 497 fallecidos. Todavía no hay una cifra que pueda ser oficial pero posiblemente pueda pasar de 500, lamentablemente", expresó el presidente al ser consultado por la prensa.

"Yo he estado hace unos momentos en la catedral (de Pisco, que se derrumbó el miércoles) cuando se recuperó un cuerpo. Según los rescatistas y bomberos, todavía hay decenas de cuerpos

Fotos: EFE

Más 500.000 personas mueren anualmente de Enfermedad Coronaria en USA[1]



CHD = Coronary heart disease

1.- American Heart Association. Heart Disease and Stroke Satistic – 2003 Update.

2.- Davies MJ. Satbility: Two faces of coronary atherosclerosis. Circulation 1999 , 94:2013 - 2020

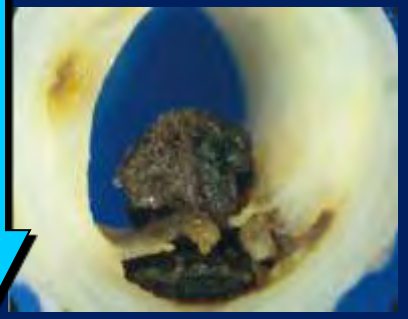
SCA enfoque moderno

SINDROME CORONARIO AGUDO

Sin elevación del ST

Elevación del ST

EKG inicial



IM sin ST

Angina Inestable

IMNQ

IM Q

Dx Egreso

Infarto del Miocardio

Drogas Antitromboticas usadas en SCA/PCI

I. Drogas Antiplaquetarias

- Inhibidores de la COX-1 (aspirin)
- Inhibidores de P2Y12(ticlopidine; clopidogrel; prasugrel; ticagrelor)
- Inhibidores Glycoprotein IIb/IIIa (abciximab; eptifibatide; tirofiban)

II. Drogas Anticoagulantes

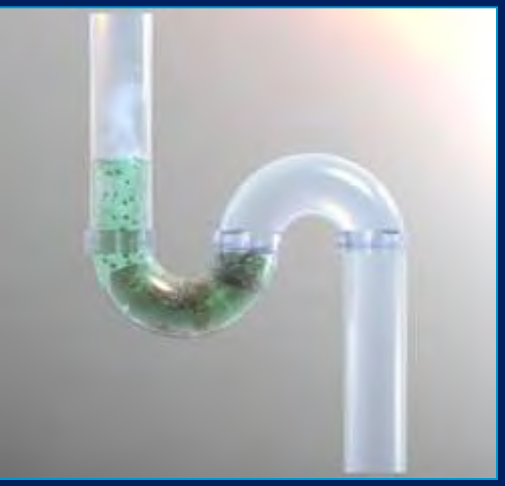
- Anti-Factor II (anti-thrombinicos)
  - Inhibidores Indirectos de la Trombina (UFH & LMWH)
  - Inhibidores Directos de la Trombina (Bivalirudina),Dabigratan
- Anti-Factor X
  - Fondaparinux, rivaroxaban, apixaban

Drogas antitromboticas usadas en SCA/PCI

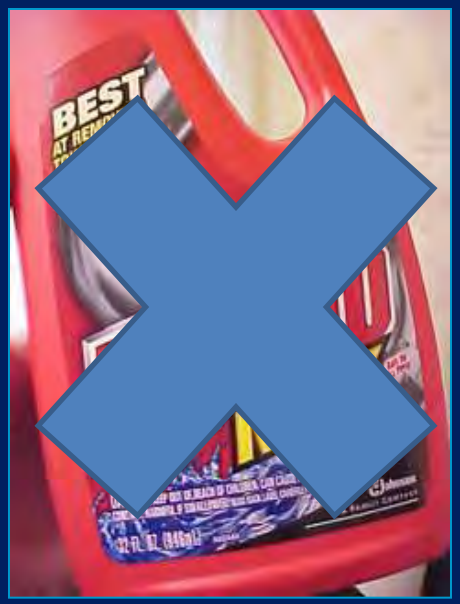
Cual es tu Cocktail?

CAFE
CON
LECHE

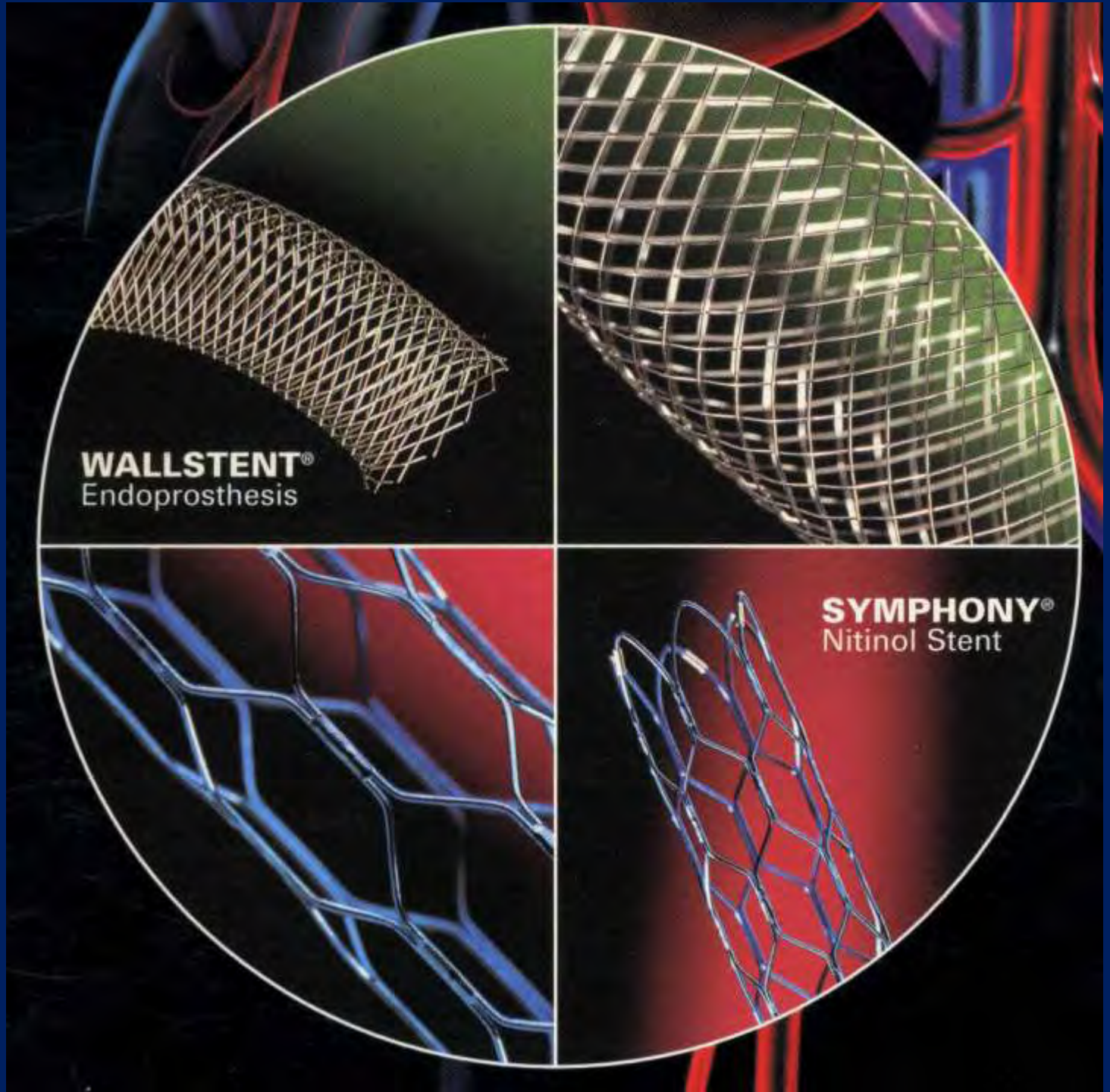
Infarto de miocardio



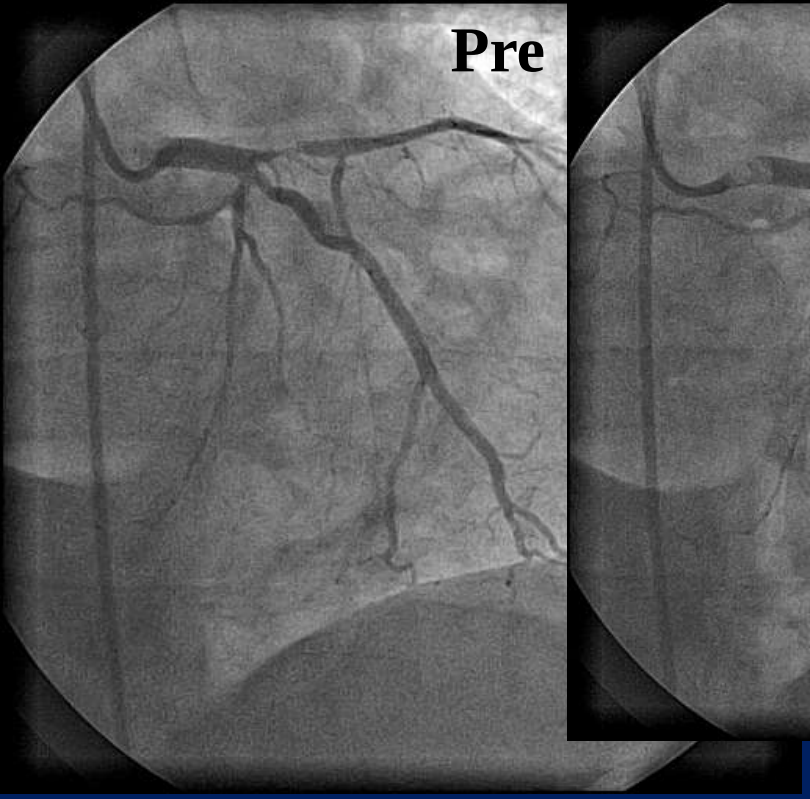
Solución médica

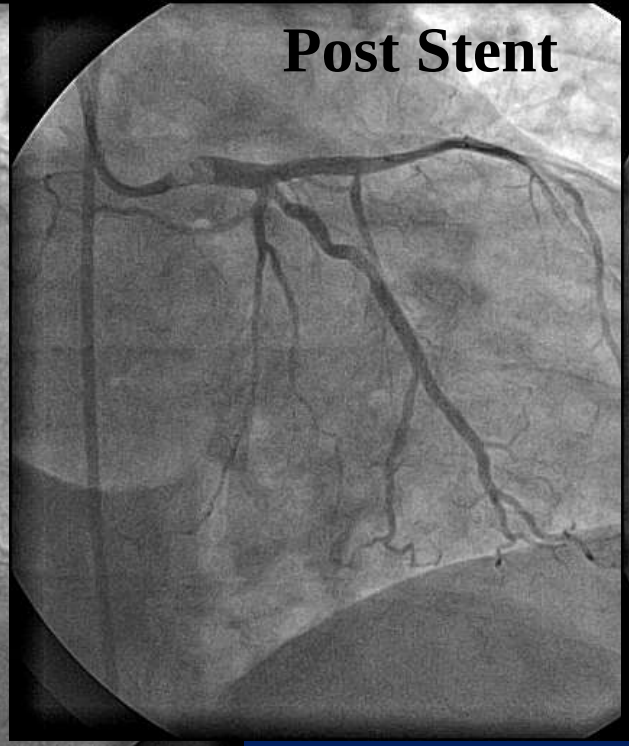


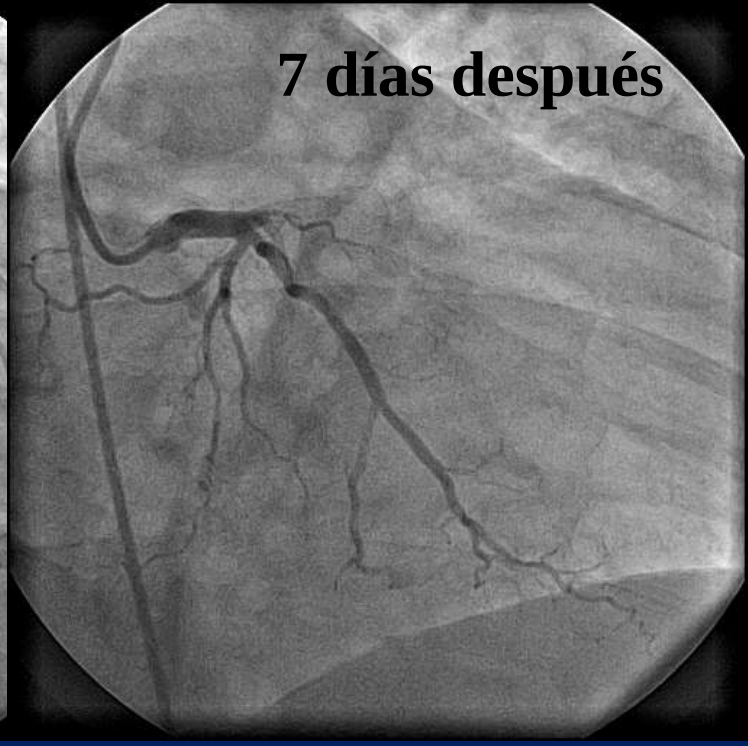
Solución mecánica

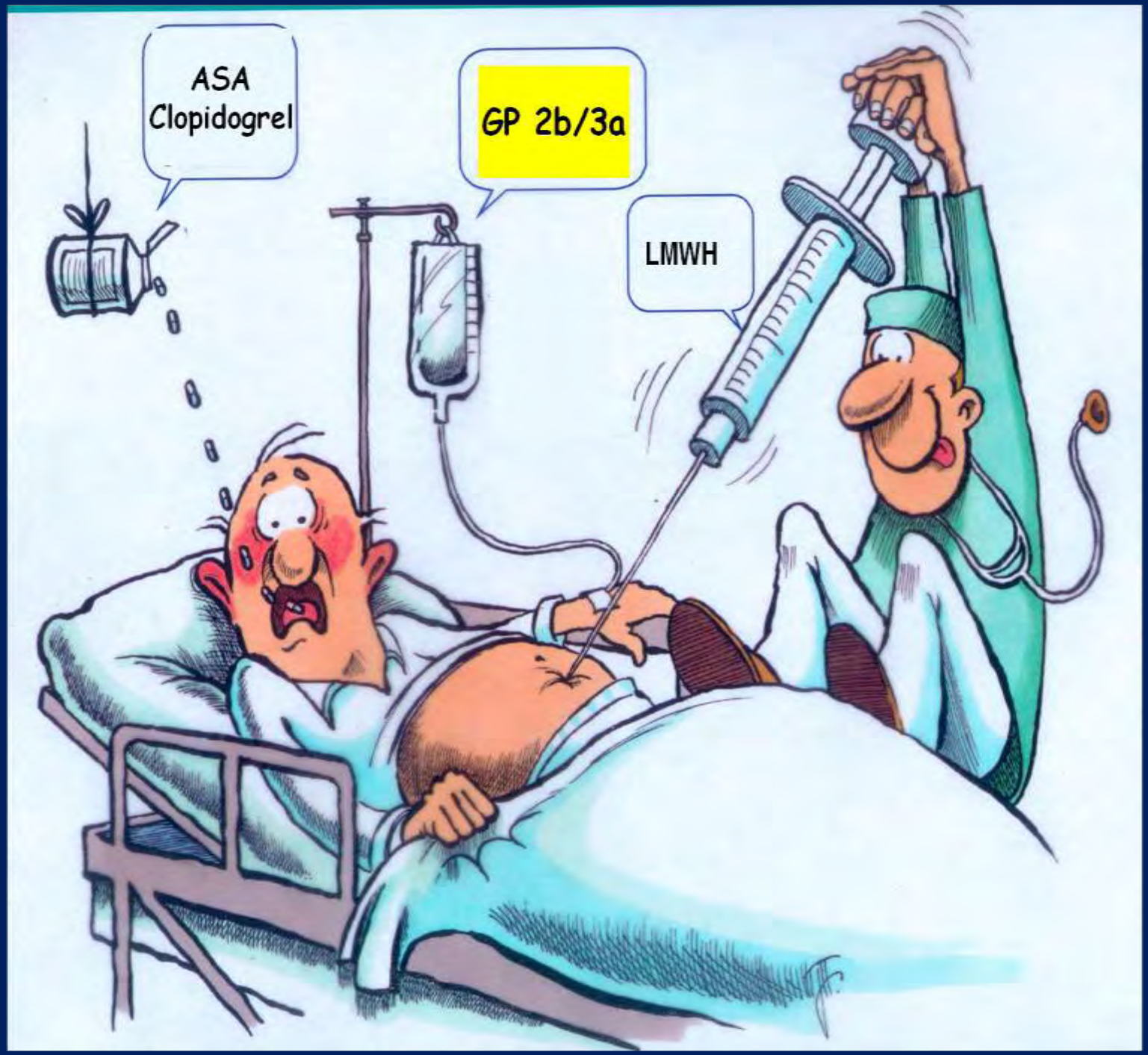

WALLSTENT®
Endoprosthesis
SYMPHONY®
Nitinol Stent

Stents Recubiertos de Drogas vs. Metálicos Desnudos:

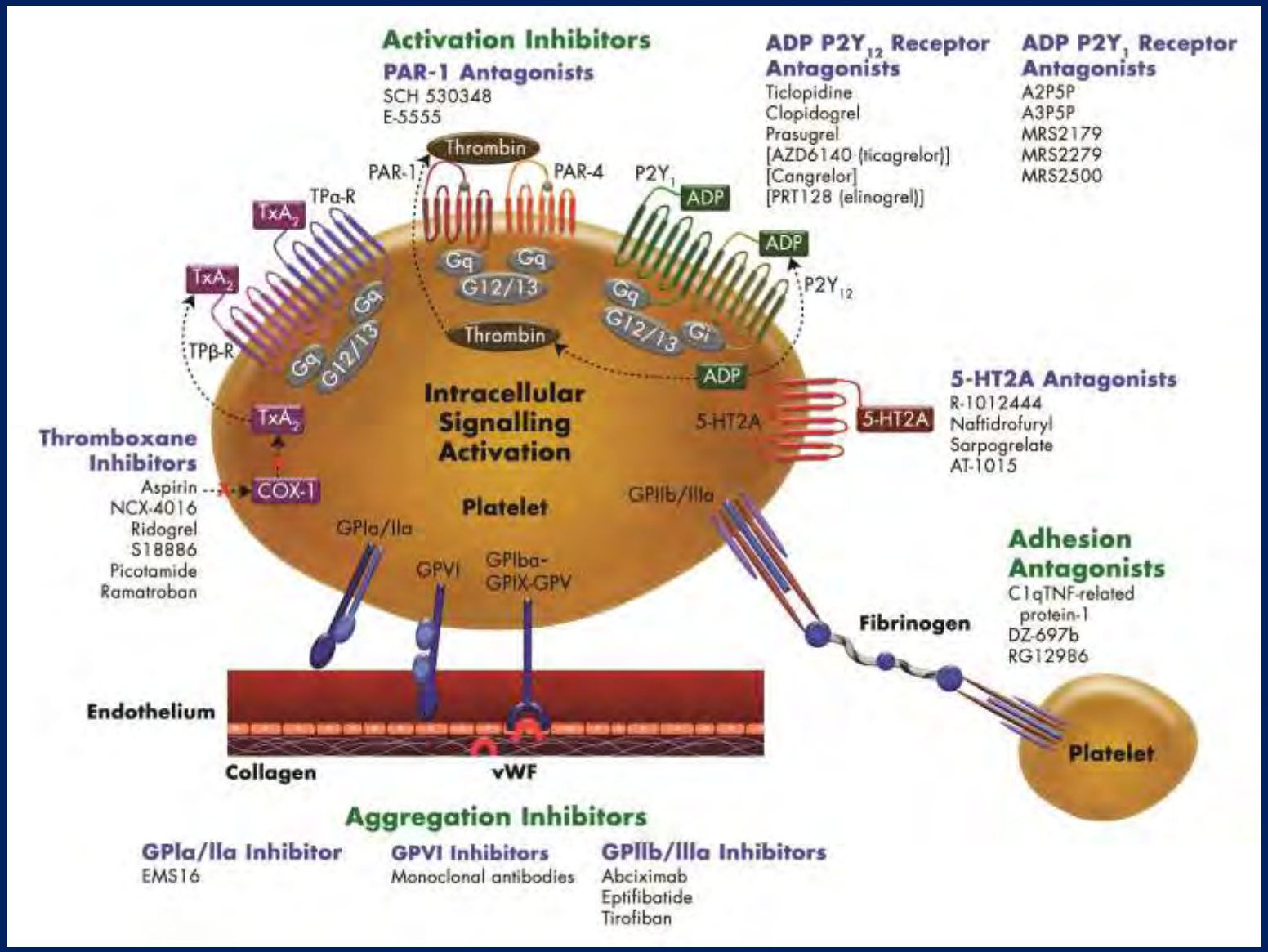

Pre


Post Stent


7 días después


ASA
Clopidogrel
GP 2b/3a
LMWH

Antiagregación Plaquetaria, nos está faltando algo aun ?

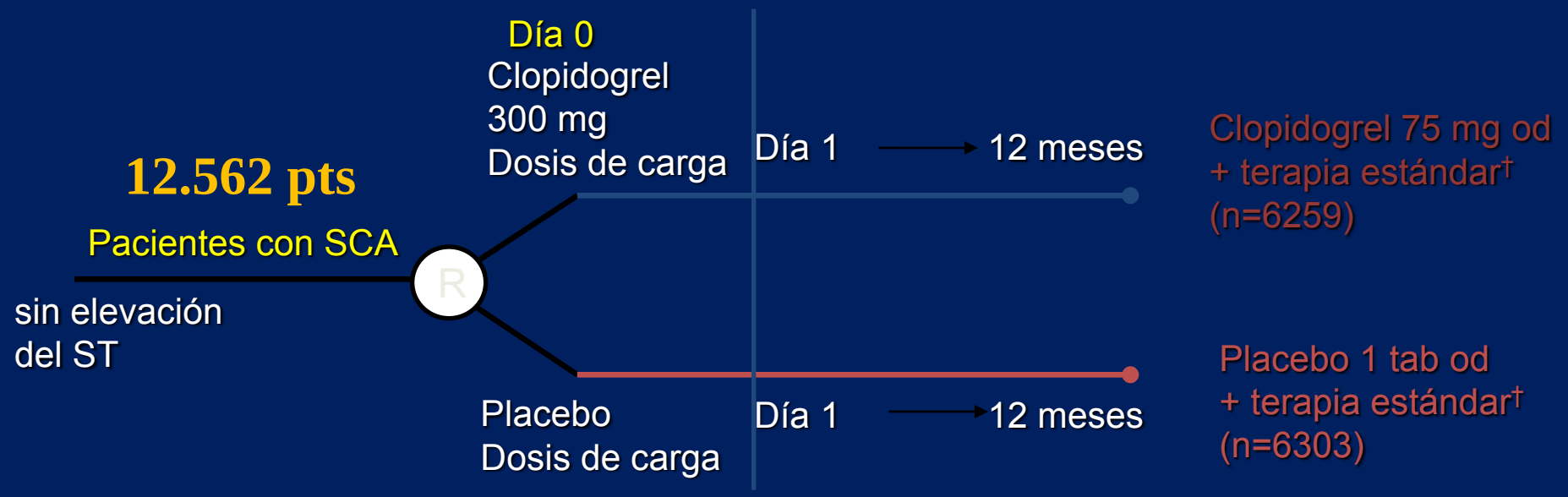


European Heart Journal, 2010

PARTE 1

CLOPIDOGREL

CURE: Diseño

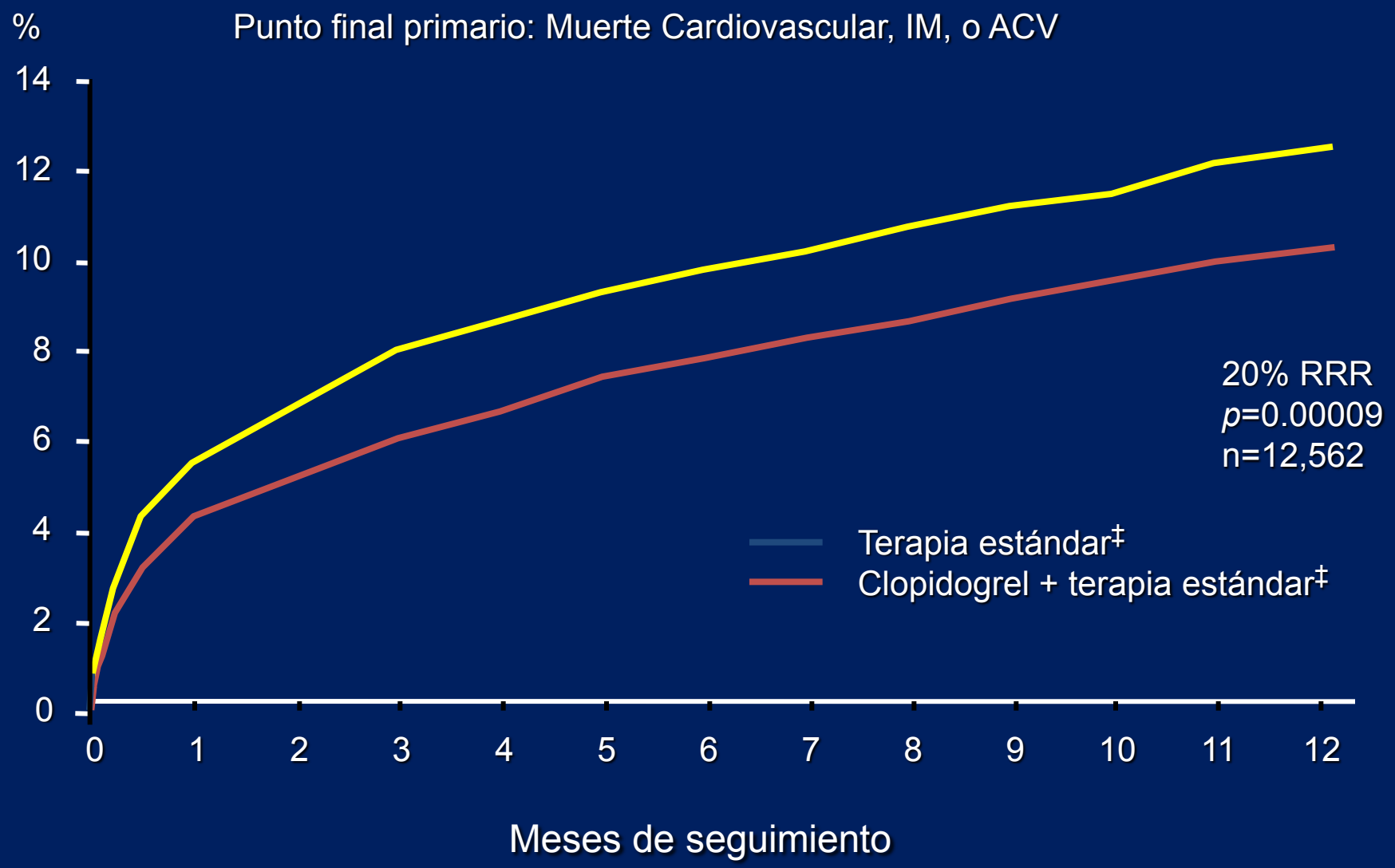


R=Randomización, occurrida dentro de las 24 horas de inicio de síntomas

† La terapia estándar siempre incluyó ASA, y pudo también incluir heparina, HBPM, inhibodores GP IIb/IIIa post-randomización, beta-bloqueadores, IECAs, agentes hipolipemiantes, y/o otras terapias o intervenciones (e.g. PTCA, CABG) a discreción del médico.

CURE Study Investigators. *Eur Heart J* 2000; 21:2033–2041
The CURE Investigators. *N Eng J Med 2001; 345: 494-502*

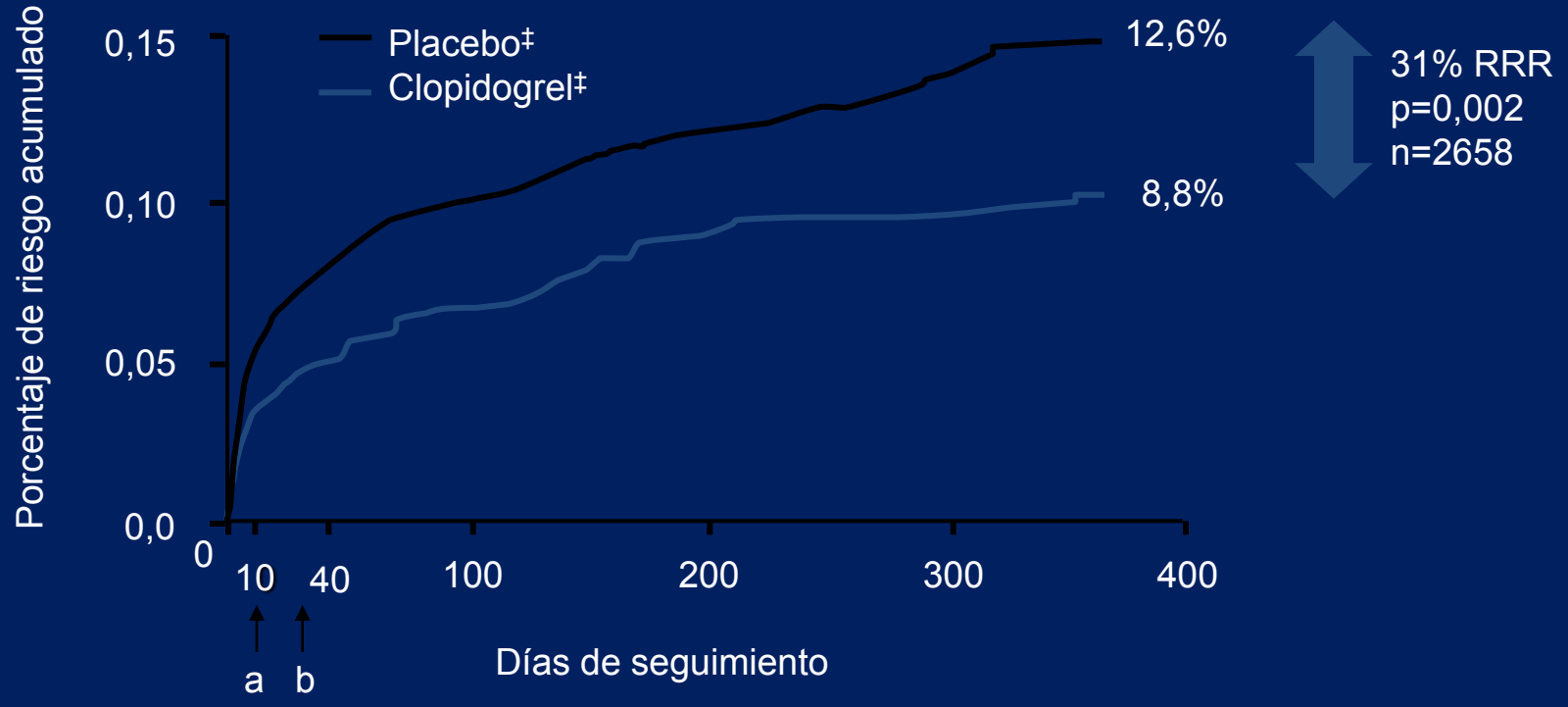
Resultados de Eficacia: Variable Primaria



The CURE Investigators. *N Eng J Med 2001; 345: 494-502*

PCI-CURE –Eficacia del clopidogrel a largo plazo

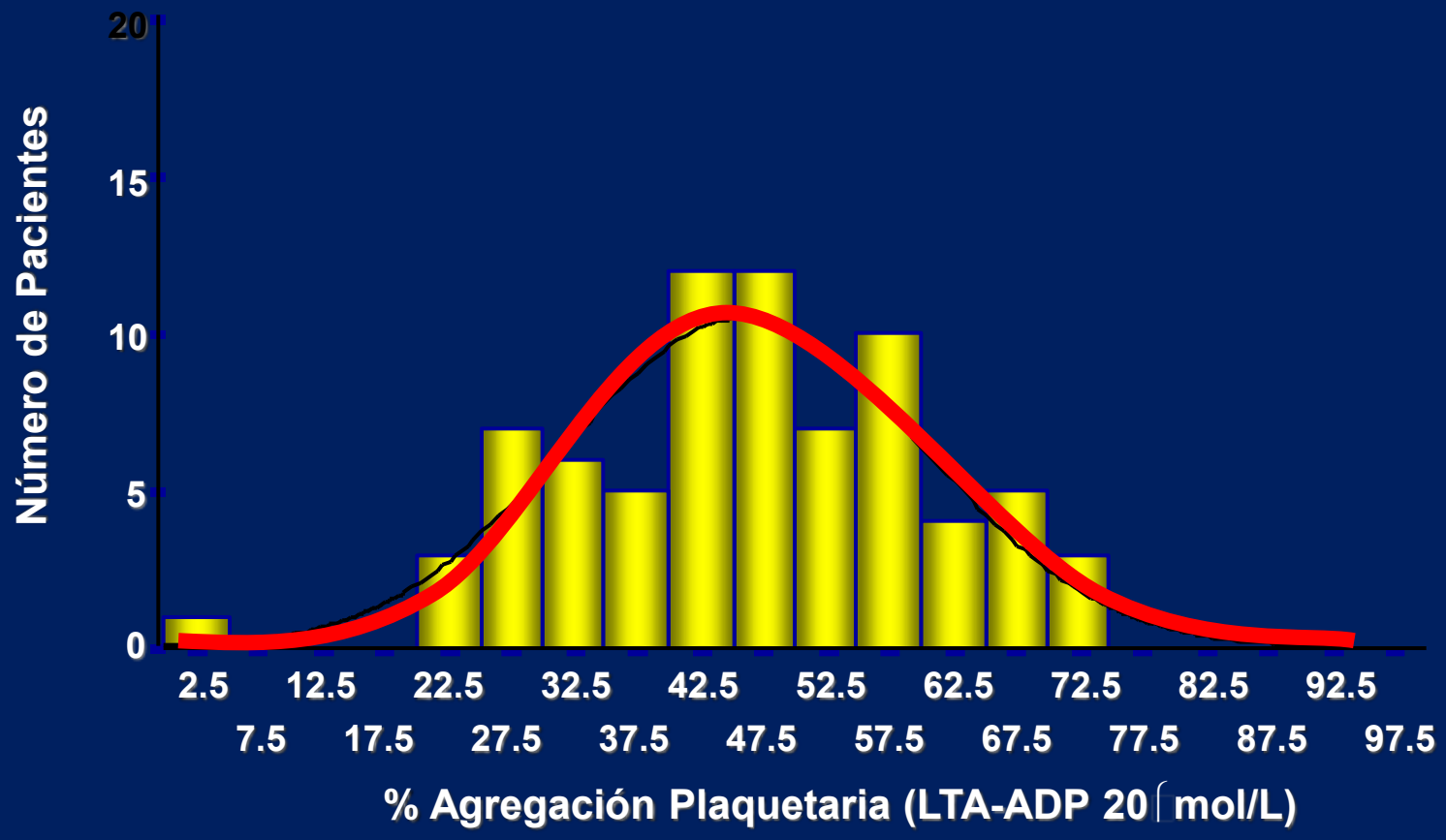
Muerte cardiovascular o IM desde la randomización hasta el final del seguimiento†



The CURE Investigators. Lancet August 2001

a = tiempo medio desde la randomización hasta el PCI (10 días)
b = 30 días después del tiempo medio del PCI
†hasta 12 meses ‡sumado a la terapia standard incluyendo ASA

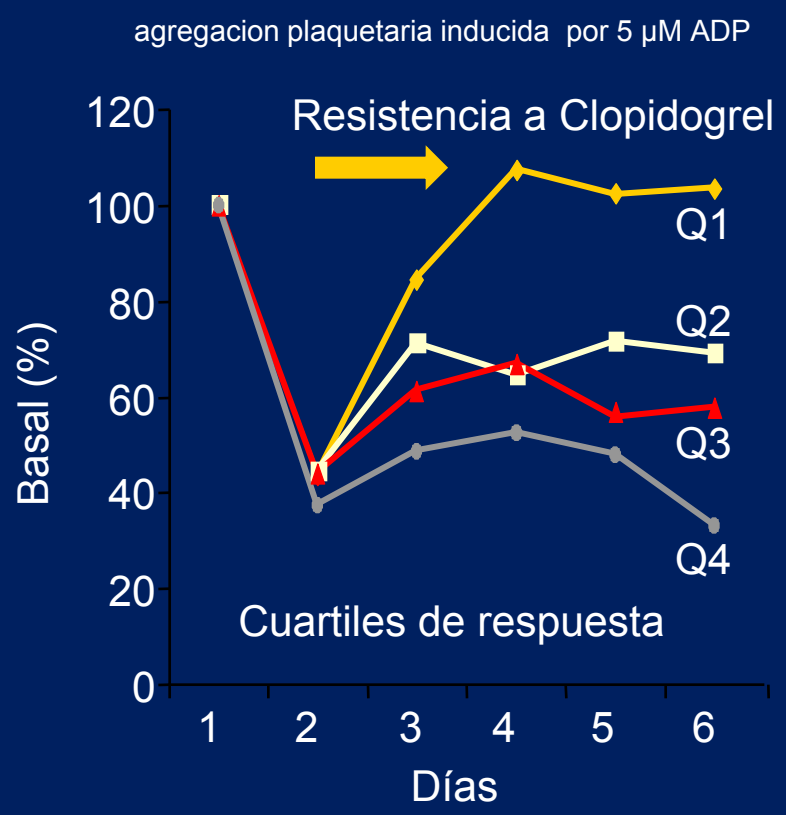
Variabilidad de respuesta individual a la Terapia Antiplaquetaria Dual en la Fase Estable del Tratamiento

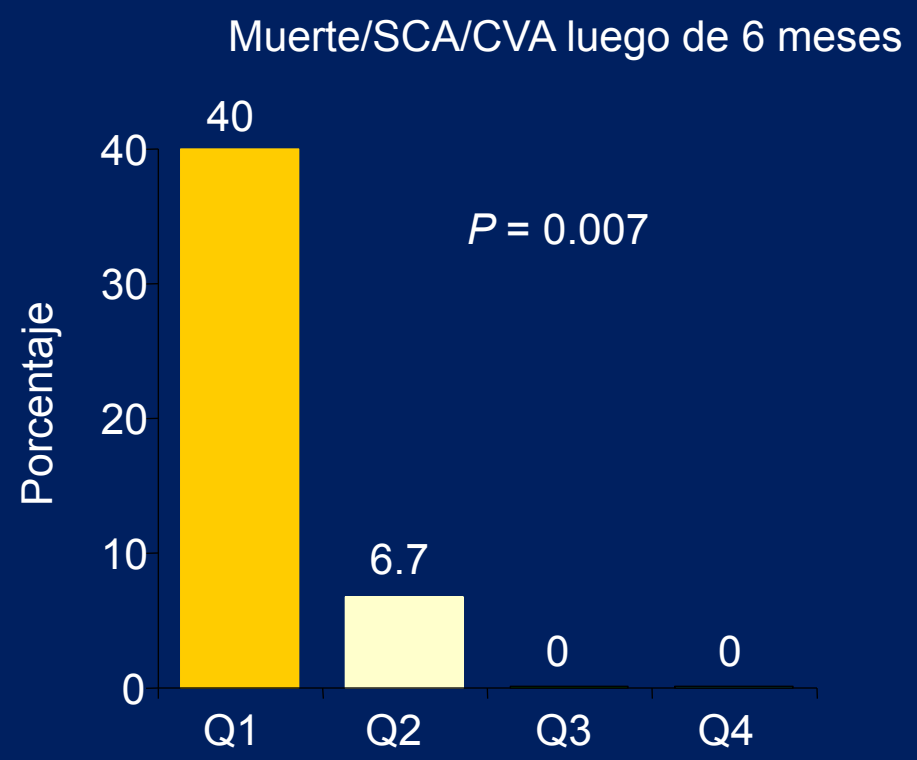


Angiolillo DJ, Fernandez-Ortiz A, et al. *Am J Cardiol*. 2006;97:38-43.

Variabilidad de Respuesta a Clopidogrel 300 mg (LD) y 75 mg (MD) y Riesgo Aumentado de Eventos Isquémicos seguidos por 6 meses

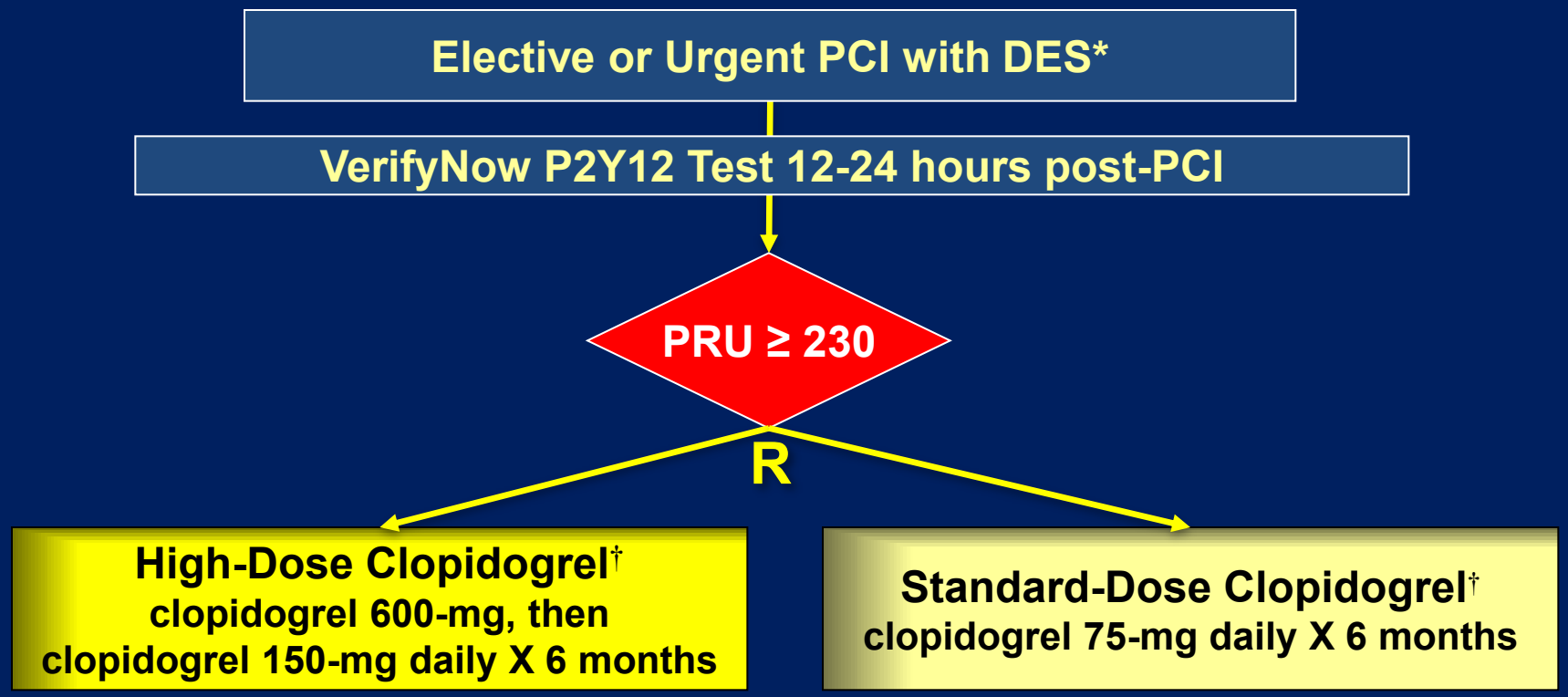
PCI Primaria para STEMI (n = 60)





Matetzky S, et al. *Circulation*. 2004 Jun 29;109(25):3171-5.
Wiviott SD, Antman EM. *Circulation*. 2004 Jun 29;109(25):3064-7.

GRAVITAS Study Design



Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
Key Safety Endpoint: GUSTO Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled All patients received aspirin (81-162mg daily)

RESISTENCIA AL CLOPIDOGREL….

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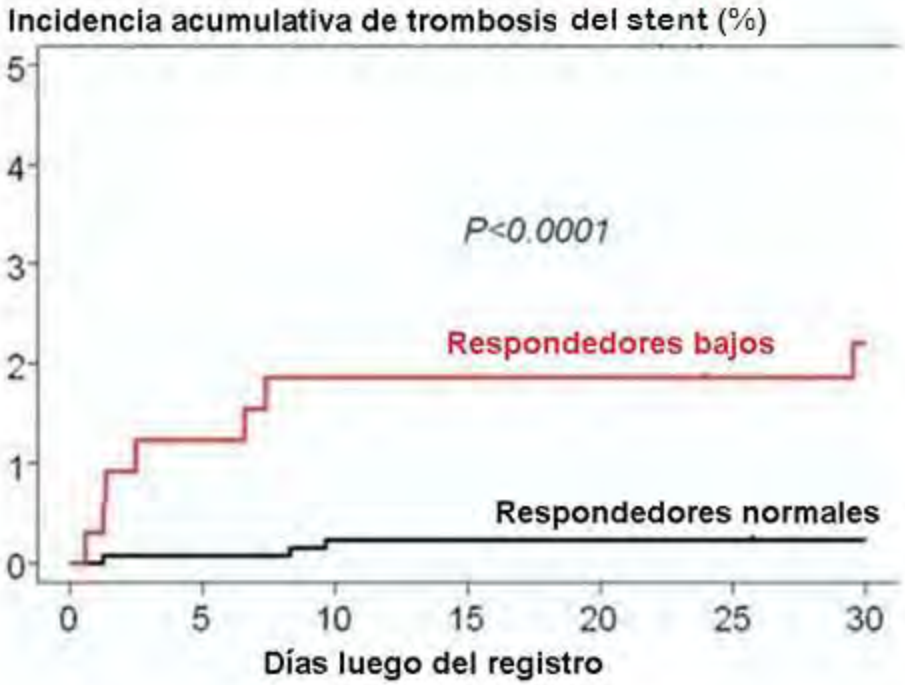
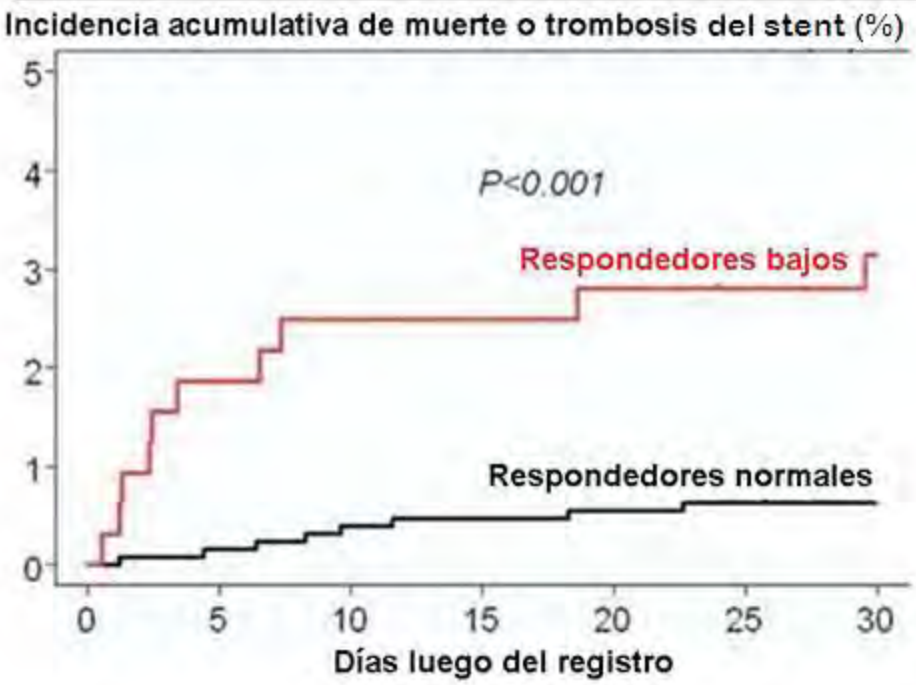
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.11.030

Platelet Reactivity After Clopidogrel Treatment Assessed With Point-of-Care Analysis and Early Drug-Eluting Stent Thrombosis

Dirk Sibbing, MD, Siegmund Braun, MD, Tanja Morath, MS, Julinda Mehilli, MD, Wolfgang Vogt, MD, Albert Schömig, MD, Adnan Kastrati, MD, Nicolas von Beckerath, MD

Munich, Germany

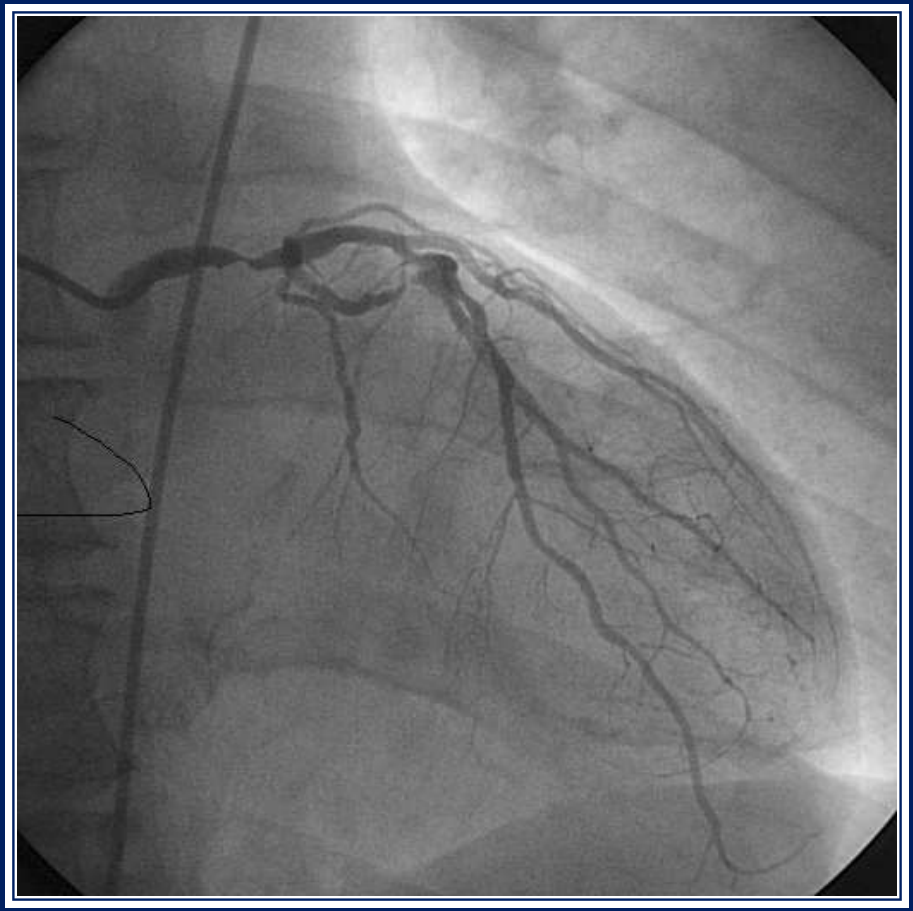


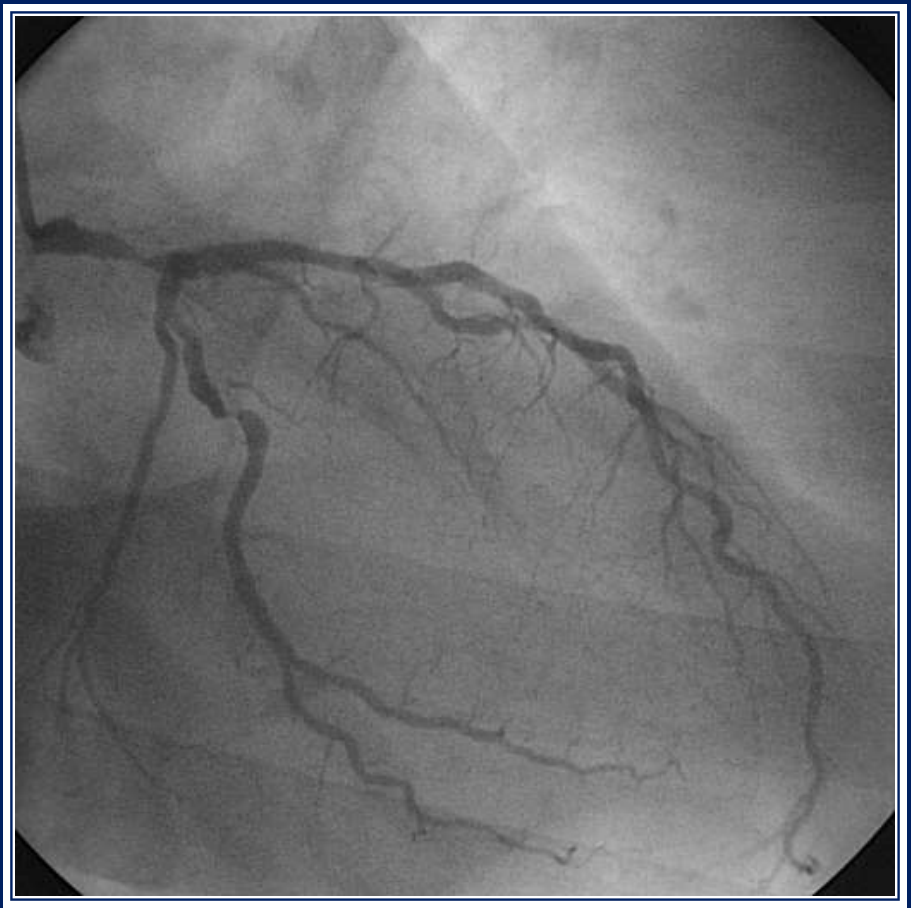


Sibbing D, et al JACC 2009;53:849-856

Caso clínico III:

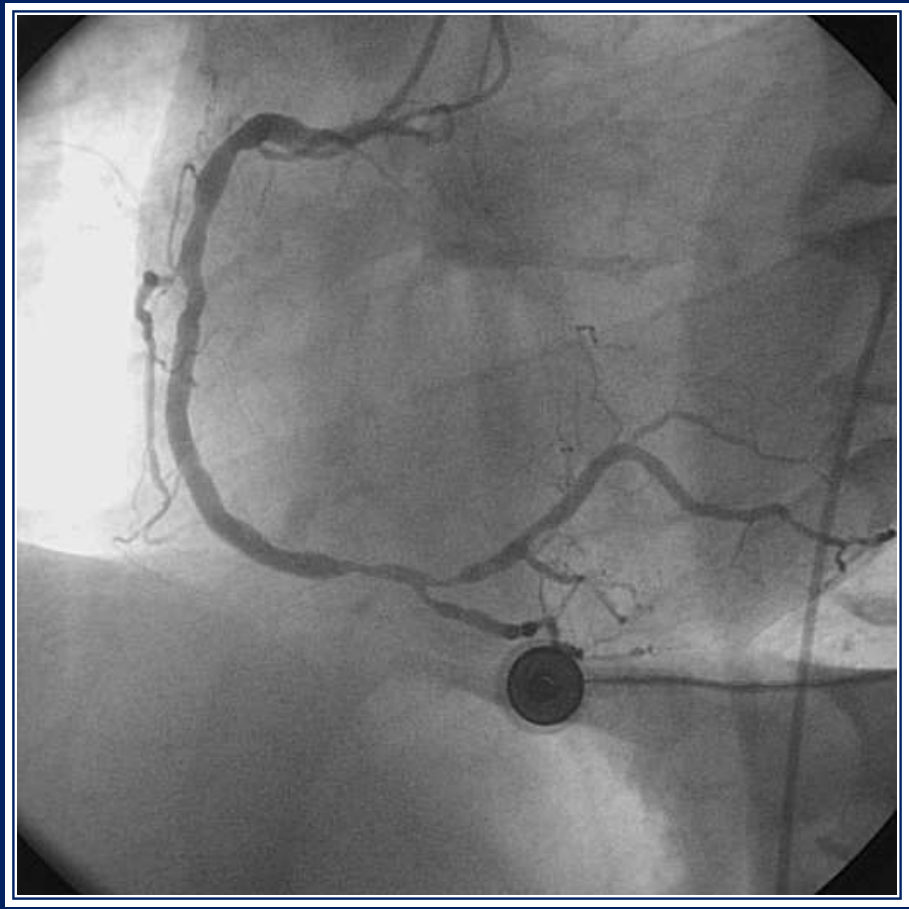
Coronariografía: arteria coronaria izquierda

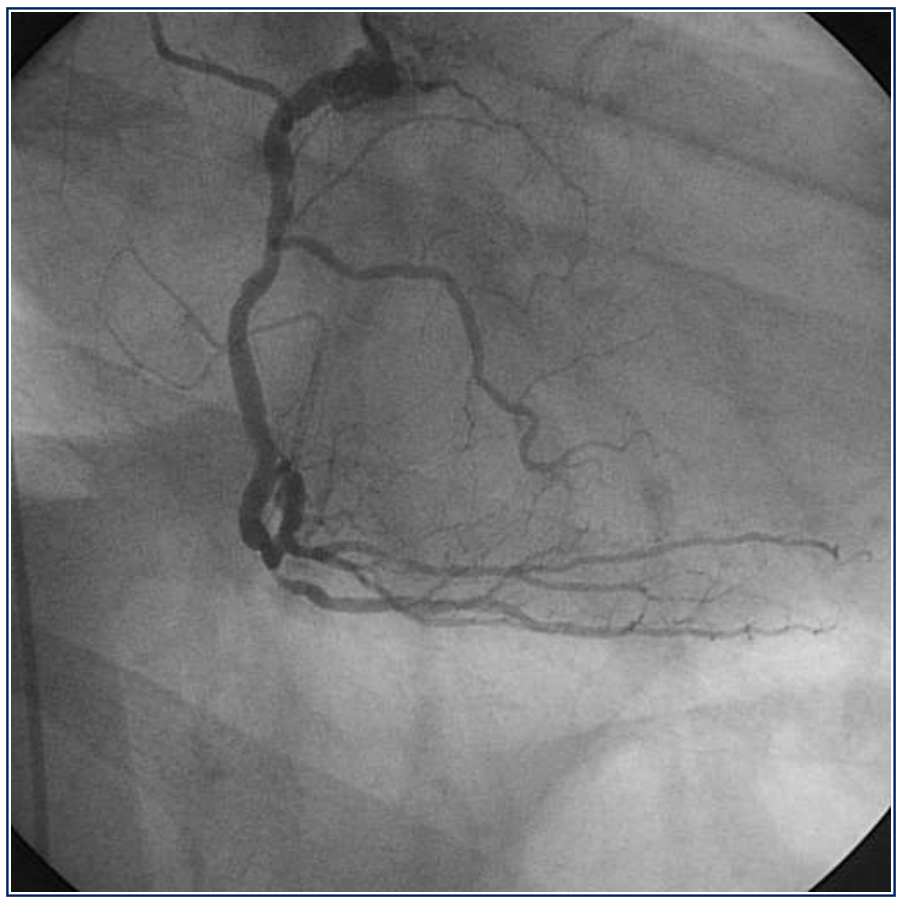




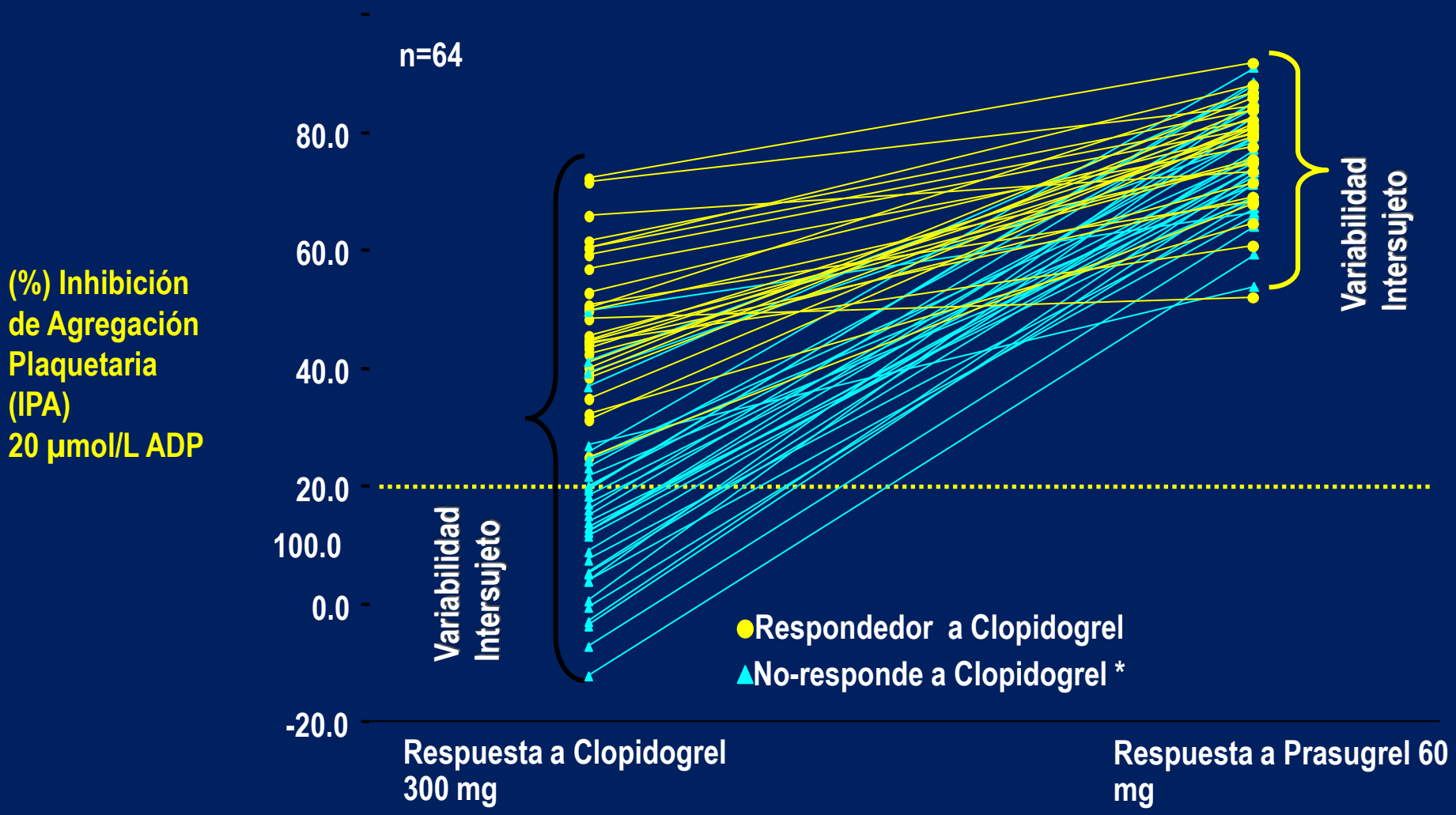
Caso clínico III:

Coronariografía: arteria coronaria derecha





Variabilidad Intersujeto Reducida con Prasugrel a las 24 Horas (Voluntarios Sanos)



*no responde a Clopidogrel =IAP < 20% medida a las 4-horas o a las 24-horas.
ADP=Adenosine Diphosphate. IPA=Inhibición de Agregación Plaquetaria.

Adaptado de Brandt JT et al. *Am Heart J* 2007;153:66.e9-e16.

PARTE 2

PRASUGREL

TRITON-TIMI 38 Trial

The NEW ENGLAND JOURNAL of MEDICINE

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

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

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

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,600

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1° endpoint: CV death, MI, Stroke

2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch

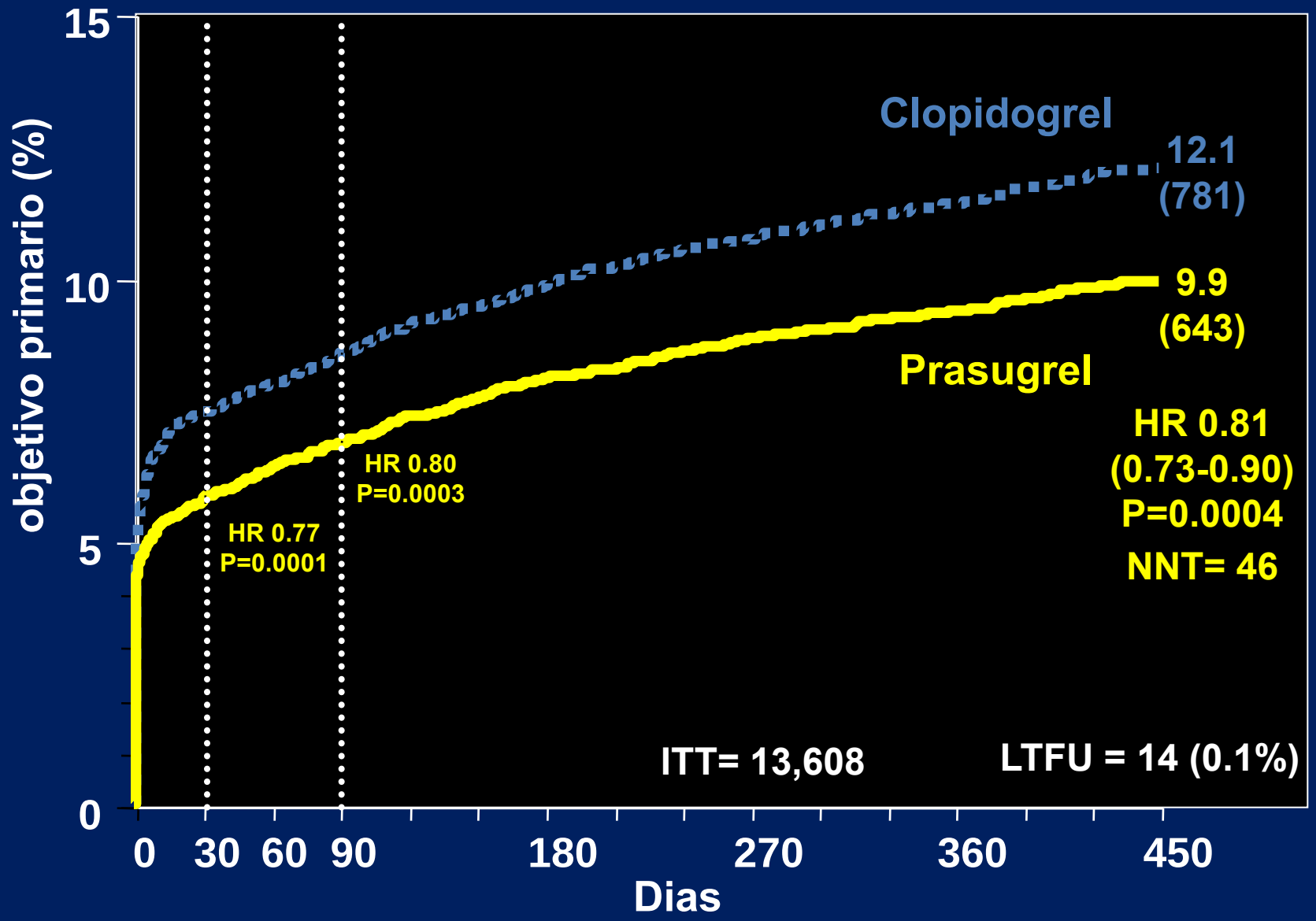
CV death, MI, UTVR

Stent Thrombosis (ARC definite/prob.)

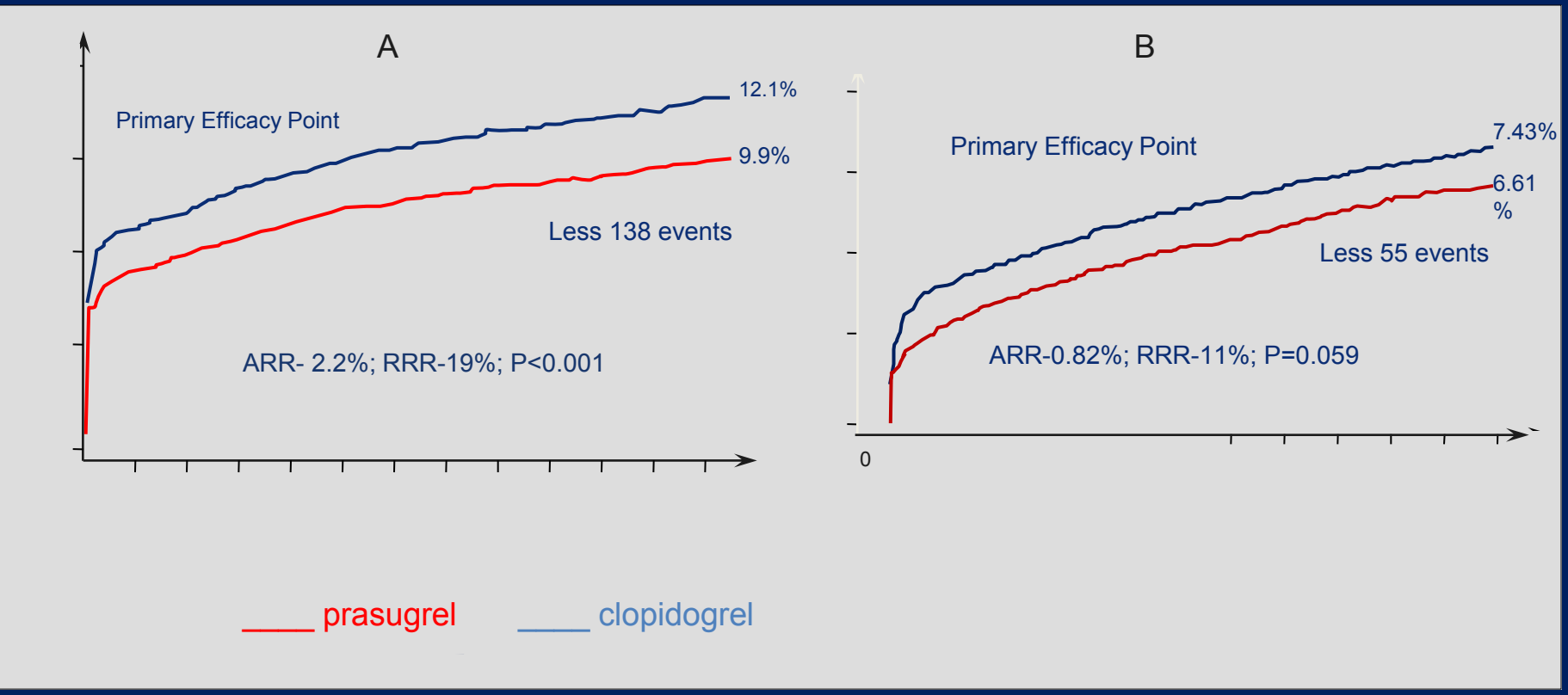
Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Objetivo Primario
Obito CV ,IM o ACV



Estudio TRITON, controversia en Eficacia



A : Eventos adjudicados NEJM; 2007

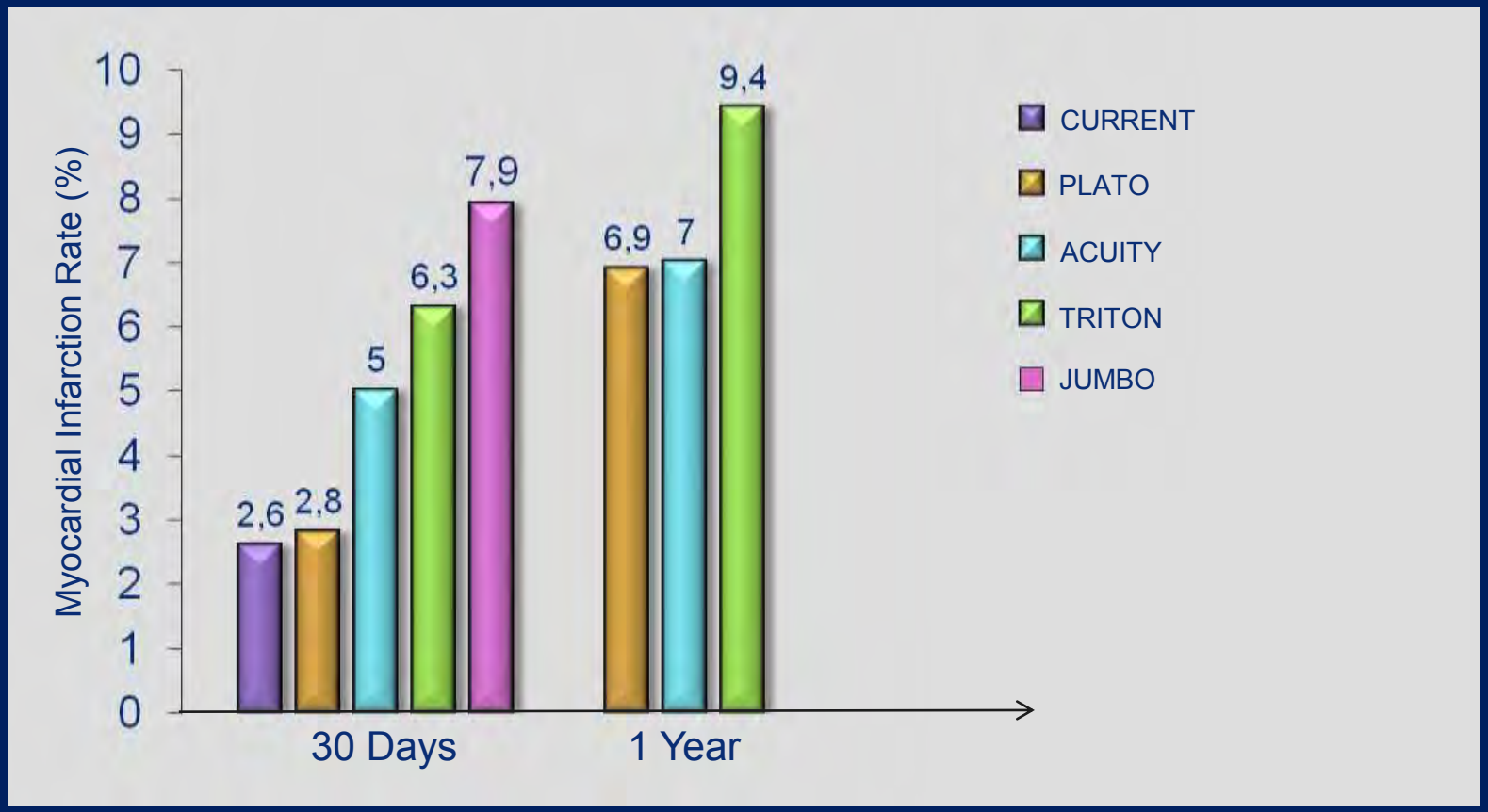
B:Evento reportados FDA; 2009

Adjudicación Controversial: "No todos los IM valen igual"

"Ordinariamente, los eventos reportados por los investigadores y los adjudicados difieren muy poco, sin embargo, en el TRITON, **solamente la mitad de los eventos adjudicados,** fueron identificados por los investigadores"

The FDA Pasugrel Secondary Review, 2009

Tasas de IM en los ensayos con SCA



Thrombosis & Haemostasis, 2009

Excess Rates of Nonfatal Myocardial Infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With *Prasugrel* (Preventing Clinical Events or Chasing Enzymatic Ghosts?†)

Victor L. Serebruany, MD, PhD*

Caracteristicas comparativas de los IM en el TRITON

Type of MI (n)	Difference between arms (n)	Adjudicated	Associated Mortality (%)	Associated Heart Failure	Timing of MI	Excessive MI rate for ACS trials
SRE* (298/226)	72	Yes	14.2 - 18.8	?***	Mostly periprocedural	No
AAE** (620/475)	145	Yes	2.8 – 5.3	No	Across the entire follow-up	Yes

* SRE – site reported events; **- AAE - all adjudicated events; *** - to be reported in the FDAA Action Package

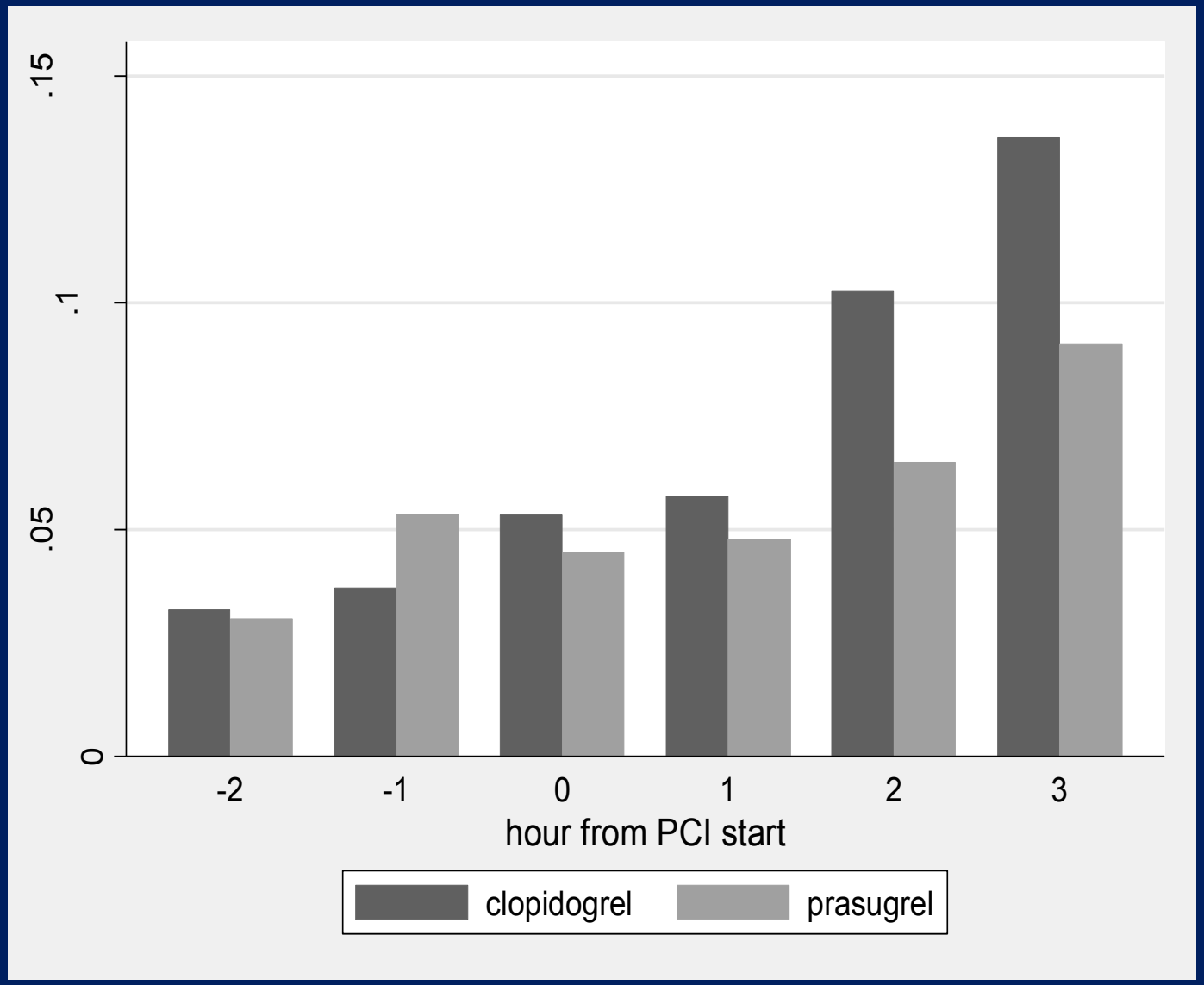
Cardiology, 2009

Tipo de eventos reportados en el TRITON

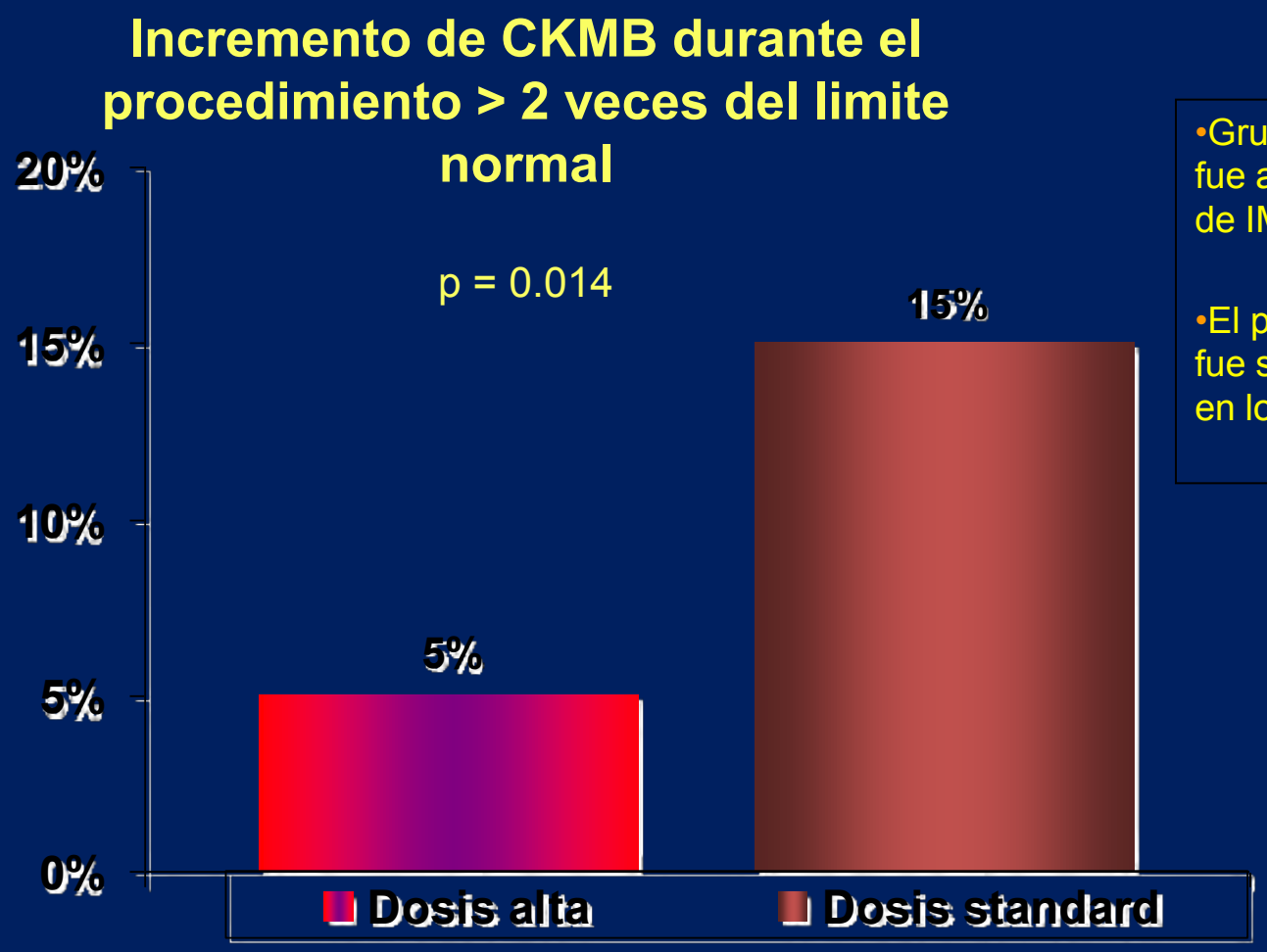
	UA/NSTEMI			STEMI			all		
	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ
MI	235	175	60	62	48	14	297	223	74
stroke	43	43	0	24	22	2	67	65	2
death	83	113	**-30**	58	49	9	141	162	**-21**

The FDA Secondary Prasugrel Review, 2009

Tiempo de incio de la dosis de carga en el TRITON



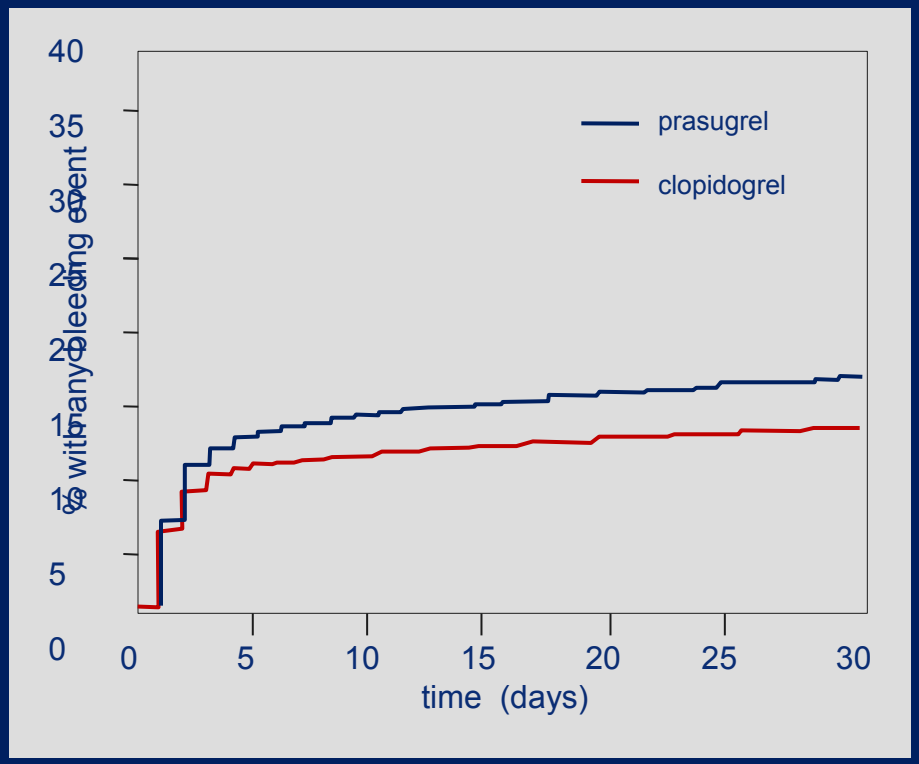
ARMYDA-2 Trial: Puntos Finales Secundarios



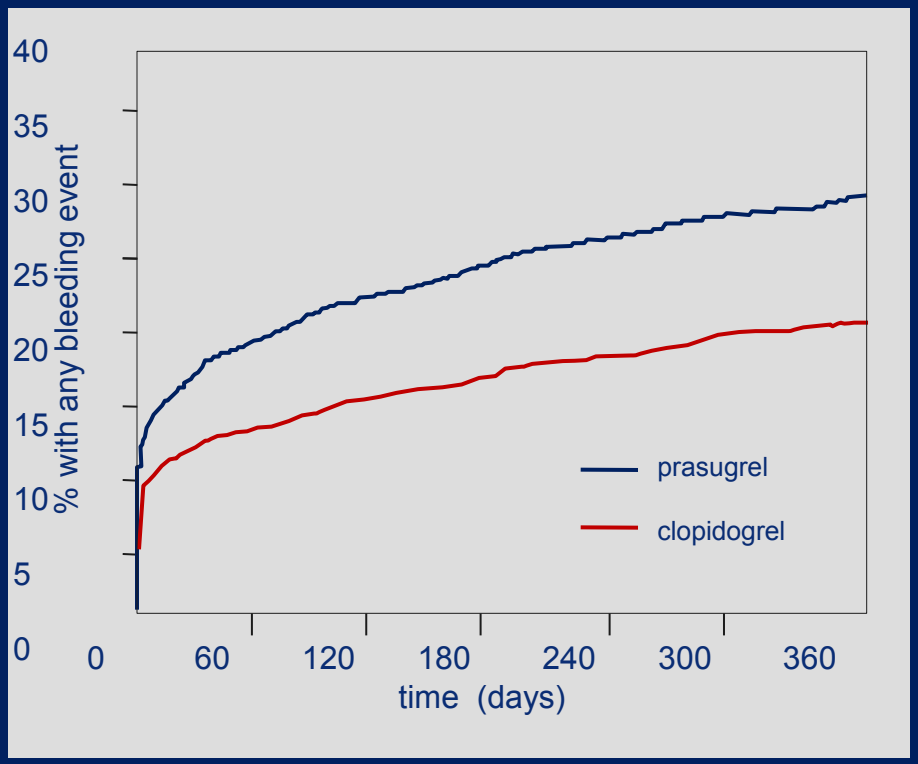
- Grupo dosis alta de Clopidogrel fue asociado con un bajo indice de IM preriprocedimiento
- El pico de niveles de PCR no fue significativamente diferente en los diferentes grupos

Presented at ACC 2005

Sangramiento global en el TRITON



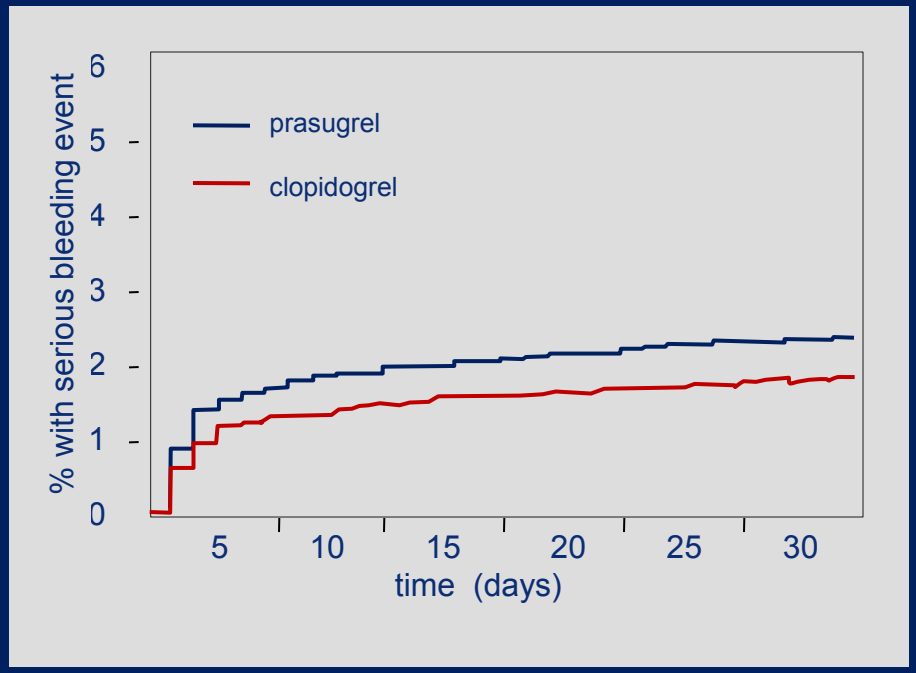
Day 0 -30

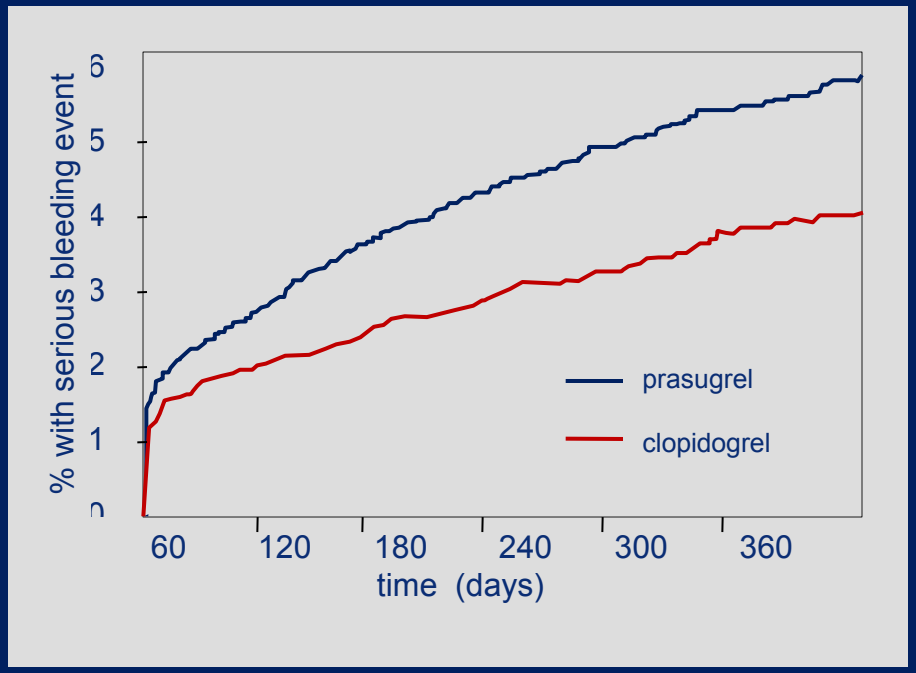


Day 0 - 360

The FDA Secondary Prasugrel Review, 2009

Sangramiento mayor en el TRITON



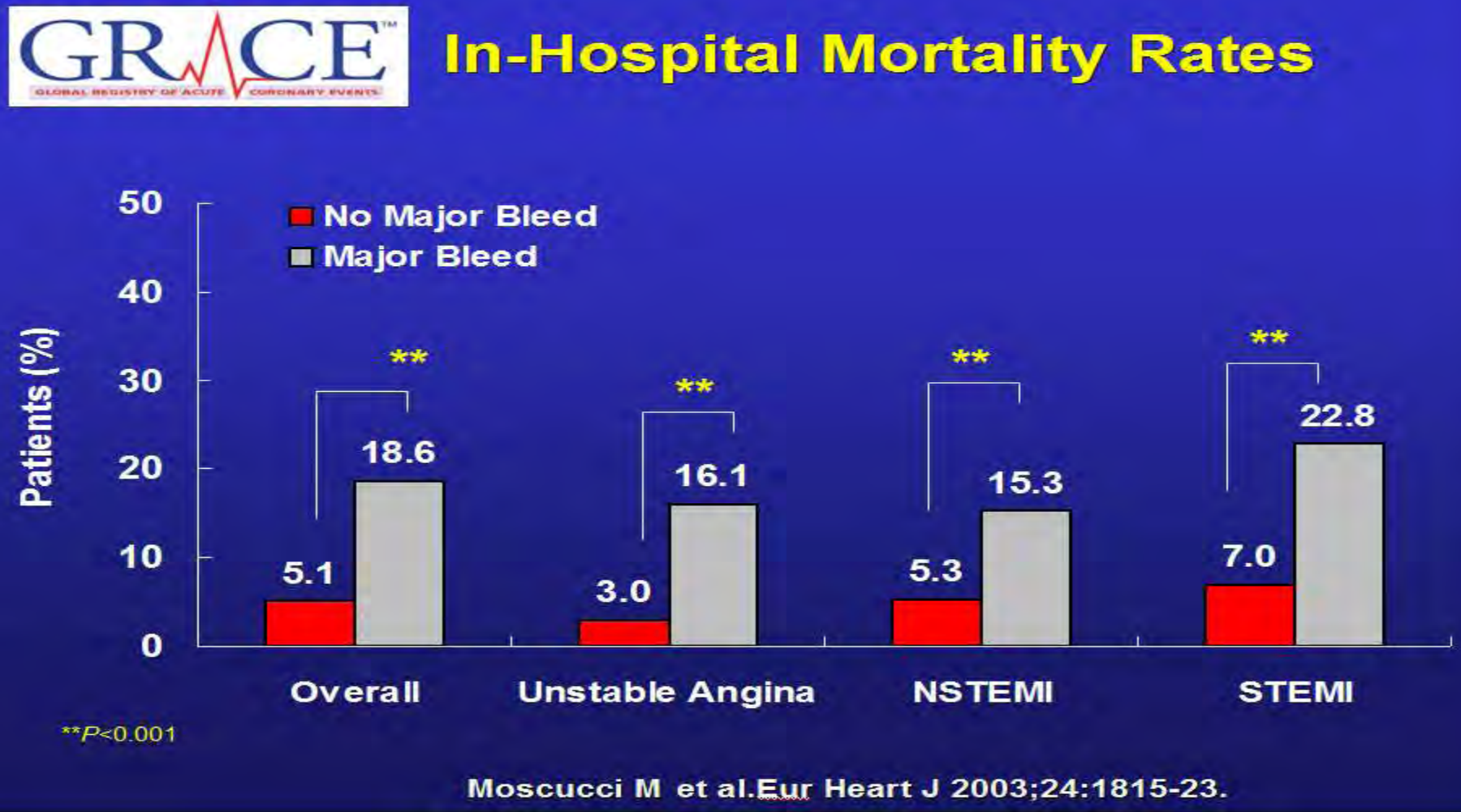


Day 0 -30

Day 0 - 360

The FDA Secondary Prasugrel Review, 2009

Epidemiología.



http://www.outcomes-umassmed.org/grace/study.cfm. acceso 04 de Mayo 2009.

Prasugrel versus clopidogrel for patients with unstable angina/non-ST-segment elevation myocardial infarction who are medically managed after angiographic triage — Results from the TRILOGY ACS Trial

Stephen D. Wiviott, MD, Harvey D. White, MB, ChB, DSc, E. Magnus Ohman, MB, ChB,
Keith A. A. Fox, MB, ChB, Paul W. Armstrong, MD, Dorairaj Prabhakaran, MD, DM, MSc, Gail Hafley, MS,
William E. Boden, MD, Christian Hamm, MD, Peter Clemmensen, MD, DMSc, Jose C. Nicolau, MD, PhD, Alberto Menozzi, MD, PhD, Witold Ruzyllo, MD, Petr Widimsky, MD, DSc, Ali Oto, MD,
Jose Leiva-Pons, MD, Gregory Pavlides, MD, Matthew T. Roe, MD, MHS, and Deepak L. Bhatt, MD, MPH

On behalf of the TRILOGY ACS Investigators

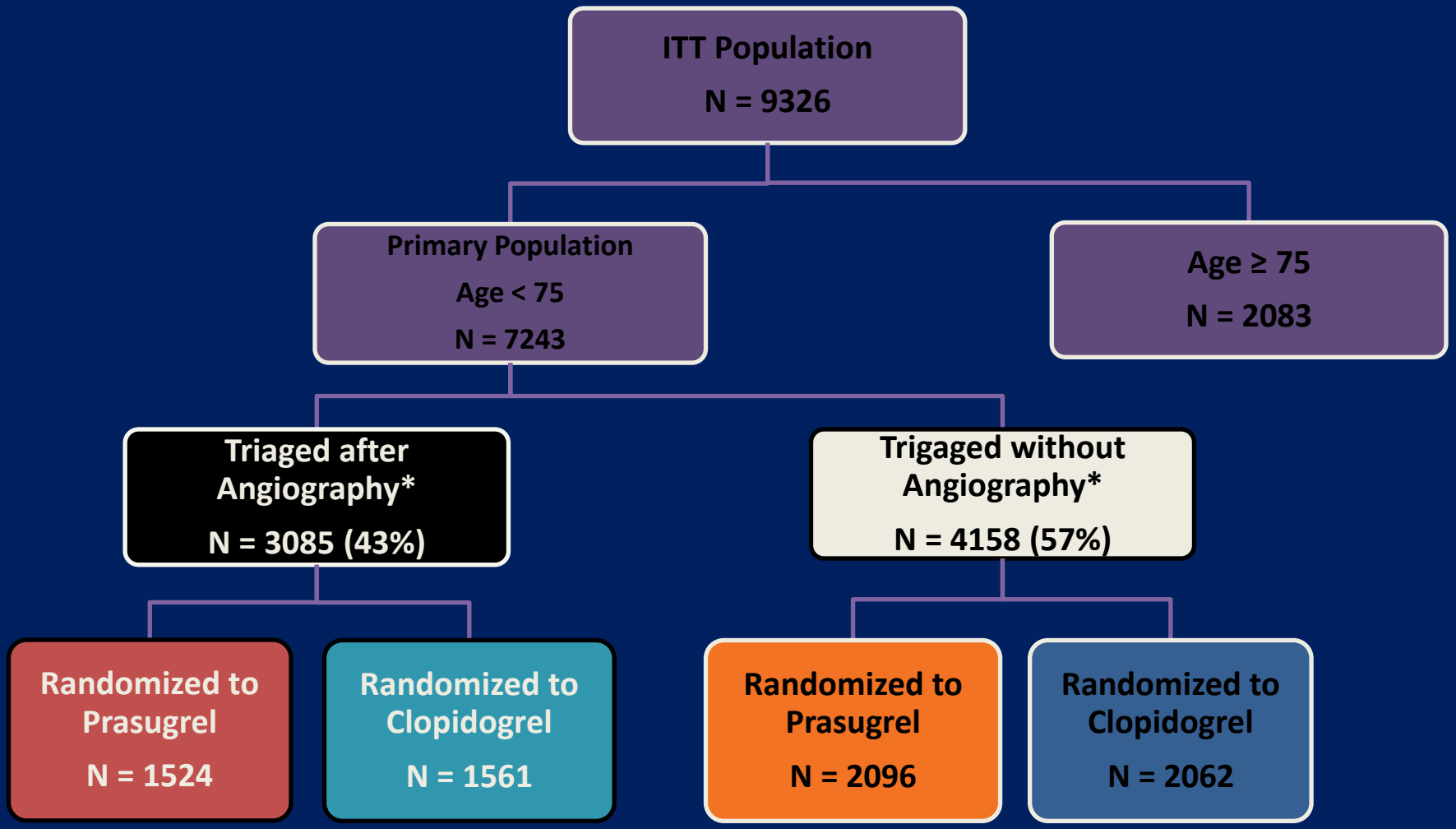
www.clinicaltrials.gov Identifier: NCT00699998

Angiography Background

- The proportion of ACS (UA/NSTEMI) patients worldwide who are managed medically without revascularization (PCI or CABG) is 40–60%.
  This includes 2 distinct sets of patients:
  - triaged to medical therapy after angiography
  - for whom angiography is not performed
- Prasugrel, a thienopyridine $P2Y_{12}$ inhibitor, improved ischemic outcomes in ACS patients undergoing PCI in the TRITON-TIMI 38 trial,
  with an increase in major bleeding.

Wiviott SD et al NEJM 2007

Prespecified Analysis of Angiographic Cohort



*For angiography vs no angiography comparisons — p-values unadjusted, for prasugrel vs clopidogrel - p-value adjusted for clopidogrel stratum

Conclusions

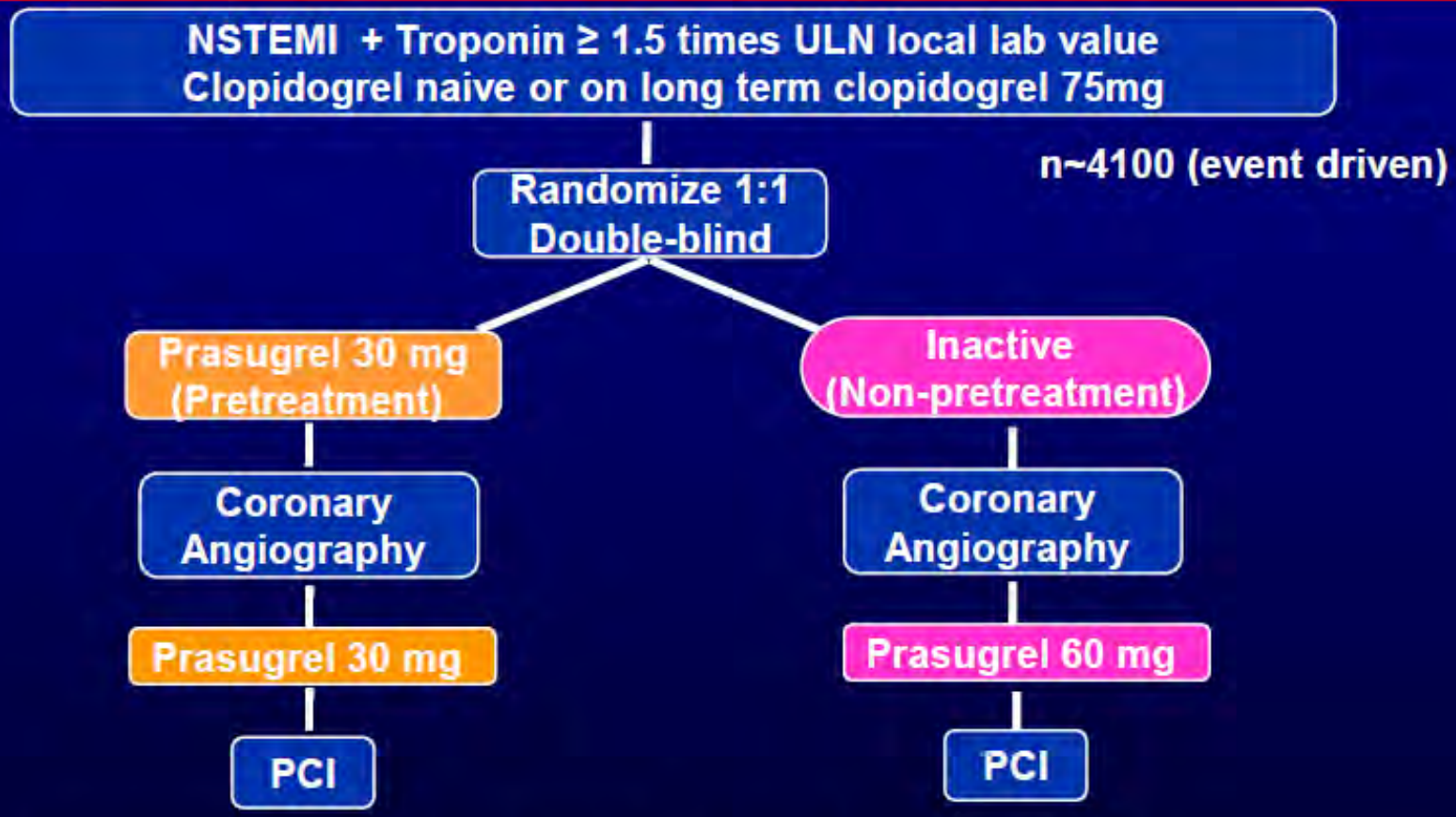
- Overall, in the TRILOGY ACS Trial prasugrel did not reduce cardiovascular events among patients managed medically for ACS.
- When treated with prasugrel compared to clopidogrel, patients triaged to medical therapy following angiography tended to have:
  - lower rates of the combined endpoint of CVD/MI/CVA
  - Lower rates of MI, CVA alone, and recurrent ischemic events
  - higher rates of bleeding.
- Though hypothesis generating, these results are consistent with previous trials and suggest when angiography is performed and coronary disease is confirmed, the benefits and risks of intensive antiplatelet therapy exist whether medical therapy or PCI is elected.

Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pretreatment At the time of diagnosis in patients with non-ST-elevation myocardial infarction: design and rationale for the ACCOAST study

Study funded by Daiichi Sankyo Company, Limited and Eli Lilly and Company

Montalescot, et al. Am Heart J 2011;0:1-7.e1.

Trial Design



Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

Primary Endpoint

CV Death, MI, Stroke, Urgent Revascularization, GP IIb/IIIa inhibitor bailout at 7 days

Conclusiones.

1. El prasugrel como antiagregante, ha mostrado beneficios significativos en pacientes con IAMCST sometidos a angioplastia primaria con implante de stent < 6 horas y diabeticos con un perfil de seguridad inferior al clopidogrel.
2. No ha mostrado resultados solidos en estudios multicentricos randomizados en SCASEST ni en IAMCEST tratado con trombolíticos o conservadoramente.

RUNALDINHO
10
SOVECI
CONGRESO DE LA SOCIEDAD VENEZOLANA
DE CARDIOLOGIA INTERVENCIONISTA

PARTE 3

TICAGRELOR

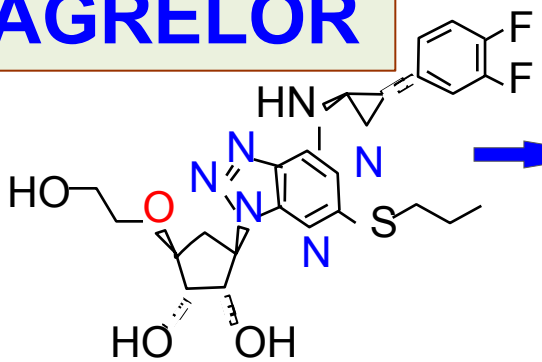
Ticagrelor: Potential Mecanismo de accion

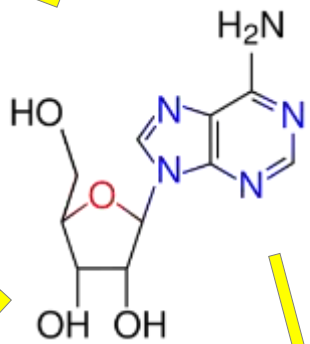
Asystole
Cytoprotection
Apoptosis
Vasodilatation

Dyspnea
Bronchospasm

Agitation
Anxiety

TICAGRELOR





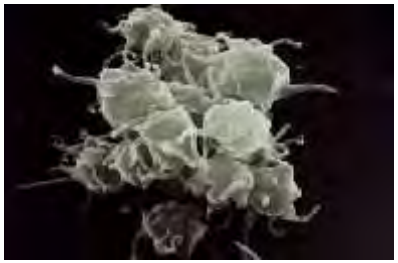
A1

A2A

A2B

A3

ADENOSINE



P2Y12
↓ inhibition
Aggregation
↓ Secretion

↑ Uric acid
↑ Creatinine

PLATO Diseño del Estudio

SCA sin EST (moderado a alto riesgo)SCA EST(PCI primaria)
Tratados o no con Clopidogrel al azar en las 24 horas del evento
(N=18,624)

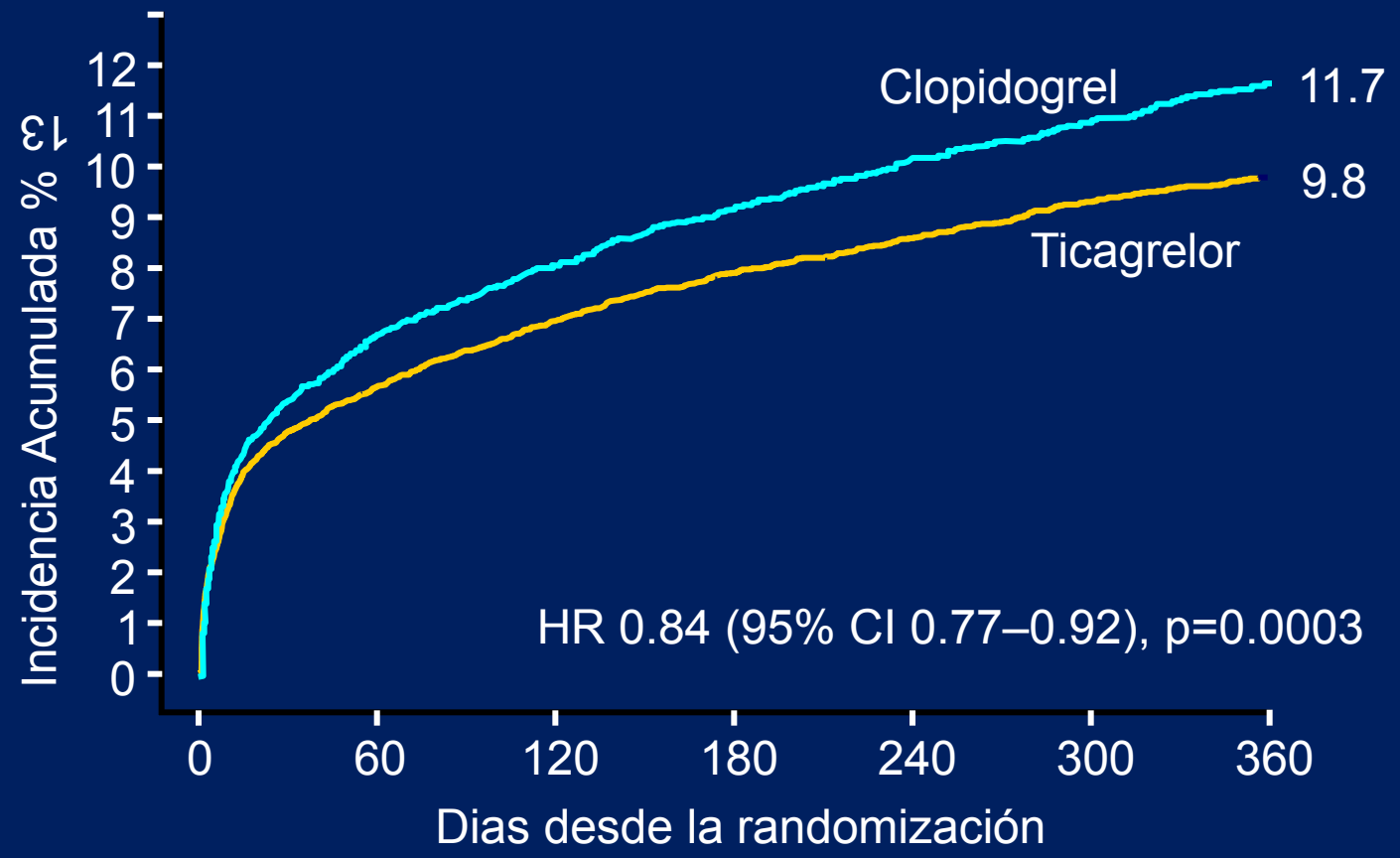
Clopidogrel
Si estaba pretratado no dosis de carga
Si no usa Clopidogrel : Carga de 300 mg
Luego 75 mg de mantenimiento
(300 mg adicionales pre PCI)

Ticagrelor
180 mg Dosis de carga,luego 90 mg BID
De mantenimiento
(90 mg adicionales pre PCI)

6-12 meses

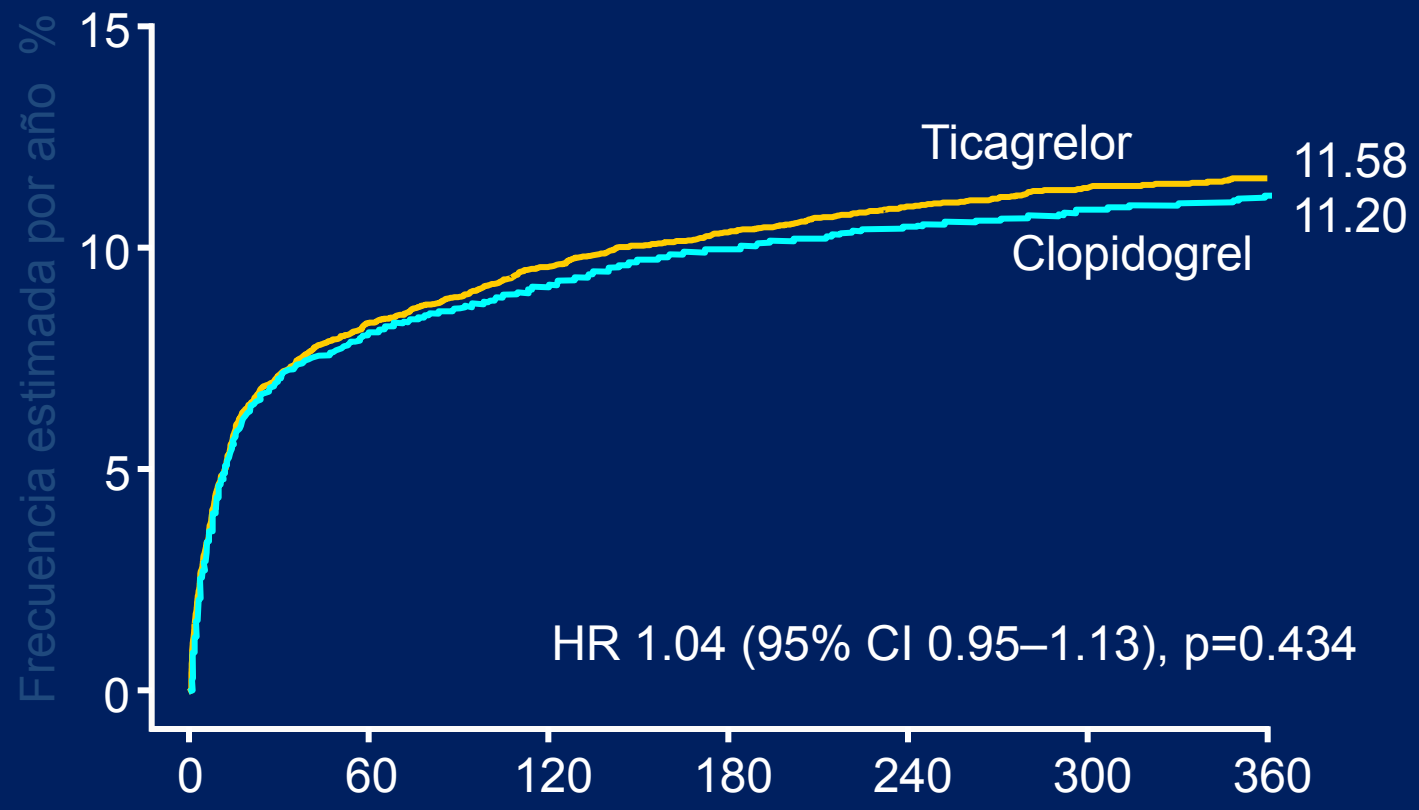
Punto Final Primario: Muerte Cardiovascular + IM + ACV
Punto Primario de seguridad: Sangramiento total mayor

Tiempo al primer evento de eficacia(PFP compuesto de Muerte Cardiovascular, Infarto del Miocardio o ACV)



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

Tiempo hasta un evento primario de seguridad: Sangramiento mayor



No. A 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

Otros Hallazgos:Parámetros de Laboratorio

Todos los pacientes	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p valor*
% Aumento de creatinina desde el inicio			
Al 1er mes	10 ± 22	8 ± 21	<0.001
A los 12 meses	11 ± 22	9 ± 22	<0.001
Visita de seguimiento	10 ± 22	10 ± 22	0.59
% Aumento del ácido úrico desde el inicio			
Al 1er mes	14 ± 46	7 ± 44	<0.001
A los 12 meses	15 ± 52	7 ± 31	<0.001
Visita de seguimiento	7 ± 43	8 ± 48	0.56

Otros Hallazgos

Todos los pacientes	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p valor*
Disnea, %			
Cualquier	13.8	7.8	<0.001
Tratamiento Descontinuado	0.9	0.1	<0.001
Tumores apareciendo durante el tratamiento, %			
Cualquiera	1.4	1.7	0.17
Malignos	1.2	1.3	0.69
Benignos	0.2	0.4	0.02

Diferencias en el objetivo primario: TRITON and PLATO

Parametro	Prasugrel	Ticagrelor
Muerte cardiovascular (n)	-17	-89
IM no fatal (n)	-122	-80
ACV no fatal (n)	+1	+19
Eventos Totales(n)	-138	-150

NEJM, 2007; 2009

Como fue la eficacia del Ticagrelor en el estudio DISPERSE y DISPERSE-2?

Eventos (%)	Ticagrelor (n=663)	Clopidogrel (n=327)
Obito CV IM/ACV	3.9	4.9
Obito CV	1.8	1.2
IM	2.4	4.3
ACV	0.3	0.3
SRI	2.1	0.9
RI	3.3	2.8
Obtito total	**1.96**	**1.2 (NS)**

DISPERSE + DISPERSE -2, FDA Ticagrelor Review

The Cooking Lessons

???

PEGASUS
TIMI-54

PLATO

DISPERSE

DISPERSE-2

Temores del PLATO

Efectos Adversos

Reversible

Resultados en U.S.A

Ticagrelor

MORTALIDAD

The Rapid Trial. Jacc 2013

50 patients with STEMI Planned PCI

ASA ↓ ***Bivalirudin***

Double-blind

Ticagrelor
180mg LD/ 90 mg bid

PRASUGREL
60 mg LD/ 10 mg MD

Emergency room or cath lab

1º endpoint: PRU at 0-2-4-8-12 hours
Stent trombosis(ARC definite/prob.)

The Rapid Trial

Conclusiones.

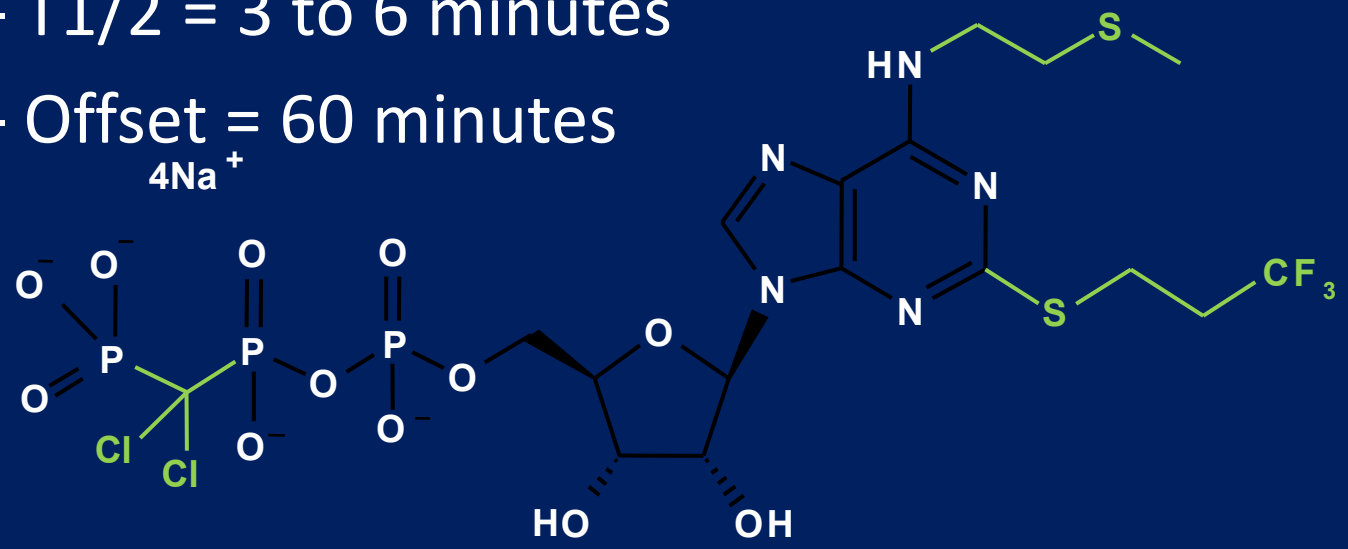
1. No hubo diferencia significativa entre la PRU en ambos brazos(217 vs. 2.75)p=o,20.
2. Menos de la mitad de los pacientes de ambos grupos tenia niveles optimos de PRU en 2 horas(3 horas para prasugrel y 5 horas en promedio para Ticagrelor).

PARTE 4

CANGRELOR

Cangrelor

- Direct platelet $P2Y_{12}$ receptor antagonist
- ATP analogue MW=800 Daltons
- Parenteral administration
- T1/2 = 3 to 6 minutes
- Offset = 60 minutes



Angiolillo DJ, Schneider DJ, Bhatt DL, et al. Pharmacodynamic effects of cangrelor and clopidogrel: the platelet function substudy from the cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) trials. J Thromb Thrombolysis 2012;34:44-55.

Cangrelor

- Cangrelor is an intravenous ADP receptor antagonist that is rapidly acting, potent, and reversible, with return of normal platelet function within an hour.
- Cangrelor was studied previously in two large Phase 3 PCI trials, CHAMPION PCI and CHAMPION PLATFORM. Neither study met its primary endpoint, but the secondary endpoint of stent thrombosis at 48 hours was significantly reduced in CHAMPION PLATFORM and in a prespecified pooled analysis of the two trials. There was no excess in severe bleeding.
- The potential efficacy signal prompted us to launch the CHAMPION PHOENIX trial.

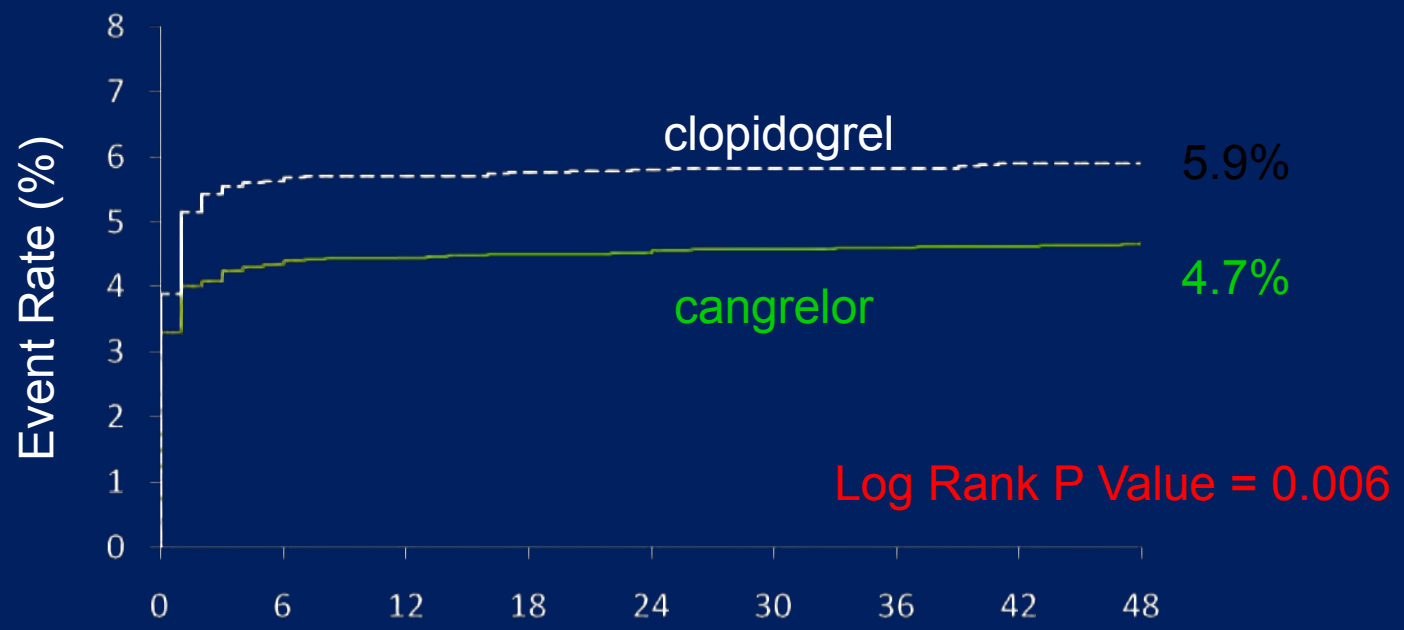
Harrington RA, et al. CHAMPION PCI. NEJM 2009
Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009
White HD, et al. Meta-Analysis of CHAMPION PCI and PLATFORM. AHJ 2012

CHAMPION PHOENIX Study Design

- Randomized, double-blind, double-dummy, superiority
- Primary efficacy endpoint: **Death/MI/IDR/ST at 48 hours**
  - Adjusted for 600 mg versus 300 mg clopidogrel use
  - Modified Intent-to-Treat (MITT) analysis (patients actually got study drug and PCI)
- Key secondary endpoint: Stent Thrombosis at 48 hours
- Efficacy endpoints also examined at 30 days
- Primary safety endpoint: GUSTO Severe Bleeding at 48 hours

Harrington RA, et al. CHAMPION PCI. NEJM 2009
Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009
White HD, et al. Meta-Analysis of CHAMPION PCI and PLATFORM. AHJ 2012

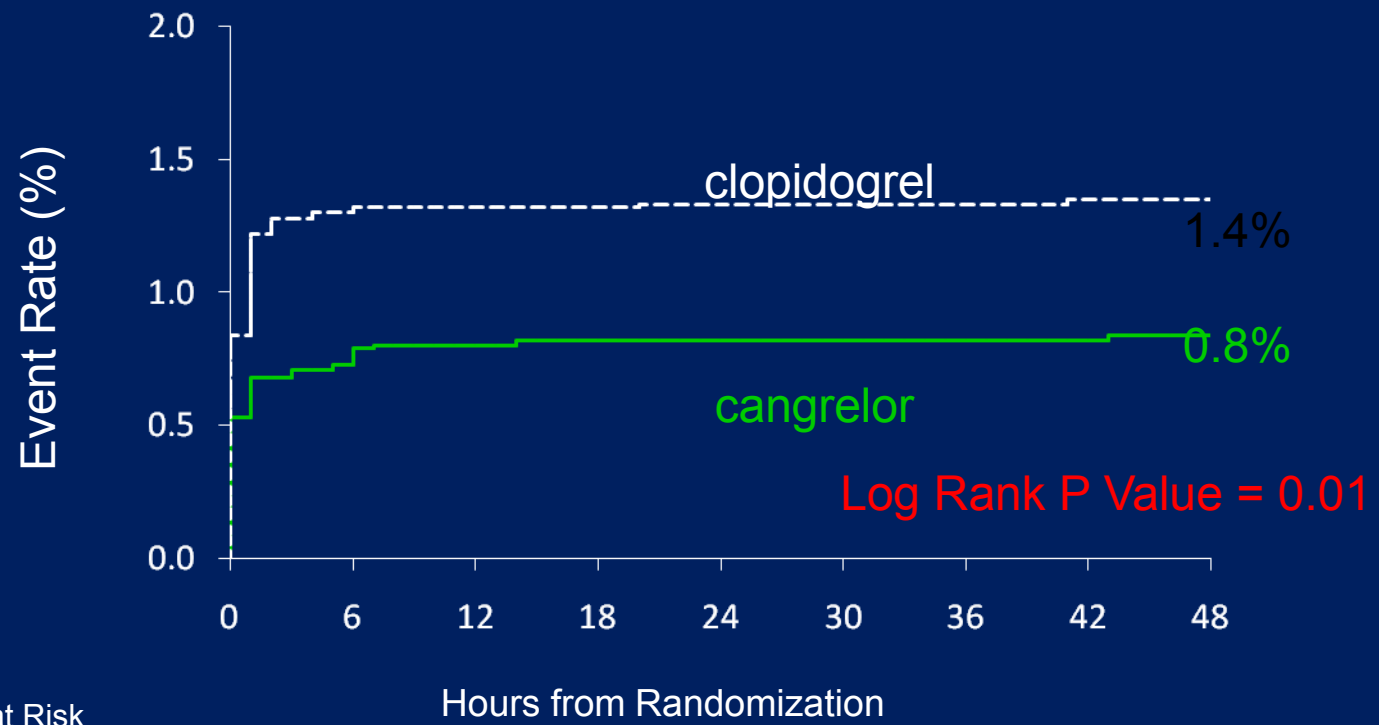
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5426	5421	5419	5419	5418	5417	5416	5414
Clopidogrel:	5470	5392	5389	5388	5386	5385	5385	5383	5383

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Conclusions

- In CHAMPION PHOENIX, intravenous ADP receptor antagonism with cangrelor significantly (p=0.005) reduced the composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours, with a 22% odds reduction.
- The key secondary endpoint of stent thrombosis was also significantly reduced, with a 38% odds reduction.
- The benefit was sustained through 30 days.
- There was no excess in severe bleeding or transfusions.
- Intravenous cangrelor may be an attractive option across the full spectrum of PCI, including stable angina, NSTEMI, and STEMI.

Conclusiones.

1. El Cangrelor muestra beneficios significativos en el contexto terapeutico restricto de los Sindromes Coronarios Agudos tratados en sala de hemodinamia como coadyuvante a la terapia antiagregante disponible por via oral.
2. Necesita mas evidencia en mayor numero de pacientes.

TERAPIA ANTIPLAQUETARIA DUAL

Por cuanto Tiempo ?

Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials

Salvatore Cassese[†], Robert A. Byrne[†], Tomohisa Tada, Lamin A. King, and Adnan Kastrati*

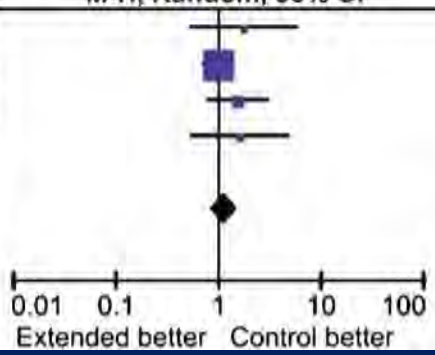
All-cause death in patients extending dual antiplatelet therapy (DAPT) after percutaneous coronary interventions.

Death

Study or Subgroup	Extended DAPT Events	Extended DAPT Total	Control DAPT Events	Control DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI
EXCELLENT	7	712	4	715	5.8%	1.76 [0.51, 6.06]
PRODIGY	65	984	65	979	69.4%	0.99 [0.70, 1.42]
REAL/ZEST-LATE	20	1348	13	1334	17.8%	1.53 [0.76, 3.09]
RESET	8	1042	5	1044	7.0%	1.61 [0.52, 4.93]
Total (95% CI)		**4086**		**4072**	**100.0%**	**1.15 [0.85, 1.54]**
Total events	100		87			

Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 3 (P = 0.56); I² = 0%

Test for overall effect: Z = 0.91 (P = 0.36)



Cassese S et al. Eur Heart J 2012;eurheartj.ehs318

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European Heart Journal

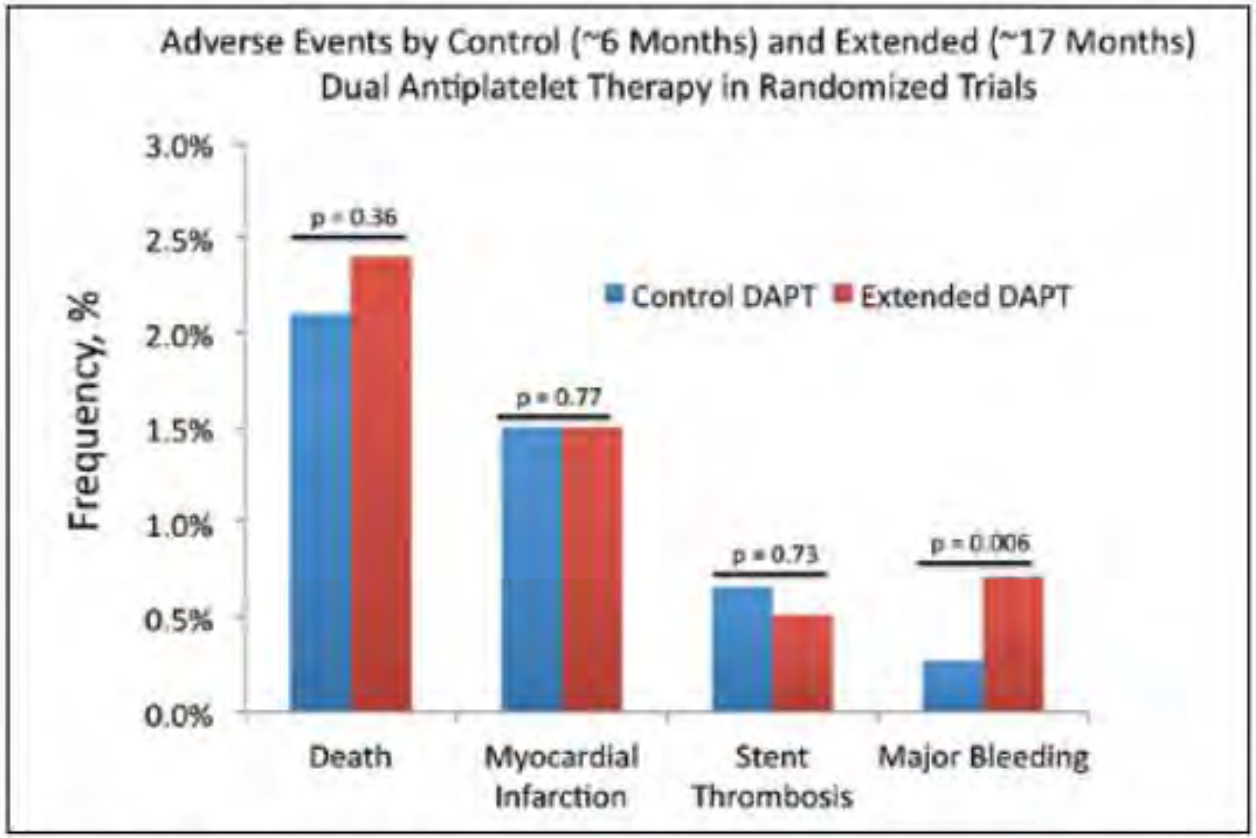


Figure 1. Frequency of adverse ischemic and bleeding events by different DAPT durations. Data abstracted from Cassese et al. *Eur Heart J.* 2012;33:3078–3087.[8]

Main Arena III - Plenary Sessions XVI
Late Breaking Clinical Trials III - Featured Trial of the Day:

OPTIMIZE: A Prospective, Randomized Trial *of 3 Months Versus 12 Months* of Dual Antiplatelet Therapy with the *Endeavor Zotarolimus-Eluting Stent*

- Fausto Feres, MD, PhD
- On behalf of the OPTIMIZE Trial Investigators
- Instituto Dante Pazzanese de Cardiologia
- São Paulo, Brazil

Thursday, October 31st, 2013 – 9:30 to 9:45 am
San Francisco, CA, USA

Study Design

Broad patient population
undergoing PCI with Endeavor ZES
RVD 2.5 mm – 4.0 mm

3 Months DAPT
N = 1560

N = 3120 patients
1:1 Randomization
33 Sites in Brazil

12 Months DAPT
N = 1560

Clinical endpoints

30-d. | 3-mo. | 6-mo. | 12-mo. | 18-mo. | 24-mo. | 36-mo.

Primary Endpoint: NACCE (Death / MI / Stroke / Major Bleeding) at 12 months

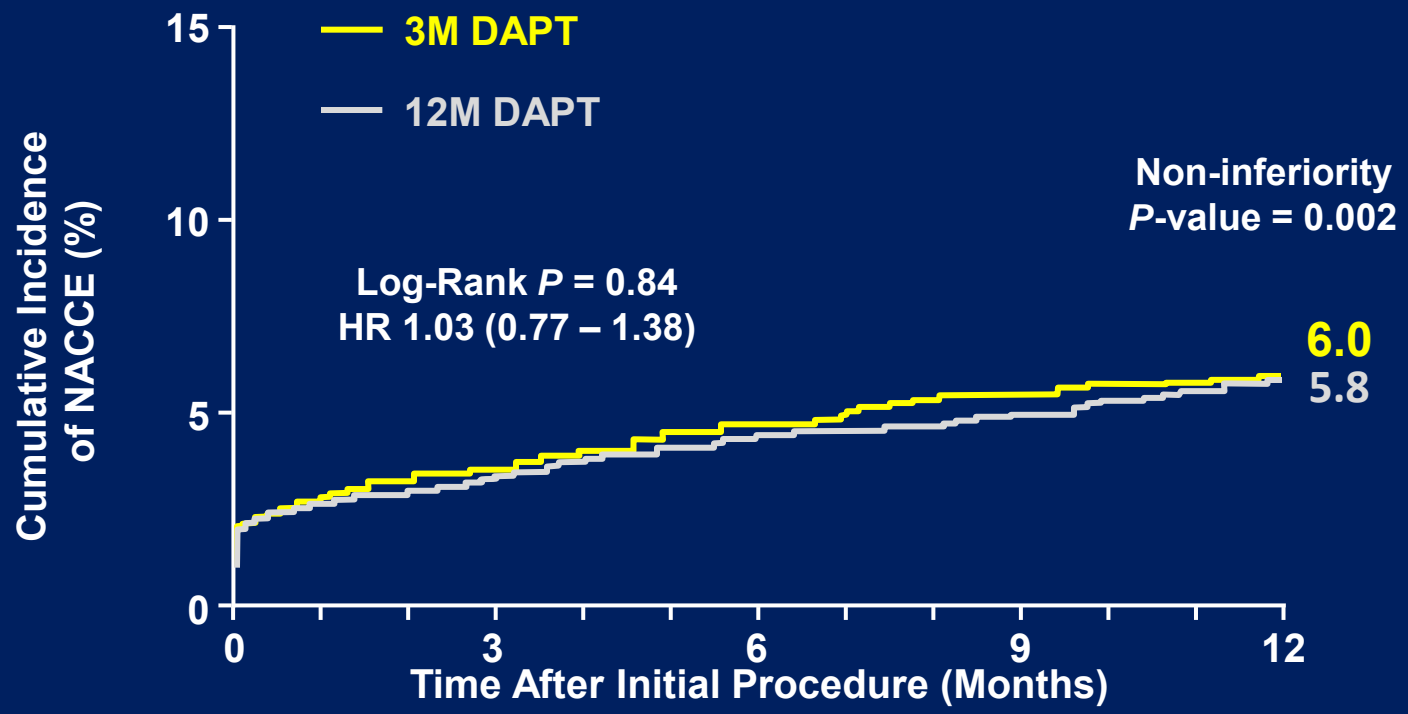
Secondary Endpoints: ARC defined ST, TVR, TLR, MACE, DAPT compliance, and major bleeding (REPLACE-2 & GUSTO definitions)

NACCE = Net Adverse Clinical and Cerebral Events

MACE is composed of Death, MI, Emergent CABG, TLR

Feres F. et al, *Am Heart J*. 2012;164:810-6

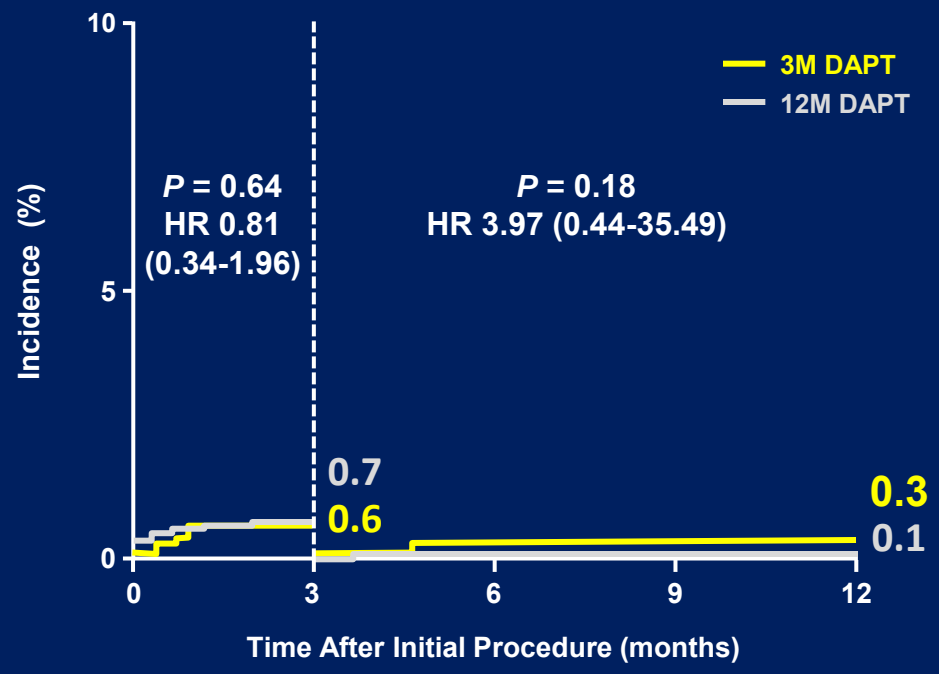
Primary Endpoint: NACCE at 1 Year



Month	0	1	3	6	12
No. at risk	1563	1520	1504	1468	1384
No. events	18	25	11	18	21
No. at risk	1556	1514	1497	1466	1381
No. events	16	25	11	16	22

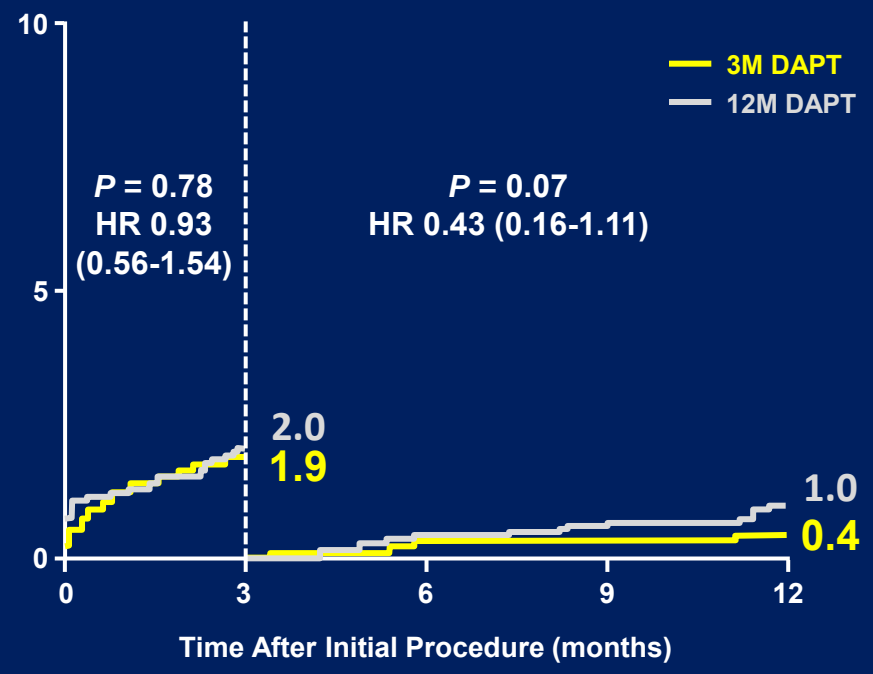
Stent Thrombosis *vs.* Bleeding

ARC Def./Prob. Stent Thrombosis



Month	0	1	3	6	12
No at risk	1563	1555	1540	1506	1505
No events	0	6	3	4	0
No at risk	1556	1541	1525	1501	1500
No events	5	3	3	1	0

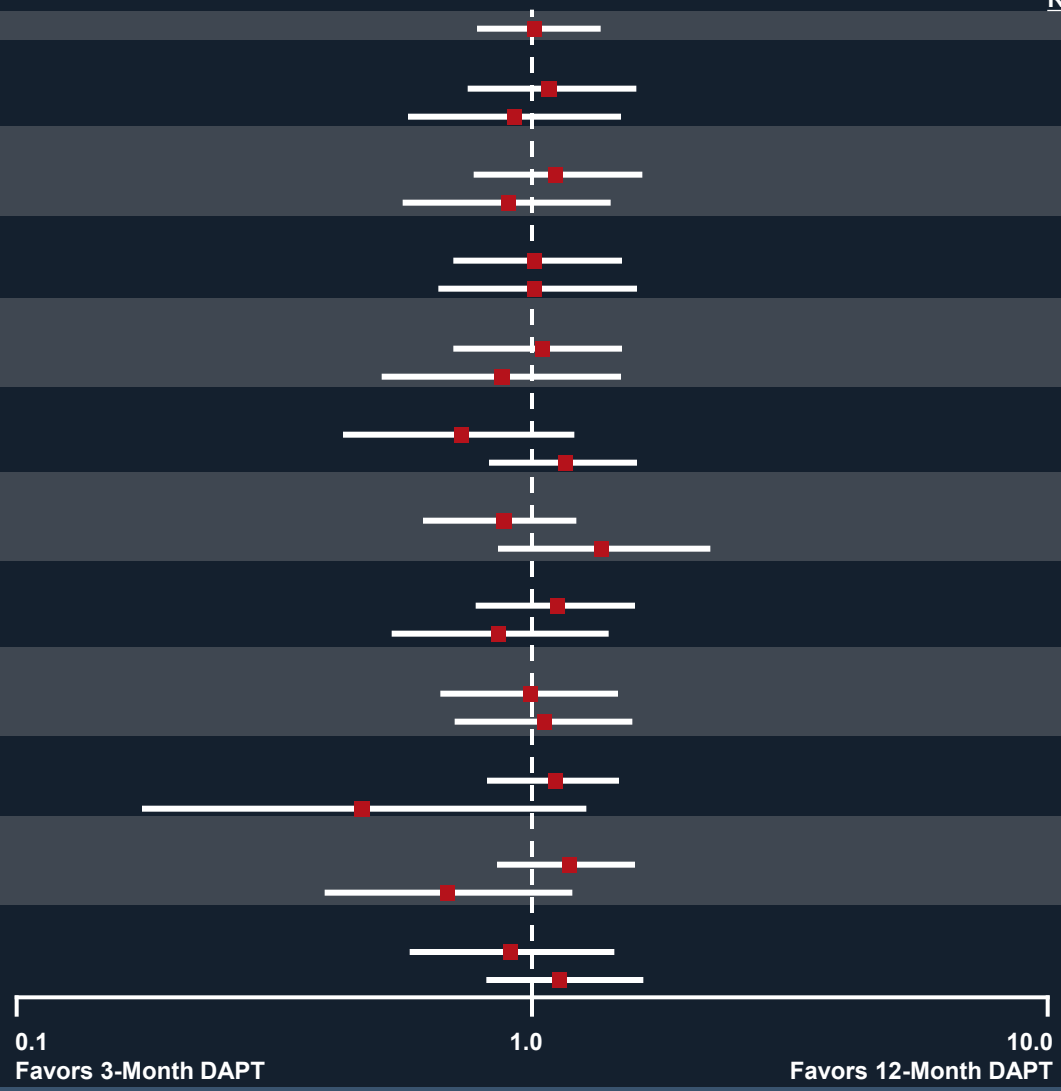
Any Bleeding*



Month	0	1	3	6	12
No at risk	1563	1538	1516	1482	1439
No events	4	15	10	4	2
No at risk	1556	1528	1501	1472	1387
No events	11	8	12	6	8

*Any bleeding according to the combined REPLACE-2 and GUSTO criteria.

Subgroup Analysis: NACCE at 1 Year



Subgroup	Risk Ratio (95%CI)	*P* Value
All patients (N = 3119)	1.03 (0.78-1.36)	0.84
Sex		
Male (n = 1973)	1.08 (0.76-1.55)	0.66
Female (n = 1146)	0.94 (0.59-1.49)	0.80
Diabetes mellitus		
No (n = 2016)	1.12 (0.78-1.60)	0.55
Yes (n = 1103)	0.90 (0.58-1.41)	0.65
Clinical presentation		
Non-ACS (n = 2119)	1.04 (0.72-1.49)	0.84
ACS (n = 1000)	1.04 (0.67-1.61)	0.88
Bifurcation		
No (n = 2572)	1.09 (0.78-1.51)	0.62
Yes (n = 547)	0.88 (0.52-1.51)	0.65
Lesion complexity		
Simple (n = 1273)	0.74 (0.44-1.27)	0.27
Complex (n = 1846)	1.18 (0.85-1.65)	0.32
Extent of disease		
Single vessel (n = 2310)	0.88 (0.62-1.26)	0.48
Multivessel (n = 809)	1.38 (0.87-2.19)	0.17
Vessel size		
Small vessel (n = 1889)	1.12 (0.79-1.58)	0.53
Large vessel (n = 1230)	0.88 (0.55-1.42)	0.60
Lesion length		
Short lesion (n = 1832)	1.01 (0.67-1.50)	0.98
Long lesion (n = 1287)	1.06 (0.71-1.57)	0.78
Lesion type		
De novo (n = 2795)	1.11 (0.83-1.49)	0.48
In-stent restenosis (n = 324)	0.48 (0.18-1.27)	0.13
Interventional center		
Non academic (n = 2283)	1.18 (0.85-1.64)	0.33
Academic (n = 836)	0.70 (0.40-1.22)	0.21
Stent number		
Single stent (n = 1787)	0.92 (0.59-1.42)	0.69
Multiple stents (n =1332)	1.14 (0.79-1.64)	0.48

ACC.14

A1859
JACC April 1, 2014
Volume 63, Issue 12

TCT@ACC-12: The Interventional Learning Pathway

IMPACT OF SHORT- VERSUS LONG-TERM DAPT IN PATIENTS WITH DIABETES MELLITUS UNDERGOING PERCUTANEOUS INTERVENTION WITH ENDEAVOR ZOTAROLIMUS-ELUTING STENTS - A SUBANALYSIS OF THE LARGE, PROSPECTIVE, RANDOMIZED, MULTICENTER OPTIMIZE TRIAL

Poster Contributions
Hall C
Sunday, March 30, 2014, 3:45 p.m.-4:30 p.m.

Session Title: Complexities and Complications
Abstract Category: 38. TCT@ACC-12: Complex Patients/Comorbidities
Presentation Number: 2108-297

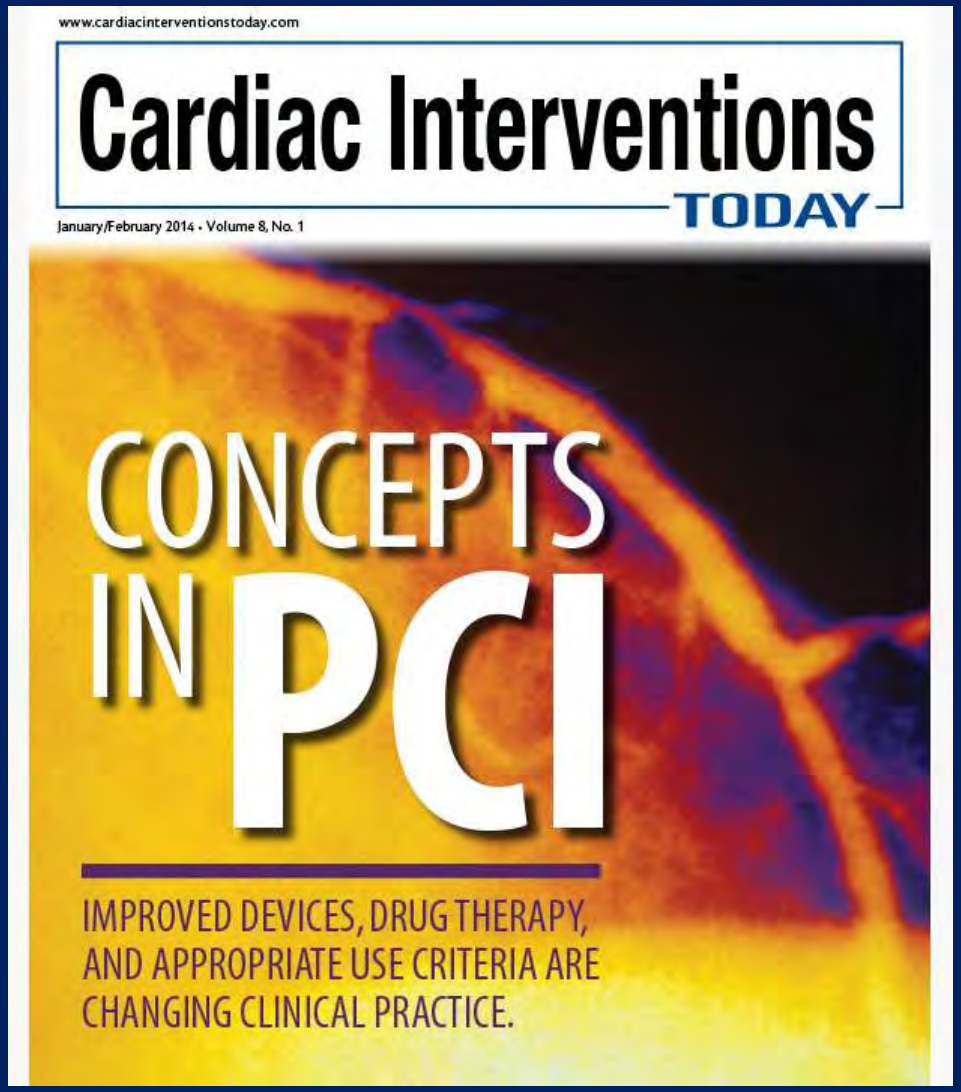
Authors: Fausto Feres, Ricardo Costa, Deepak Bhatt, Joao De Paula, Roberto Botelho, J. Antonio Marin-Neto, Sergio Berti, Pablo Tessmann, Rene Padilha, Rogério Sarmento-Leite, Adrian Kornan, Andres Sanchez, Aurea Chaves, Andrea Abizaid, Alexandre Abizaid, Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil, Cardiovascular Research Center, São Paulo, Brazil

Background: Current recommendation is for ≥ 12 months dual antiplatelet therapy (DAPT) after drug-eluting stents (DES). Patients with diabetes mellitus (DM) have higher incidence of thrombotic events after DES compared to non-diabetics. Still, the optimal DAPT duration with specific DES type remains unknown. Our objective was to assess the clinical impact of short- (3 months) versus long-term (12 months) DAPT in patients undergoing percutaneous coronary intervention (PCI) with the 2nd generation DES Endeavor zotarolimus-eluting stents (E-ZES).

Methods: The OPTIMIZE trial was a randomized (1:1), active-controlled, open-label non-inferiority study including 3,119 patients in 33 sites in Brazil between April/2010-March/2012. After PCI with E-ZES, patients were prescribed aspirin 100-200mg daily and clopidogrel 75mg for 3 months (n=1,563) or 12 months (n=1,556) DAPT. Clinical follow-up was performed at 1, 3, 6 and 12 months. The 1ary endpoint was net adverse clinical and cerebral events (NACCE), a composite of all-cause death, MI, stroke, or major bleeding at 1 year follow-up. Stent thrombosis (ST) was defined according to the Academic Research Consortium. Overall, 35% of patients had DM and randomization was stratified by its presence. Also, a DM subgroup analysis was pre-specified in the protocol.

Results: Considering 1,103 patients with DM at 3 months (n=554) vs. 12 months (n=549) DAPT, mean age was 62.1 vs. 61.7 yrs (p=0.52), female gender 44% vs. 47% (p=0.08), prior MI 38% vs. 32% (p=0.04), renal insufficiency 11% vs. 6% (p=0.003), and clinical presentation of unstable angina (19% vs. 18%, p=0.53) or non-ST MI (5% vs. 6%, p=0.49), for 3 vs. 12 months groups, respectively. At 12 months, there were comparable rates of NACCE (6.3 vs. 6.9%, [difference -0.6%, 95% confidence interval (CI) -3.65, 2.29], p=0.65) and definite/probable ST (1.7 vs. 1.1%, [dif. 0.53, 95% CI -0.67, 1.93], p=0.46), for 3 vs. 12 months, respectively.

Conclusions: In this pre-specified subgroup analysis of the OPTIMIZE trial, short-term DAPT did not significantly increase risk for clinical events at 1 year in patients with DM undergoing PCI with a specific 2nd generation DES.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TODAY
January/February 2014 • Volume 8, No. 1
CONCEPTS IN PCI
IMPROVED DEVICES, DRUG THERAPY, AND APPROPRIATE USE CRITERIA ARE CHANGING CLINICAL PRACTICE.

European Heart Journal

Triple terapia antitrombótica. ¿Prefieres trombosis del stent, sangrado o ictus? Una pregunta sin respuesta

Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study

P J Devereaux (philipj@mcmaster.ca), cardiology resident [a] [a], David R Anderson, associate professor [a], Martin J Gardner, professor [a], Wayne Putnam, associate professor [b], Gordon J Flowerdew, associate professor [c], Brenda F Brownell, project coordinator [a], Seema Nagpal, research associate [d], Jafna L Cox, associate professor [a]

BMJ 2001;323:1218

Mayo Clinic > Mayo Clinic Talks

Triple Therapy: When AF and Stents Collide

Bernard J. Gersh, MB, ChB, DPhil, Robert D. McBane, MD | Disclosures

July 18, 2014

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Dr Willem JM Dewilde MD [a], Tom Oirbans MSc [b], Prof Freek WA Verheugt MD [c], Johannes C Kelder MD [b], Bart JGL De Smet MD [d], Jean-Paul Herrman MD [c], Tom Adriaenssens MD [e], Mathias Vrolix MD [f], Antonius ACM Heestermans MD [g], Marije M Vis MD [h], Prof Jan GP Tijsen MD [h], Arnoud W van 't Hof MD [i], Jurriën M ten Berg MD [b], for the WOEST study investigators

The primary outcome was the rate of bleeding during the first year following stent implantation. The rate was 19.4% in patients on double therapy and 44.4% in those on triple therapy, for a highly significant 64% reduction in relative risk favoring the less aggressive antithrombotic

secondary endpoint of death/MI/stroke/target vessel revascularization/stent thrombosis was also higher in the triple-therapy group,”

Lancet 2013;381:1107-15).

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

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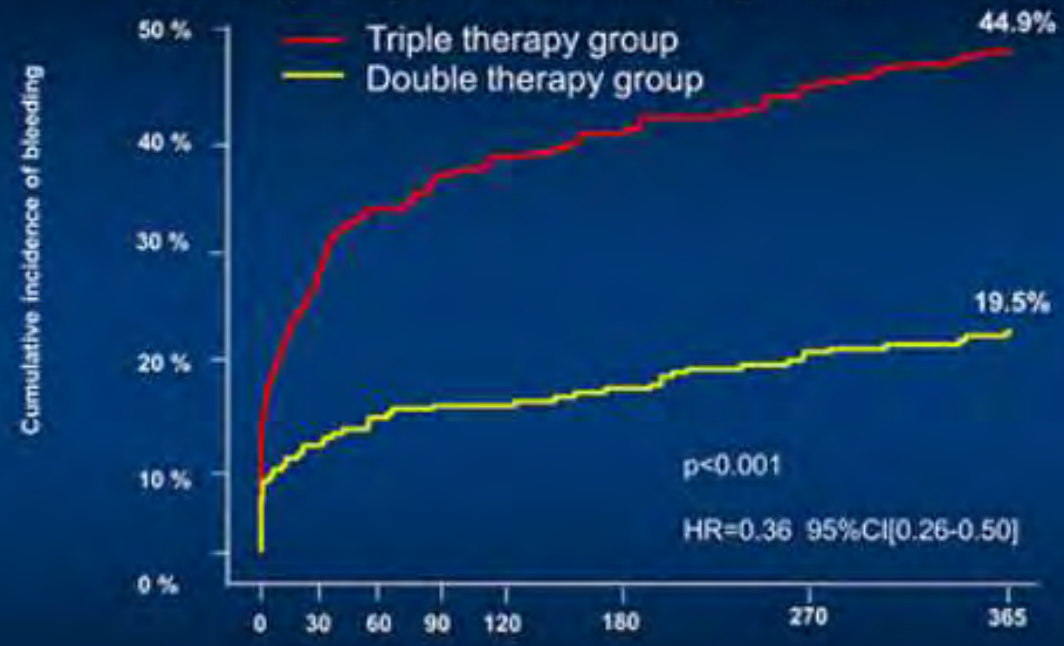
WOEST: What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting?

Primary Endpoint: TIMI bleeding events

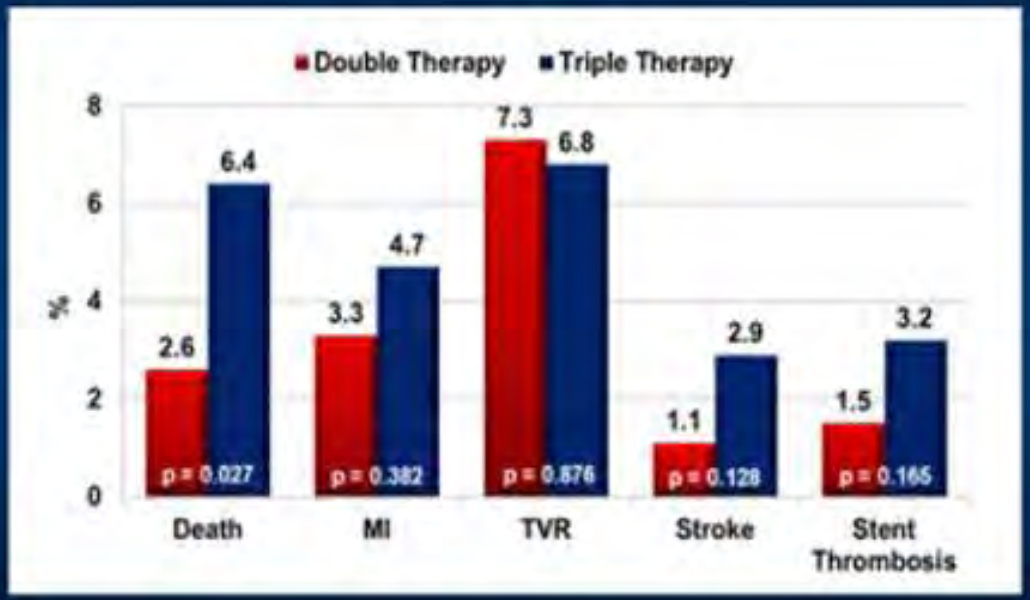


n at risk:	284	210	194	186	181	173	159	140
	279	253	244	241	241	236	226	208

Dewilde WJ et al. Lancet. 2013;381:1107-15.

WOEST: What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting?

Secondary Endpoints



DeWilde WJ et al. Lancet 2013;381:1107-15

Manejo de AP para paciente con stent que deben usar ACO(07.8.2014)

- Son 5-7%(fa, valva protesica, trombo en vi o embolismo pulm.
- - La triple combinacion aumenta sangrado y muerte(con warfarina) de manera que en pac con bajo riesgo(chads 0-1) de stroke solo usar dap, en riesgo moderado o alto, usar dosis ajustada de aco.
- En aquelos con alto riesgo de sangramiento deben usarse stents metalicos, bomba de protones, solo un mes de dapt y aco con inr en 2-2,5).
- - Stents recubiertos solo en alto riesgo de retenosis usar triple terapia por 6 meses y luego solo clopi con aco.
- Como ningiun otro AP y Aco HA SIDO ESTUDIADO SOLO SE PUEDE USAR WARFARINA Y CLOPIDOGREL). El estudio woest sugiere que clopidogrel mas warfarina es suficiente

Por que ser tan agresivo?

- La incidencia de los SCA sigue siendo muy alta a pesar de la prevención primaria.
- Alta tasa de morbi-mortalidad 12 a 15% en el 1er año a pesar del tratamiento estándar.(eventos vasculares mayores)
- El proceso trombotico juega un rol principal

OASIS, Lancet,1998;352: 507

FRISC –II, Lancet,1999;354(9180):708

ATLAS-2 SCA STUDY.(Timi 51)

- 15.526 Pacientes.
- Fase III. Multicentrico, doble ciego, randomizado
- Rivaroxaban 2,5 o 5 mg bid
- Síndromes Coronarios Agudos recientes.
- 13 meses de tratamiento en promedio.
- 2,5 mg bid, redujo significativamente el objetico primario compuesto de muerte, infarto o ACV(9,1 Vs 10,7%) con un aumento significativo de la hemorragia mayor o intracraneal(2,1 Vs 0,6%) sin diferencias significativas en hemorragia fatal(0,3 Vs 0,2%).
- Rivaroxaban Mostro reduccion significativa de muerte total(2,9 Vs 4,5%) y de muerte cardiovascular(2,7 Vs 4,1%).
- La dosis de 2,5mg bid mostro significativamente menos sangramiento mayor que la dosis de 5 mg bid

ATLAS-2 SCA STUDY.(Timi 51)

- El tratamiento con Rivaroxaban disminuye significativamente el Riesgo Relativo de Eventos Cardiovasculares Isquemicos en un 16% con un NNT DE 56.
- - La dosis de 2,5 mg bid, redujo significativamente la mortalidad total y cardiovascular sin un aumento de la hemorragia fatal.
- Los eventos adversos no hemorragicos fueron iguales al grupo placebo.
- - La dosis de 2,5 mg bid redujo significativamente la tasa de trombosis sub aguda y tardia de stent.
- La terapia a largo plazo con rivaroxaban tras un Sindrome Coronario Agudo puede representar una nueva estrategia en los pacientes con SCA.

Manejo de AP Y ACO en prevencion secundaria posterior a SCA

- Son10% los pacientes que tienen eventos vasculares posterior a un SCA en el primer ano a pesar de la dapt
- - Rivaroxavan disminuyo muerte cardiovascular y eventos a pesar de aumentar el sagrado mayor mas no el sangrado fatal cuando asociado a clopidogrel y asa.
- Tambien redujo trombosis del stent.
- - PERO LA HEMORRAGIA INTRACRANEAL FUE SIGNIFICATIVAMENTE MAYOR.
- Como ningiun otro AP HA SIDO ESTUDIADO SOLO CON ASA Y CLOPIDOGREL).
- - Ya fue aprobado en europa para prevencion secundaria en SCA(nivel de evidencia 2B.

Manejo de AP Y ACO en prevencion secundaria posterior a SCA (PANORAMA A 5 ANOS)

- SE UTILIZARA EN LOS PACIENTES atlas 2(alto riesgo isquemico y bajo riesgo hemorragico) es una indicacion clase 2b y aun no ha sido aprobada en USA

Estudios con endoxavan o rivaroxaban asociados a ticagrelor, vorapaxar y prasugrel son necesarios.

Manejo de AP Y ACO en prevencion secundaria posterior a SCA (PANORAMA A 5 ANOS)

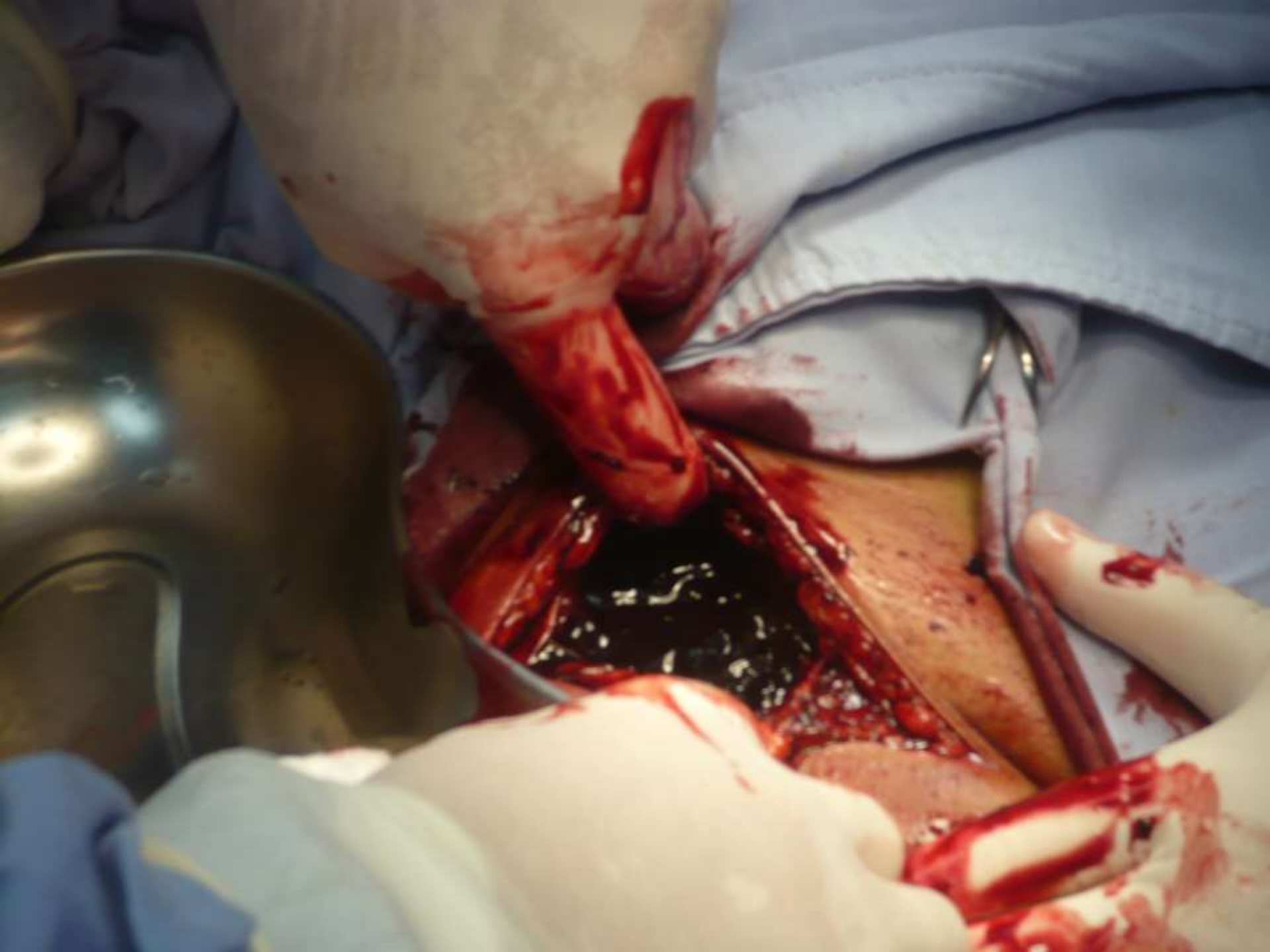
El problema es como incluir los nuevos antiagregantes plaquetarios en los esquemas de prevencion secundaria post sca y como incluir a los nuevos anticoagulantes no cumarinicos en los esquemas de tratamiento de los pacientes con riesgo mediano o alto de stroke que deben someterse a implante de stents.

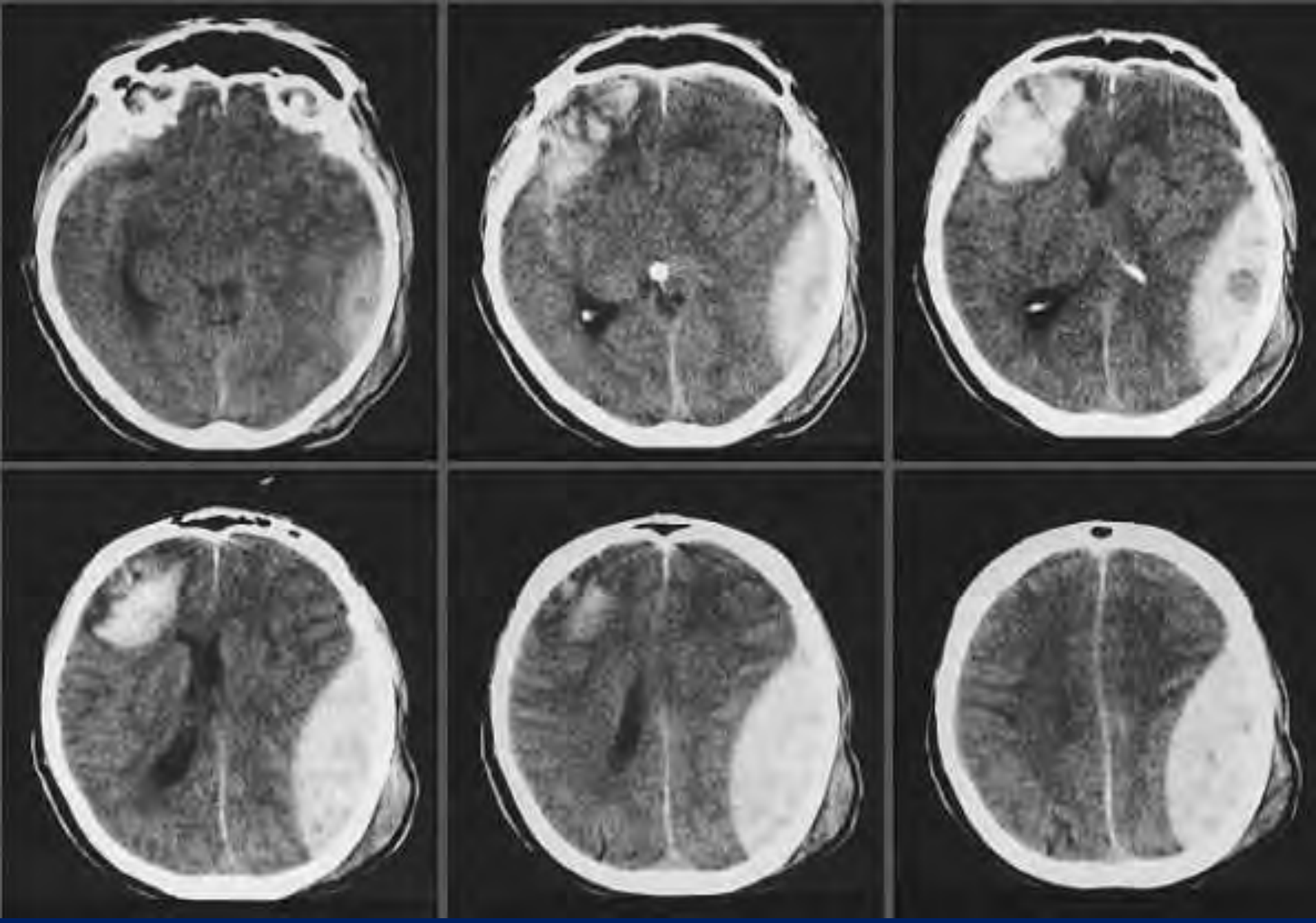
PIONEER AF-PCI Phase IIIb clinical study

An open-label, randomized, controlled, multicenter trial that is planning to enroll 2100 patients with AF undergoing PCI. Patients will be randomized to three arms: rivaroxaban 15 mg once daily and a P2Y12 inhibitor; rivaroxaban 2.5 mg twice daily, a P2Y12 inhibitor, and aspirin 75-100 mg daily; or a vitamin K antagonist, a P2Y12 inhibitor, and aspirin 75-100 mg daily. The primary endpoint will be clinically significant bleeding. This intriguing trial hopes to provide data for the use of rivaroxaban in patients with AF after PCI, while comparing the low-dose TOAT regimen used in ATLAS ACS 2-TIMI 51 versus traditional TOAT with warfarin versus rivaroxaban and a P2Y12 inhibitor without aspirin. Furthermore, it will allow the use of newer antiplatelet agents, prasugrel and ticagrelor, which have also yet to be studied in this patient population.

Cual camino seguimos ?

ADULTO
NIVEL
PRINCIPIANTE
RESCUE





Dr. Pedro Hidalgo
Usache

“ TANTO ES NUESTRO AFÁN EN DISOLVER EL TROMBO, QUE A MENUDO TERMINAMOS DISOLVIENDO AL PROPIO PACIENTE”

Dr. Pedro Hidalgo

San Juan 7.8.14

La ciencia consiste en sustituir el saber que parecía seguro por una teoría, o sea, por algo problemático.

José Ortega y Gasset

CAFE
CON
LECHE

GRACIAS
ALTA DENSIDAD

ESTUDIANTES
CONSTRUYENDO UN PAIS